Alex V. Levin
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The Eye in Pediatric Systemic Disease

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Preface

This book truly is a "labor of love." When we were pediatric ophthalmology fellows at The Hospital for Sick Children in Toronto from 1989 to 1990, we were both already board-certified pediatricians. Going to SickKids was like being children in a candy shop. With our interest in pediatric systemic disease and love of children, combined with our interest in ophthalmology, the possibilities seemed endless. Our Fellowship Director and mentor, Dr. Donald Morin, taught us much and pushed us towards excellence. He made it seem like any goal could be achieved. When we came up with the idea for a comprehensive textbook on the ocular manifestations of pediatric systemic disease, he was encouraging but warned us about the enormity of the effort. He had written one of the great pediatric ophthalmology textbooks, *The Eye in Childhood*, and was well published in many areas. As an academic pediatric ophthalmologist, he knew the rigors of putting a project like this together. Yet, he believed in us, and also knew that there was no similar publication on the market. So, along with our co-fellow, Dr. James Elder, who has authored two of the chapters in this book, we set forward trying to make the book a reality.

Some chapters were drafted, others never began. Time passed. Our careers developed, we went to separate parts of the world, we raised our families, and the project found its way to the "back burner." It was not till recent years that we got the idea of bringing the project back to life. There was no other book available like the one we were planning. Our goal is an encyclopedic reference to be used by non-ophthalmologists and ophthalmologists. For the pediatricians and other non-ophthalmologists, it would be a place where they can learn about the ocular manifestations of diseases they see. For the ophthalmologists, it was a place where they can learn more about the systemic disorders that present to them with ocular findings. Readers might be asking questions such as: "What are the eye findings of this disease that need to be considered? Is the eye finding in my patient a manifestation of the disease? What tests should I be ordering? For what should I be screening?" And for those who want to delve further, the chapters are heavily referenced to provide an entry point into the literature regarding any detail the reader wishes to explore. Although the book is not an atlas, key pictures of findings specific for diseases, rather than generic ocular findings, are provided. Our comprehensive approach is designed to fill the gaps in each reader's knowledge outside their own specialty.

So we recruited new authors and contacted some of the old authors. We believe strongly in the importance of collaboration between pediatricians and pediatric ophthalmologists. Therefore, every chapter has at least one author who is a pediatric ophthalmologist as well as one coauthor who is a non-ophthalmologist with expertise in the field being discussed. We encouraged the use of trainees and other collaborators to write each chapter understanding the huge amount of work that was required. We carefully vetted the chapters and edited them thoroughly to ensure accuracy as well as a comprehensive approach. Each chapter covers many disorders. We decided to allow redundancy between chapters as the approach between authors of different disciplines to a given disease, which covers more than one organ system, might offer unique perspective. Each disease is discussed where possible in sections: definition, history, epidemiology, systemic manifestations, ophthalmic manifestations, diagnosis, and management. We believe the result is unique and uniquely useful.

Everyone who contributed to this book learned in the process. We hope that readers will also experience an expansion of their horizons as they step outside their daily lives of practice to reach into the world of the disciplines with whom they collaborate. We hope that this textbook will become the "go to" source for physicians from all areas, who deal with children, and are trying to understand the ocular manifestations of pediatric systemic disease. We look forward to having physicians come together through this book and establishing appropriate consultation patterns and collaborations. Together, we will all benefit the children we care for. Dr. Morin has unfortunately passed away, but this book is dedicated to everything he believed in: learning, supportive training, collaboration, and above all, thoughtful informed care of the child.

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Normal Postnatal Ocular Development

1

Laura J. Heinmiller and Alex V. Levin

Although detailed normative data regarding the volumetric and topographical analysis of the eyeball and its contents are available [1] this discussion will be confined to the clinically relevant dimensions.

Visual Acuity

Fixation

Perhaps the most frequent question which parents ask pertaining to their infant's eyes is "What does my baby see?" The answer to this question depends in part on the type of method used to assess visual acuity. The majority of babies should show some fixational behavior at term birth. At 4 weeks, the baby looks at their mother's face while breast feeding [2]. When the mother moves her face, the child will follow it visually. This movement is interrupted if the mother turns her face away so that only her profile is presented [2]. By 2 months the baby is following better but the pursuit movements tend to be jerky rather than smooth [2]. Smooth pursuit eye movements show the most maturation from 2 to 6 months old, and reaching almost an adult-like gain by 18 months old [3]. Pieh and coworkers found that tracking time was highest when a larger stimulus of 4.78° of visual angle was applied ($p<0.022$) and when the stimulus was moved at a medium stimulus velocity of 15 degree/s ($p<0.0002$) [3].

Often, the human face is a better stimulus of fixation than a light source [2]. Goren et al. were able to show that 9 min old infants had a preference for a face-like stimulus over a scrambled face image. Both of these were preferred by the infant over a blank face image [4]. One and four month old infants show greater pupillary dilation (a substitute measure for arousal and interest) to faces than to other nonsocial patterns [5]. By 12 weeks of age only 5 % will not fixate on a light although 13 % do not fixate well [6]. Actually, by 12 weeks, half appear to fixate clinically but do not accommodate to focus as judged by the appropriate change in the red reflex [6]. By 6 months, almost 100 % will both fixate and focus normally with either eye although some researchers believe that full adult fixational behavior is not achieved until 1 year [6]. Both eyes do not have to develop normal fixational behavior symmetrically [6]. By 6 months, only 4 % of children will have be a fixational abnormality in one eye due to an underlying ocular problem [6].

Optokinetic Nystagmus (OKN)

More objective values for visual acuity in infants depend largely on the method used. In a comparative review of the literature, Dobson and Teller found that visual acuity in the first month of life measured 20/200–300 by observation of optokinetic nystagmus (OKN), visual evoked potentials (VEP) or preferential looking responses [7]. By 6 months the vision improved to 20/100–200 by OKN and preferential looking but to 20/25 by VEP [7]. Normal values for grating acuity and OKN have been developed for the first 3 years of life [8]. The range of normal values is very wide in the first 6 months. Visual development, as measured by these tools, appears to accelerate in the second year of life [8].

Visual Evoked Potential (VEP)

VEP can be used to measure visual acuity although the reliability of this technique has been questioned [9]. The data depends in part on the type of VEP used [7]. With sweep VEP,

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Table 1.1 Visual acuity in infants by method [11, 12]

Method	OKN	VEP	Preferential looking (tellar cards)	Otago photoscreener
Full term newborn	20/400	20/100–20/200	20/200–20/545	–
2–3 months	20/400	20/80	20/285	20/20–20/25
4 months	20/200	20/80	20/167	–
5–6 months	20/100	20/20–20/40	20/100–20/120	20/20
1 year	20/60	20/20	20/50	–

OKN optokinetic nystagmus, *VEP* visual evoked potential

a pattern of vertical lines of varying width move across the visual field in a continuous fashion, usually on a video monitor. As the lines get thinner, they also become proportionately closer together until the subject can no longer perceive that lines are present. Results of this technique are often reported in cycles/degree which must then be approximately translated into the standard Snellen acuity values (20/x where x = 600/cycles/degree). This simple conversion may not be entirely accurate as it does not take into account other factors such as retinal-neural processing and contrast sensitivity. But if one accepts this technique, visual acuities ranging from 20/133 in the first month to 20/30 by the end of the first year can be found [9]. Norcia and Tyler have cautioned that these values should be used as the lower boundary of infant performance rather than absolute limits [9]. Further investigations using a dual-frequency technique VEP in infants 10–39 weeks old showed that both central and peripheral visual acuity improved by a factor of 2.6 and 2.2 respectively with central acuity higher by a factor of 2.3 [10].

Current Consensus on Ages for Maturity of Visual Acuity

Depending on which method is used to test visual acuity there can be large variations in the expected norms throughout the first years of life (Table 1.1) [11, 12].

Preferential Looking/Tellar Acuity Cards

Using Tellar Acuity cards, the visual acuity in full-term newborns was estimated at 20/200 [11].

Otago Photoscreener

Molteno and coworkers made estimations of visual acuity using the Otago photoscreener, a system which uses the variations in the red reflex to assess fixation, accommodation, refractive error, and ocular alignment [6]. They estimated that the visual acuity at 3 months ranges from 6/6 to 6/15, at 6 months almost 70 % are 6/6 with a further 15 % having 6/9 in the worse eye, and by 1 year over 90 % have at least 6/9 vision in both eyes [6]. A summary of visual acuity in infants by method can be found in Table 1.1 [11, 12].

Contrast Sensitivity

Contrast Sensitivity begins to develop through the first 3 months of life [12]. Fiorentini and coworkers showed that infants aged 2.5–6 months exhibited contrast sensitivity by VEP at a mean luminance of 6 and 0.06 cd/m^2. They showed that scotopic contrast sensitivity develops earlier than photopic contrast sensitivity, and by 4–5 months old are nearly at the level of an adult [13]. Contrast sensitivity develops similarly in the central and peripheral visual fields [10].

Globe Size

Axial Length

The axial length of the globe increases in a direct relationship with age until approximately 8 years old with a stronger correlation for hyperopes as compared to myopes [14]. The eyeball increases 2.86–3.25 fold between birth and adulthood [1, 15]. The most rapid portion of this growth occurs in the first 40 weeks of postnatal life [16]. Stafford and coworkers found the maximum axial length at term, as measured by ultrasound (A scan), to be 18.6 mm with a mean of 17.0 ± 0.65 standard deviation [17]. Other authors have found similar values [16]. Formulas are available for more detailed analysis of the ocular growth patterns [16]. Axial growth of the eye occurs in three phases: from birth to 18 months a rapid period from mean of 16 to 20.3 mm; a 1.1 mm increase between years 2 and 5; and 1.3 mm of growth thereafter leveling off at age 13 [18].

Saggital, Transverse and Vertical Size

At birth, the mean saggital, transverse, and vertical diameters of the globe are 17.5, 17.1, and 16.5 mm respectively representing approximately 71 % of the adult equivalents [1]. The anterior segment of the infant globe is roughly 75–80 % that of adults. The posterior segment is less than half of the aver-

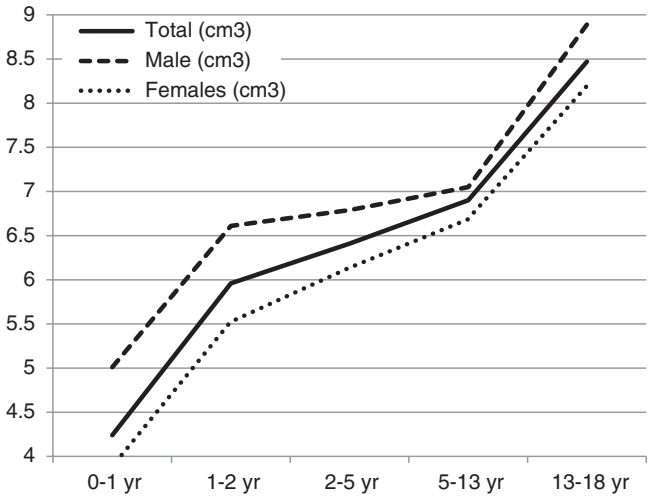

Fig. 1.1 Ocular volume with CT scan in children [21]

age adult. The total sclera surface in infants averages 822 mm^2 which is about 1/3 that of the average adult [19]. Therefore, a majority of the change in globe size stems from the expansion of sclera surface in the posterior segment with 50 % of growth occurring in the first 6 months of life, reaching adult averages at around 13 years [19].

Volume

Through childhood, the ocular volume increases about 300 %; from 2.5 to 7.5 cm^3 [20]. Hahn and Chu performed a study showing ocular volume measured by CT scan and found that rapid eye growth occurs during the first 24 months of life and peaks between the ages of 18 and 24 years old [21]. Figure 1.1 illustrates these findings [21].

Refractive Error

Cycloplegic Retinoscopy

The refractive error of the eye may be measured by a variety of techniques. It is standard to use some form of cycloplegic retinoscopy in children. As the differences in the absolute level of cycloplegia which is obtained through various cycloplegic regimens is small, we will discuss the development of refractive error in the normal infant based on the reported values obtained through various cycloplegic regimens as if they were equal. However, retinoscopy in infants and young children without the use of cycloplegia may be prone to significant error. Data collected under these circumstances will not be included. Likewise, the definition of amblyopia may vary between authors. We have chosen as our definition a two line difference between each eye based on projected acuity charts, visual acuity in an eye with 6/9 acuity or worse, or any other objective test result (e.g. visual evoked potential, preferential looking) which indicates an equivalently significant difference between the eyes.

Trend Towards Emmetropia

In general, there is a trend towards emmetropia throughout early childhood regardless of the initial refractive error [22]. The main changes towards emmetropia occur in the first 2 years [23, 24]. Further studies have shown that hyperopia decreases with age along with astigmatism found in infants. In a prospective study on childhood myopia ranging from −0.25D to −3.50 diopters, Ehrlich and coworkers showed that emmetropization was found to occur by 3 years old. The rate of change in myopia from age 8.5 to 38.5 months occurred at a relatively constant rate of +0.44 diopters per year [25]. Ultimately, emmetropization occurs through a combination of passive and active means. Passive means include a growth in axial length, reduction in the power of the lens, a mild reduction in power of the cornea as the radius lengthens and a lengthening of the anterior chamber [26]. The active component relies on the feedback given by the image clarity of the retina, for which the exact mechanism is unclear [27].

Spherical Equivalent Anisometropia

In 88.5 % of children, there is no significant difference between the spherical equivalent of the right and left eye [28]. One group found only 1 % of 519 children less than 48 months old to have anisometropia [29]. This group also established 99th percentile curves for normal refraction. They found the range to decrease with age, staying fairly stable after the first year. In a cross-sectional study of healthy children under the age of 5 years old, Kuo and coworkers showed that 95 % of the children had less than 1.50 D of anisometropia [24]. Deng and Gwiazda measured refractive error in children ages 6 months (n = 1120), 5 years (n = 395) and 12–15 years (n = 312) and found the mean difference in refraction between the two eyes was similar at 6, 14 months (0.11 D) and 5 years (0.15 D), increasing to 0.28 D at 12–15 years [30]. The prevalence of <1.00 D of spherical equivalent anisometropia, was 1.96 %, 1.27 %, and 5.77 % respectively [30]. Infants with significant astigmatism (≥1.00 D) in one or both eyes have an increased risk of anisometropia ($p < 0.05$) [30].

Hyperopia

Over the first 3 years of life, the average spherical equivalent in normal children is −0.75 to +3.00 diopters [28, 31]. Only 7–8 % will have hyperopia (farsightedness) in excess of 2.75 diopters during this time period [28, 32] with only 2 %

having greater than 4.00 diopters of hyperopia in the steepest meridian [32]. Those who have greater than 4 diopters of hyperopia at 6 months and stay hyperopic thereafter, have a very high risk of developing accommodative esotropia particularly if there is a family history of strabismus [23]. Kuo and coworkers found that greater than 95 % of children less than 5 years old had less than +3.25 diopters of hyperopia [24]. One cross sectional study involving almost 10,000 children analyzed risk factors for hyperopia and found that children whose parents had health insurance and a history of maternal smoking during pregancy were more likely to be hyperopic [33]. The relationship between hyperopia and maternal smoking appears to be linear and dose dependent with a 6 % higher prevalence of hyperopia for every increase of 10 pack-months of maternal smoking [33]. There was an unexpected higher prevalence of hyperopia in 6 year old children as compared to 1–3 year olds [33]. African-American children are significantly less at risk for hyperopia than non-Hispanic or Hispanic children [33].

Myopia

Myopia (nearsightedness) is unusual in the first year of life. In the first 4 years, only 3 % of children are myopic with the incidence of myopia being less than 2 % by the age of 5 years old [29, 34]. Approximately 17 % of children will have up to 4 diopters of myopia with less than 0.5 % having more [32]. Unlike hyperopia, the prevalence of myopia is greater in children 4–6 years of age compared to those 3 years and younger [33]. Racial predilection for myopia is strongest in African-American and Hispanic children when compared to non-Hispanic white children [33]. There are two main theories regarding the development of myopia including the increased demand for near work theory and genetic disposition theory [26]. The near work theory is supported by the higher prevalence of myopia in populations with higher education levels and increased near demands [35, 36]. The genetic theory is supported both by the increased prevalence of myopia in monozygotic twins and increased prevalence of myopia in children with myopic parents [37, 38].

Astigmatism

Most authors have found that the incidence of astigmatism is much higher in young children than in adults [28]. In the first year of life, 19 % of children will have astigmatism [28]. Myopic infants have larger astigmatism which decreases with age [25]. The incidence of astigmatism peaks at approximately 25 % between the ages of 7 to 12 months [28]. Over the first 4 years of life the incidence is still 25 % [29]. Against the rule cylinder is more common than with the rule or oblique axes (56, 29, and 14 % respectively) [29]. One group found that oblique cylinder was always a mirror image axes in the two eyes [29]. The incidence and amount of astigmatism gradually decreases after the first year [28, 32] and may even decrease after the first 4 months [29]. In fact, astigmatism in excess of 3.00 diopters is uncommon prior to 10 months or beyond 2 years [28]. Only 5.7 % of children will experience astigmatism greater than 2 diopters in the first 3 years of life [28]. The axis of astigmatism is predominately (70–90 %) against-the-rule (plus cylinder at axis 180° ± 15) [22, 28]. With-the-rule astigmatism (plus cylinder at axis 90° ± 15) represents 6–20 % of astigmatism [22, 28]. Oblique astigmatism is the least common and accounts for only 3–8 % of astigmatism in normal children [22, 28]. The axis of the two eyes is almost always symmetrical [22]. The amount of astigmatism tends to lessen in the first 4 years of life, increasing in only 10 % of patients [22]. The etiology of astigmatism in children is unknown however, like hyperopia, maternal smoking during pregnancy was found to be a risk factor. Hispanic and African American race, hyperopia and myopia are all associated with higher incident of astigmatism [39]. Children with astigmatism are more likely to come from families that have an income of <$20,000 per year and lack vision insurance [39]. The risk for amblyopia in patients with astigmatism as the only variable is only approximately 3 % although this risk may be as high as 35 % in those children with increasing astigmatism in the first 4 years of life [22]. The risk of amblyopia may also be higher for patients with oblique axis or higher hyperopic spherical equivalents [22].

Nasolacrimal System

Tears

At birth tear production is very close to adult levels with premature infants having a lower rate of both basal and reflex tearing [40]. As measured by Schirmer for 5 min with and without topical anesthetic respectively, the mean basal tear secretion is 6.2 ± 4.5 mm and 7.4 ± 4.8 mm for a cohort of preterm infants between 25.4–37 weeks gestation and 583–2700 g whereas for term infants the rates were 9.2 ± 4.3 and 13.2 ± 6.5 [40]. In both groups, the secretion rate was directly proportional to weight. In term infants, total tear secretion significantly increased at both 2 and 4 weeks old while in preterm infants a significant increase in tear production occurred at 4 weeks [41].

Location of Puncta

When the lids are closed, the puncta are located 6 mm lateral to the inner canthus and sit on a mound known as the lacrimal papillae [42]. Upon opening of the lids, the upper punctum shifts 0.5 mm nasal to the lower punctum [42]. The

diameter of the punctum is between 0.2–0.3 mm [42]. The puncta are normally located medial to the nasal limbus positioned against the globe in primary position [43].

The proximal nasolacrimal system is normally patent at birth following the normal separation of the eyelids at 7 months gestation, followed by canalization at the level of the punctum [44]. It has been shown that the last part of the duct to canalize during development is the valve of Hasner [45]. Incidence of congenital nasolacrimal duct obstruction was found to be 73 % in a study reviewing stillbirth fetuses with all obstructions being secondary to a mucous membrane at the level of the inferior meatus [46]. The duct enters the nose within the inferior meatus under the inferior turbinate 2.5 cm posterior to the naris and is approximately 5 mm in length [42].

It should be noted that in children there can be variations in the distance within the nasolacrimal system secondary to immaturity. In children, typically the distance between the canaliculus and nasal floor is 20 mm with adult measurements being between 30–40 mm [42].

Cornea

Endothelium

The corneal endothelium in infancy has a regular mosaic pattern of small hexagonal cells although there may be some smaller or larger cells and cells with an increased number of sides [47]. Twinning cells may also be seen [47]. Cell population density (CPD) ranges from 2987 to 5624 (mean 4252) cells/mm^2 in babies less than 1 year of age without a general pattern of decline over that year [47]. However, infants with more than 5000 cells/mm^2 tend to be less than 2 months old [47]. The calculated endothelial surface area changes from 91.9 to 129.8 mm^2 from birth to 1 year of age with an assumed constant growth rate of 3.16 mm^2/month [47]. Rather than loss of cells, the endothelial cells spread over this increasing area which may have led some observers to note a decline in CPD [47]. Clinically, some infant corneas show non-inflammatory retrocorneal particles on the endothelium which may represent dividing cells [47].

Keratometry

The cornea is steeper at birth with progressive flattening towards adult values in the first months of life. At birth, Inagaki found the mean keratometer reading to be 47.00 ± 1.19 diopters (range 45.69–49.06) [31]. By 1 and 3 months of age the cornea has flattened to 46 ± 2.15 and 44 ± 1.70 diopters respectively [31]. Isenberg and coworkers found the mean central corneal power to be 48.5 diopters (range 41.4–56.0) at birth decreasing to 43.0 diopters (range 41.3–43.1) [48]. It has been hypothesized that this relatively rapid change occurs to offset the increase in axial length which is occurring the same time therefore resulting in stabilization of the infant's refraction [31].

Size

The mean horizontal diameter of the term newborn cornea is 10.0 mm with a thickness of 0.8 [1]. Stafford and coworkers recorded a slightly smaller mean corneal diameter of 9.55 ± 0.5 standard deviation at term [17]. By adulthood, the diameter will have increased to a mean of 12.5 [20]. The thickness is almost 90 % of adult thickness at birth [1].

Tactile Corneal Reflex

The tactile cornea reflex is present in at least one eye in only 10 % of babies at 2 days of age [49]. This increases to 25 % at 1 week, 50 % at 3.5 weeks, 75 % at 6 weeks, and 100 % by 3 months [49]. Postpartum age is more important in the development of this reflex than gestational age [49]. Birth weight also has a significant positive correlation [49]. This is particularly relevant to corneal protection only if one considers the developments of the Bell's phenomenon: 36 % at 1–3 days old, 50 % at 4–8 weeks, and 100 % by 4 months [49]. The corneal reflex is developing more rapidly.

Central Corneal Thickness

Portellinha and coworkers examined 74 newborn infants and found that the mean central corneal thickness and mean peripheral corneal thickness was 0.573 ± 0.052 mm and 0.650 ± 0.062 mm respectively [50]. Remon and coworkers showed an average central corneal thickness of 0.585 ± 0.052 mm in 152 one day old infants. They also measured superior, inferior, nasal and temporal peripheral corneal thickness (Table 1.2) finding measurements of 0.696 ± 0.055 mm, 0.744 ± 0.062 mm, 0.742 ± 0.58 mm, and 0.748 ± 0.055 mm respectively [51]. Both studies found the corneal measurements during the first day of life to be significantly higher than the following days of life [50, 51]. They failed to find any difference between sex, gestational age, type of delivery or right and left eyes [50].

Lopez and coworkers found an average CCT in children 8 months- to 6 years old of 0.558 mm (0.489–0.614 mm) and for ages 6–17 years 0.560 mm (0.467–0.662) [52]. They failed to find any significant association between CCT and age [52]. Ehlers and coworkers found that central corneal thickness reaches adult measurements around 3 years of age [53]. They found an average CCT measurement in children ages 2–4 years old to be 520 ± 0.007 μm and ages 5–9 to be 520 ± 0.005 μm [53].

Table 1.2 Infant central and peripheral corneal thickness by age, sex and laterality [51]

	Number of subjects	CCT	SCT	ICT	NCT	TCT
1 day old	108	611 ± 58	713 ± 61	761 ± 69	756 ± 64	760 ± 62
2 days old	114	573 ± 60	686 ± 62	737 ± 72	756 ± 64	744 ± 61
4 days old	20	572 ± 28	691 ± 31	725 ± 35	732 ± 43	738 ± 38
6 days old	16	561 ± 36	681 ± 31	724 ± 34	722 ± 35	731 ± 27
Male	154	598 ± 54	699 ± 59	748 ± 65	744 ± 60	752 ± 58
Female	150	581 ± 50	693 ± 51	740 ± 59	740 ± 56	744 ± 52
Right	152	585 ± 52	694 ± 52	745 ± 64	745 ± 62	748 ± 55
Left	152	585 ± 52	698 ± 58	743 ± 60	739 ± 54	748 ± 55

CCT central corneal thickness, *SCT* superior corneal thickness, *ICT* inferior corneal thickness, *NCT* nasal corneal thickness, *TCT* temporal corneal thickness

A recent review of the genetics of central corneal thickness looked at the four published studies of the heritability of central corneal thickness including twin and family pedigrees which shows that CCT is one of the most highly heritable human traits with tremendous variation amongst different ethnic groups [54]. While there is strong evidence that central corneal thickness is genetically driven, no genes have been identified to date [54].

Corneal Hysteresis

Corneal hysteresis is the difference in the pressure required to flatten the cornea and the force at which the cornea becomes flat again which is a direct measurement of the biomechanical properties of the cornea [55]. Kirwan and coworkers studied 91 normal eyes of 42 children and found mean corneal hysteresis of 12.5 mmHg. There was no correlation between age and corneal hysteresis [56]. In a separate study, Kirwan found the average adult hysteresis was 10.8 ± 1.5 mmHg indicating corneal hysteresis reduces with age from childhood to adulthood [57]. Ortiz et al. found a mean corneal hysteresis of 10.8 ± 1.5 mmHg in 165 eyes and found hysteresis to be lower in older eyes with the difference between the younger group (9–34 years) and oldest group (60–80 years) to be statistically significant [58]. Lim and colleagues noted that in a study of 257 healthy patients (age 13.97 ± 0.9 years) in the Singapore Cohort Study, that corneal hysteresis (11.80 + 1.55 mmHg) and corneal resistance factor (11.83 + 1.72 mmHg) are associated with narrower retinal arterioles [59].

Anterior Chamber

Depth

Although the newborn anterior chamber often appears relatively shallow, the depth is almost 75% of adult values [1]. Kobayashi and coworkers evaluated the anterior chamber of 46 infants age 1–60 months and showed average anterior chamber depth was 1.724–3.743 mm with depth increasing linearly with age [60]. The iridocorneal angle is almost completely developed at birth although some further recession will gradually take place such that the infant's ciliary body is less visible on gonioscopy than an adults [61]. Kobayashi and coworkers showed the trabecular-iris angle in infants from 1 to 60 months of age ranged from 15.35 to 44.79° and increases in angle size correlated positively with an increase in age [60].

Trabecular Meshwork

The normal insertion of the iris and ciliary body at birth is at the level of the scleral spur. As the first year of life progresses, a posterior migration occurs forming the angle recess. Additionally, the endothelium that lines the angle becomes fenestrated while an endothelial layer of cells migrates into the underlying uveal meshwork [62]. The uveal and trabecular meshwork are relatively transparent at birth, becoming more pigmented through the first year of life [63]. While iris processes are rarely present, they are either faintly pigmented or nonpigmented [64]. The trabecular meshwork has been described as a "moist," transparent membrane and appears somewhat translucent [65]. The peripheral iris appears to be more flat and thin than seen in adults [62]. By 1 year old, the trabecular development is complete [64–66].

Intraocular Pressure (IOP)

Values Goldman Vs. Pneumotonometry Vs. I-Care® Vs. Tono-Pen® Vs. Perkins

Stafford and coworkers found a mean IOP of 15.2 ± 3.4 at term [17]. Giles produced higher values while using a Schiotz tonometer to measure intraocular pressures in 32 babies less than 1 h old and found the pressure approaches the upper limit of adult normal levels with 25.8 mmHg used as the upper limit of normal [67]. Six infants exceeded this level while none had measurements exceeding 30.4 mmHg [67]. Radtke and Cohan used a Perkins tonometer on 60 infants between 19 and 173 h of age and found a mean IOP

Table 1.3 Infant intraocular pressure studies [68, 70–74]

Author	Anesthesia	Method by which pressure obtained	Intraocular pressure (mmHg) mean (range)	Patient age	Number of measurements
Hörven [70]	Topical	Schiotz	16.3 (10.2–24)	4 h–10 days	50 infants (60 attempts)
Kornblueth and assoc [71]	Diethyl ether	Schiotz	22.5RE, 20.9LE (15.9–29)	5–24 h	47 eyes
Westby and Skulberg [72]	Diethyl ether	Schiotz	16.9 (8.5–22.4)	1.5–9 years	110 eyes
Hetherington and Shaffer [73]	Fluothane	Draeger and Schiotz	12.5 (7–22)	3 months–7 years	30 eyes
Sampaolesi [74]	Methoxyflurane	Goldmann and Draeger	10 (7.81–12.19)	Few days–5 years	85 eyes

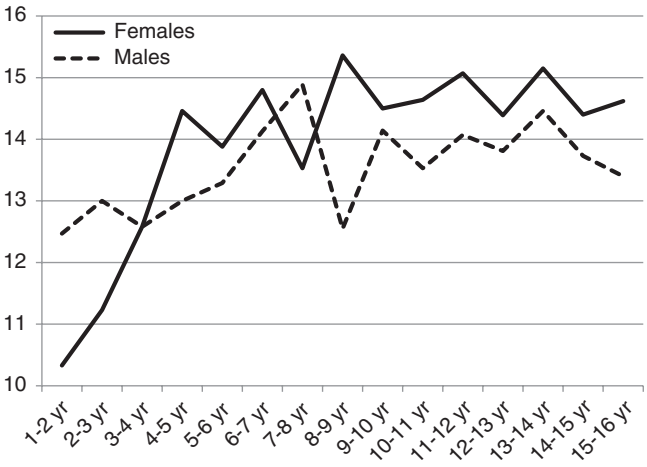

Fig. 1.2 Mean tonometric readings (in mmHg) by sex and age [76, 77]

of 11.4+2.4 mmHg (range 6–17) [68, 69]. A summary of other studies of infant intraocular pressures can be found in Table 1.3 [68, 70–74].

By the second decade, there is no significant difference between mean IOP in the sitting (16±2.4 mmHg) or supine (17±2.3 mmHg) position as compared to adults over 20 years [75]. Values for tonometric readings by sex and age found by Pensiero and colleagues [76] using the noncontact Keeler Pulsair tonometer and Youn and colleagues [77] using the Perkins tonometer can be found in Fig. 1.2.

These findings were used to break the increase in intraocular pressure in children into three groups. First, the neonatal phase with average value of 9.59+2.3 mm followed by an exponential phase up to age 7–8 years and finishing with a gradual steadying of eye pressures until the 16th year of life [76]. Jaafar and Kazi utilized regression analysis to show IOP of children and adults are equal using Perkins tonometry by age 12 [78]. Using Perkins tonometry, IOP increases gradually from infants (4.55+0.51 mmHg age 0–1 year) to children (7.85+1.27 mmHg by age 4–5 years) to adults (13.21+2.11 mmHg) however, there was no statistically significant different when measuring IOP with pneumotonometry [78]. Sihota and colleagues also noted in their study of 810 eyes in 405 patients ranging in age from 0 to 12 years that IOP reached adults levels by age 12 and found that IOP correlated directly with refraction (r=0.69) and pachymetry (r=0.39) and inversely with axial length (r=−0.1) [79].

Normal values may depend on the measurement method. One group found that the normal values using Goldmann applanation tonometry on children less than 10 years old followed the formula IOP=(0.71 × age in years)+10 whereas the linear fit worsened after the first decade when the mean IOP was 14.6±3.3 [80]. Using pneumotonometry, the same authors found no age related effects with a mean IOP of 16.8−3. They showed that for all ages the IOP by Goldmann was approximately equal to 1+(pneumotonometer × 0.78). After 10 years a more accurate estimation was IOP by Goldmann=(0.94 × pneumotonometer value)−1.2. Under general anesthesia (agent not specified) they found that readings by Perkins tonometer=2.6 log (age)+pneumatonometer value−10.3. Percentile charts are available in their paper. They conclude that normal adult values for IOP are reached by 10 years of age. Below this age they theorize that the lower measured values are actually artifacts due to the difference in ocular wall rigidity. Johnson and collegues showed that intraocular pressures are significantly lower when succinyl choline is used during induction which is thought to be related to a temporary increase in outflow [81].

Other options for intraocular pressure measurements include the Tono-Pen® and ICare® rebound tonometer. In a study of 39 children ages 3–18 months old using the ICare tonometer, the average intraocular pressure was 11.82±2.67 mm with a median value of 10 mmHg with a range of 7.3–17.0 mmHg [82]. Bordon and coworkers compared IOP in children with several different methods and concluded that the Tono-Pen is reliable in children as there was no statistically significance compared to Perkins (P>.05) [83]. When evaluating the Schiötz measurements it was shown these values were significantly higher than those obtained with the Perkins and the Tono-pen tonometers (P<.05). Schiötz is an undesirable method for measuring IOP in children [83].

Pupils

Size

The pupillary size of newborns and infants is generally smaller than that of adults [84]. Average pupil sizes in neonates of 3.8±0.8 mm with a range of 1.5–6 mm have been

reported [84]. Wilmer and Scammon calculated that the mean pupillary size of neonates was 70 % of adult size [1]. Pupil size is significantly larger in the presence of a blue iris (4.07 ± 0.92) as compared to neonates with brown irides (3.64 ± 0.74) [84]. There are several factors that have been proposed to account for the smaller pupil in an infant. These include smaller anterior segment dimensions, loss of central inhibitory impulses to the oculomotor nucleus in a more constant state of sleep and a poorly developed iris dilator muscle [85–87]. In addition, pupil size may also be affected by the presence of quality of fixation, refractive error, amblyopia, and strabismus [6].

Anisocoria

A difference of greater than 0.4 mm between the two eyes is a common finding in the normal population. At birth, 21 % of term neonates demonstrate physiologic anisocoria [84]. There is no significant change in this rate based on iris color [84]. Roarty found that no term neonate had anisocoria of greater than 1.2 mm and 97 % of babies with anisocoria had less than 1 mm difference between their two eyes [84].

Red Reflex

The red reflex is one of the most important screening techniques for neonates and infants as it may reveal the presence of abnormalities along the visual axis, pupillary abnormalities, refractive errors, or strabismus [6]. When normal fixation and focusing occurs, the red reflex darkens to a dull homogeneous orange red color [6]. In neonates who fixate but do not accommodate properly (see above), the reflex will appear brilliant yellow or almost white [6]. A thin circle may also be seen normally within the red reflex [6]. However, if the reflex is not homogeneous or particularly when it is asymmetric between the two eyes, further investigation is warranted. A black or comparatively darkened reflex may indicate obstruction of the visual axis or ocular misalignment. Abnormal comparative unilateral "brightening" may be a sign of reduced visual acuity in that eye [6].

Responses

Isenberg and coworkers found that pupillary response was consistently present in 99 % of the infants studied if gestational age was >31 weeks [86]. In the full term neonate, convergence is variable with accurate and maintained convergence becoming well developed by 2–3 months old [88]. The appearance of the direct and consensual light reflexes occurs 30 weeks after conception [89].

Iris

Color

In general, the newborn iris is paler than in older children [90]. At birth, when not controlled for race, 39 % of babies have blue irides with the remainder having brown irides [84]. In more darkly pigmented races, the iris has a darker appearance at birth due to a greater number of stromal melanocytes [90]. In all races, the iris darkens during the first 6 months of life due to increasing maturation of melanocytes [90]. Lighter colored irides may appear more vascular in the neonatal period [90]. The Louisville twin study evaluated eye color in monozygotic and dizygotic twins and showed that by 6 years of age, most individuals achieve stable eye color. They did find a subpopulation of 10–15 % of Caucasian subjects who continue to have changes in eye color throughout adolescence and adulthood thought to reflect changes in melanin content or distribution [91]. The study further illustrated the genetic influence on iris color as concordance was high (90 %) among monozygotic twins and declined among dizygotic twins from 80 % at 3 months old to 50 % by 6 years old [91].

Structure

Iris crypts are not fully developed at birth [90]. Although this process continues for several months after birth, little maturation occurs in the first 2 weeks of life [90]. Although Purtscher originally felt otherwise, there appears to be no difference in crypt development related to iris color [90]. One group of researchers found that iris vascularity and crypt development were greater in males [90]. The infant iris is flatter and thinner than the average adult. Iris thickness evaluated at the thickest part of the iris measured 249–579 μm in infants age 1–60 months and correlated positively with age [60].

Lens

Diameter

At birth, the horizontal lens diameter is approximately 6 mm and continues to progress as illustrated in Fig. 1.3 [20, 92, 93]. The period of most rapid growth occurs in the first 2 years of life with moderate growth until age 4 and only a small amount of growth after age 5 [92]. The adolescent lens, with a diameter of 9–9.5 mm, is not yet at the same diameter of the adult lens which keeps increasing well into the final decades of life with an associated decrease in anterior lens curvature [94]. As the lens gets bigger, the distance between the lens edge and the ciliary sulcus decreases [94].

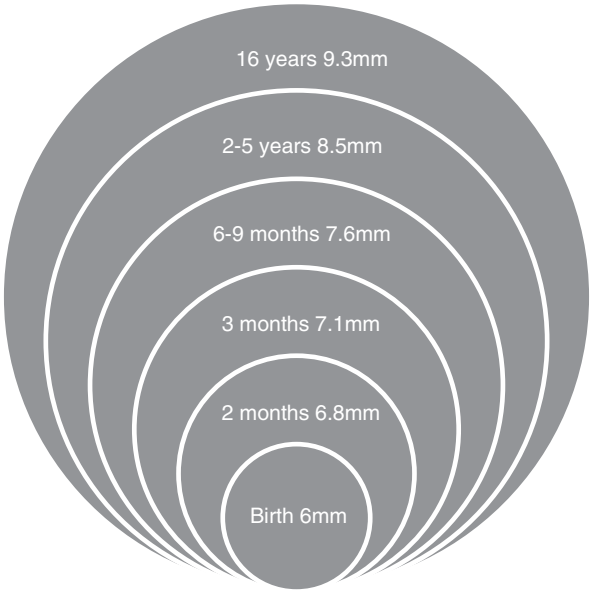

Fig. 1.3 Mean crystalline lens diameter (in mm) by age [20, 93, 96]

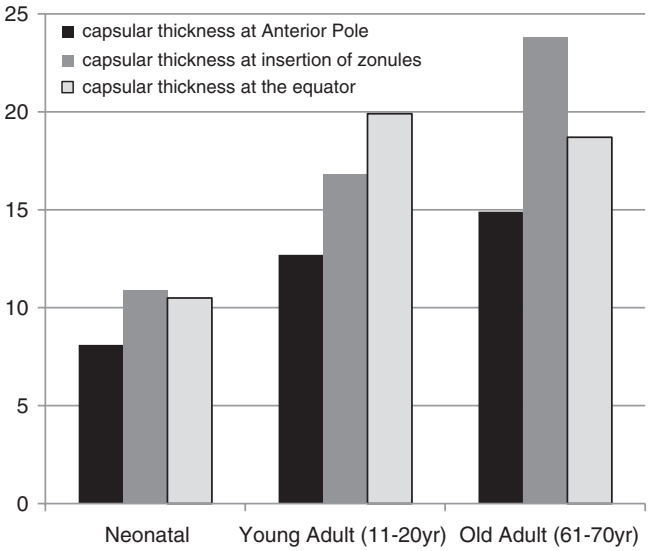

Fig. 1.4 Thickness of the anterior lens capsule by location (mean in μm) [99]

The thickness of the human lens has been measured in numerous studies and found to be 3.5–6.5 mm in the newborn, and 3.73–4.6 mm at 20–40 years old [95]. Using ultrasound, Larsen evaluated lens thickness from birth until puberty and found that the mean thickness of the lens decreases by 0.3 mm in the first year of life then by another 0.2 mm per year until leveling off at 8–10 years old [18].

Bag Size

The lens capsule remodels throughout life as the volume of the lens increases [96]. Changes to the posterior lens capsule are negligible following birth, while the anterior lens epithelium continues to secrete anterior capsule [96]. At birth, the mean diameter of the capsular bag is 7.0–7.5 mm and increases to about 9.0–9.5 mm by age 2 [97]. These values support the findings of Ohami and coworkers and Richburg and Sun who measured the capsular bag to be about 1 mm larger than lens diameter [27, 98]. There is also a change in capsular thickness with age (Fig. 1.4) [99].

When viewed with electron microscopy, the lens capsule consists of a combination of type IV collagen, as well as, types I and III collagen, laminin and fibronectin [100]. The infant anterior capsule is highly elastic in nature when compared to the adult capsule [100]. Krag and coworkers looked at the extensibility of the capsule throughout life and found its maximum extensibility was in infancy and decreased by 0.5% every year throughout life [101]. While extensibility decreases by at least a factor of two, overall strength decreased by a factor of five [101].

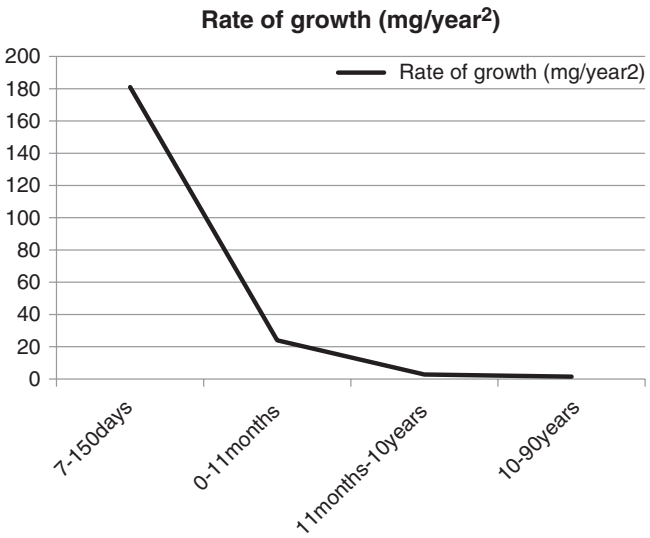

Fig. 1.5 Lens weight from birth to adulthood [96]

Weight

Figure 1.5 displays the change in lens weight with age [96].

Power

At birth, the accommodative power of the lens is between 14 and 16 diopters and then decreases with age (Fig. 1.6) [102].

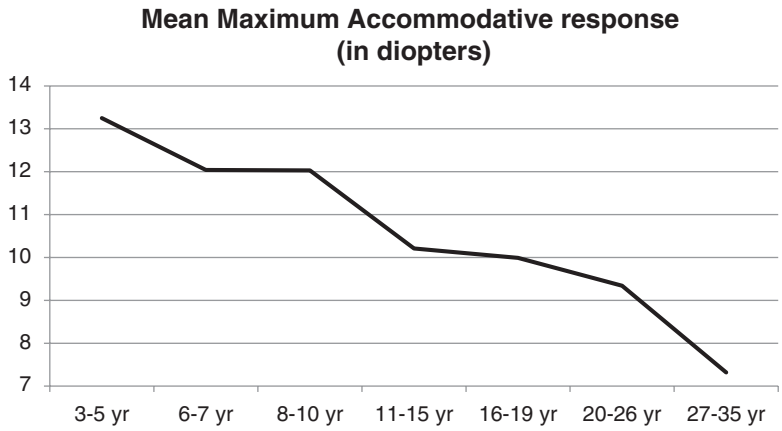

Fig. 1.6 Accommodation by age measured by dynamic retinoscopy [102]

Zonular Insertions

The zonules insert less anteriorly on the lens of an adolescent as compared to adults [94]. The distance between the anterior zonular insertion and the lens edge is approximately 0.75–1 mm with a zonular free central anterior zone on the anterior capsule of 6 mm in infancy which increases to 7–9 mm s in adolescence [20, 94]. Fetal and infantile eyes have zonular fibers that are finer, less aggregated and exhibit considerably more proteoglycan staining with Alcain blue or cuprolinic blue than in adult eyes [103, 104]. The loss of size that occurs with aging has been suggested to be the result of decreased fibrillin synthesis with age, which is also seen in the aging aorta [105]. The flat zonular insertional areas attach to the thin lens equator at its periphery with the zonular bundles appearing closely packed and thick for the first two decades of life [104]. These areas of insertion become widened and displaced more centrally as the lens grows in diameter and thickness [104].

Resolution of Tunica Vasculosa

The tunica vasculosa lentis is the anterior portion of the hyaloid vascular network that surrounds and supplies the growing lens *in utero* [63]. The tunica is made up of multiple different vascular sources including the hyaloid artery, the vasa hyaloidae propria and from the anterior ciliary vessels by way of the major arterial circle of the iris [106]. The development of the tunica peaks at 10 weeks gestation and regresses during the fourth month of gestation [63]. Complete regression occurs in stages with the posterior part (supplied by hyaloids system) regressing completely by the seventh month of gestation and the anterior part (supplied by ciliary system) regressing completely by the 8 month of gestation [106]. Occasionally, the tunica vasculosa lentis fails to completely resolve leaving a small, 1–2 mm, area of fibrosis termed a Mittendorf dot on the back of the lens [63].

Ciliary Body

Measurements Pars Plana and Plica

The lengths of the pars plicata and pars plana at different ages are summarized in Table 1.4 [107]. The pars plana represents 73–75 % of the total ciliary body length in infants and young children. The ciliary body is 76 % of adult size by 2 years old. Procedures designed to enter the posterior segment of the eye via the pars plana must therefore be appropriately adjusted so as to avoid unplanned violation of either the ciliary body or retina. Similar to the adult population, the temporal ciliary body is longer than the nasal ciliary body in the pediatric age group [107]. The anterior two thirds of the ciliary body houses the largest portion of the ciliary muscle with a few fibers passing posteriorly to the ora serrata [107]. In the young eye, the connective tissue between these muscle fibers is scarce [107].

Retina

The retina is not fully mature at birth. During the ninth month of gestation, the amount of the differentiated retina increases considerably, the retinal vessels extend to the ora serrata, the macula continues to differentiate with the foveolar reflex appearing as the foveolar depression forms [108]. Although mitotic activity during prenatal development stops at 30 weeks gestation, the surface area of the retina continues to increase at a rate of 10–15 mm^2 per week for the first 3 weeks after birth secondary to growth and maturation of individual cells [109]. The globe also continues to develop with the distance between the equator and ora enlarging until the age of 2 years old. The neonatal retina is thinner (120–150 μ) than that of an older child or adult (160–200 μ) [6]. Several studies in infants have shown that while the macular region is immature the peripheral region seemed to resemble that of the adult [110].

Table 1.4 Postnatal development of the ciliary body [107]

Age	Mean length nasal pars plicata (range in mm)	Mean length temporal pars plicata (range in mm)	Percentage of adult length nasal ciliary body (%)	Percentage of adult length temporal ciliary body (%)
7 days–6 months	3.06 mm (2.60–3.45 mm)	3.31 mm (2.80–4.30 mm)	64	57
6–12 months	3.54 mm (2.86–4.45 mm)	3.85 mm (3.10–4.56 mm)	74	67
12–24 months	3.87 mm (3.28–4.48 mm)	4.14 mm (3.46–4.99 mm)	81	72
24–72 months	4.28 mm (3.75–4.95 mm)	4.94 mm (4.15–5.50 mm)	90	85

By the fifth to eighth day of life the photoreceptors of the macula have elongated basal axons causing the photoreceptor layer to become much thicker than in the prenatal retina [111]. At birth, the rod inner segments have already reached their adult width of 2 μm, the inner segments of the cones are untapered and both rod and cone inner and outer segments are 30–50 % of adult length [111]. The cone outer segments elongate up to the age of 5 years old and rod outer segments up to 13 years old [111]. At birth, the rod and cone length varies depending on location in the retina as the mid-peripheral inner segments are slightly longer and outer segments are 50 % longer than in the parafoveal retina [111]. By 5 years old, the mid-peripheral rod outer segments are only slightly longer than in the parafoveal region with little change occurring throughout the remainder of life [111]. The photoreceptors in peripheral retina develop earlier than those in the central retina and parafoveal photoreceptors develop in advance of foveal cones suggesting that peripheral retinal regions are utilized more in the neonate before foveal cone vision becomes dominant [111]. The elongation of the fibers of Henle contribute to growth of the outer plexiform layer up to the 45th month of post gestational life [111]. The inner retina has a different path to maturity being almost adult like at birth [111].

Macula

After birth, the fovea continues to differentiate for the first 45 months of life [108]. From birth until 15 months old, the fovea continues to deepen as a result of the migration of cells in the inner retina toward the periphery [112]. The foveola, which measures over 1000 μm at birth, becomes progressively more narrow due to the central migration of cones reaching the adult diameter of 650–700 μm by 45 months old. It has been determined that this immature foveola accounts for 5° of visual angle [110]. This results in an increase in foveolar cone density from 18 cones/100 μm at 1 week postnatal to 42 cones/100 μm in the adult [112]. Elongation, maturation and an increase in packing density occurs in the development of the foveolar cones with cone diameter going from 7.5 μm at 5 days postnatal to 2 μm by 45 months [112]. During this time the foveolar cones develop both outer segments and basal axon processes. While foveolar differentiation is complete at 45 months of age, key factors in visual development including outer segment length and cone packing density are only half the adult values at 45 months of age [112]. The capillary free zone in the infant is similar in size to that of the adult [113].

Table 1.5 Macular volume and thickness variation by age and race [114]

	3–6 years old	7–10 years old	11–17 years old
Mean macular volume (mm^3):			
All	6.99	6.96	6.91
White	6.96	6.94	6.93 ($p=0.03$)
Black	6.87	6.84	6.87
Mean foveal thickness (μm):			
All	186	196	192
White	198	196	200 ($p<.001$)
Black	176	176	183

El-Dairi and coworkers evaluated variation in macular thickness and volume with age and race (white vs. black) in children ages 3–17 years (Table 1.5) [114]. They found that perifoveolar retinal thickness and foveal thickness were both significantly greater in white than in black children as were measurements of total macular volume [114]. These racial differences were more significant in the two younger age groups, 3–6 year olds and 7–10 year olds, while only the fovea was significantly thicker in white children than black children in the older group, 11–17 year olds [114]. Huynh and coworkers studied children (mean age 6.7 years) and found a mean minimum foveal thickness of 161.1 (±19.4) μm, and mean thickness measurements of the central, inner, and outer macula of 193.6 (±17.9), 264.3 (±15.2), and 236.9 (±13.6) μm, respectively [115]. They found that the temporal quadrant was thinner than other quadrants in both the inner and outer macular regions. Total macular volume was also normally distributed, with a mean of 6.9 (±0.4) mm^3 [115]. Variations in sex and ethnicity were observed with thicker measurements for the foveal minimum, central, and inner macula in white compared to East Asian children as well as in boys compared to girls [115]. Measurements of the outer macular thickness showed no significant gender-ethnic differences [115]. Changes in thickness based on axial length and spherical equivalent were noted in the inner and outer macula, but not in the central macula [115]. These changes include significant thinning with increasing axial length and significantly thicker measurements with more hyperopic spherical equivalent [115]. Huynh and coworkers went on to evaluate

older children ages 11–14 years and found mean (SD) thickness of the central 1 mm, and inner and outer macular rings to be 197.4 ± 18.7, 271.9 ± 15.0, and 239.5 ± 13.5 μm, respectively with a foveal minimum thickness of 161.6 ± 19.9 μm [116]. Minimal differences between sexes were noted [116].

Vascularization

Retinal vascular development is complete first in the nasal retina around the eighth month of gestation but the temporal retina may continue to develop through the first few weeks of life, with avascular retina relying on choroidal circulation for nourishment [63]. Stone and coworkers have shown that in animal studies, vascular endothelial growth factor (VEGF) is expressed in the developing neural retina by astrocytes in the inner surface and in Müller cells of the inner nuclear layer [117]. It was also shown that VEGF expression in the inner nuclear layer closely precedes the formation of the superficial and deep retinal vessels [117]. VEGF expression by the retinal pigment epithelium lacks temporal and spatial proximity to the normal development of retinal vessels suggesting that it does not play a role in the retinal vasculature but may be important in the choroidal circulation [117].

Electroretinography (ERG)

Age related normative values for retinal function in children based on electroretinogram (ERG) studies have been established (although the data of Birch and Anderson may not apply to non-caucasian children with more darkly pigmented retinas) [118]. It is important that comparisons of patient values to such normative data must be conducted using identical standard ERG protocols [118].

Males have slightly lower retinal responsiveness than females of the same age [118]. Rod, cone, and cone 30-Hz flicker responses can all be documented at 36 weeks postconception [118]. Rod responses are barely detectable at birth (average amplitude 2.7 μV) but develop rapidly in the first 4 months of life [118]. Cone responses show a similar but less dramatic increase [118]. By 4 months old the retinal responses are more than half normal adult values [118].

Rodriguez—Saez and coworkers looked at 296 eyes from 148 healthy subjects ages 1 week to 21 years old and found that most of the developmental changes in the ERG occur in the first 6 months of life with the a wave completing its development at 3 years old and the b component showing a smooth, gradual increase in latency between 3 and 18–21 years old and amplitude from 7–8 to 12–14 years old [119]. Westall and coworkers also examined the development of ERG specifically measuring rod response, maximal response, oscillatory potentials (OPs), cone response, flicker response, and b-wave amplitude/log intensity (V/log I) curve in 62 children ages 10 days to 15 years old, and 30 individuals 15–37 years old [120]. They determined that by 3 to 5 years old, dark- and light-adapted ERG a- and b-wave amplitudes reached adult levels recognizing that b-wave amplitudes of scotopic rod-mediated responses were slower to reach maturity than mixed rod-cone mediated responses [120]. While in early infancy oscillatory potentials were the most immature of the ERG responses, the rate of development exceeded the rate of development in other responses allowing adult amplitudes to be reached by 2 years old [120].

Vitreous

Hyaloid Remnants

The incidence of visible hyaloid remnants in the term infant has been estimated at around 3 % [121]. Hyaloid remnants may be visible by B-scan ultrasonography even when nothing is visible ophthalmoscopically [122]. These remnants are often bloodless but may be a cause of vitreous hemorrhage if blood-filled and associated with persistent hyperplastic primary vitreous, coloboma of the optic disc, optic nerve hypoplasia or posterior vitreous cysts [123, 124]. Remnants are more often in seen in eyes with shorter axial lengths [122].

Characteristics

The vitreous is composed of collagen fibrils including types II, VI, IX, and a hybrid V/XI, glycosaminoglycans such as hyaluronan, two forms of chondroitin sulfate proteoglycan, the proteoglycan heparin sulfate, and non-collagenous structural proteins including fibrillin and opticin [108]. Type II collagen accounts for 75 % of the collagen found in the vitreous [108]. The dense concentration of collagen at birth gives a darken appearance on dark-field slit-microscopy, but total collagen content in the vitreous decreases throughout the first several years of life until the third decade [125]. Hyaluronan is not present in the infant at birth but is produced in the eye, possibly by Müller cells or the ciliary body, and given its hydrophilic composition, causing swelling in the vitreous allowing the collagen fibrils to separate producing less light scatter on dark-field microscopy and contributing to the overall growth of the eye [108].

Attachments

The vitreous is firmly attached to several structures in the eye including the ciliary epithelial cells and the inner limiting membrane of the retina at the ora serrata [126].

Several studies have shown that heavy bundles in the vitreous base intertwine strongly with retinal glial cells in the peripheral retina [126, 127]. In the posterior fundus, the vitreous fibrils blend into the fibrillary material of the inner limiting membrane lamina which is very thick in this region of the fundus [128]. The peripheral shell of the vitreous (vitreous cortex) arises from the anterior vitreous forming the anterior hyaloid face which sits 1.5 mm anterior to the ora serrata, as well as coursing posteriorly from the posterior vitreous base to form the posterior cortex [108]. Zonular fibers have also been found extending posteriorly within 1.5 mm of the ora serrata [129]. The interface between the posterior vitreous and retina is extremely strong in children secondary to the unique insertion of vitreous cortex collagen fibrils into the basal laminae of the retina making the practice of separating these layer surgically virtually impossible [108]. Light microscopy and electron microscopy evaluation of the vitreo-retinal interface show that the fibrils uniting retinal cells and vitreous have the same appearance in the human fetus as in the peripheral one third of the adult retina [126]. The union between vitreous cortical fibrils and inner limiting membrane are visible in eyes under the age of twenty but these unions become difficult to demonstrate posterior to the anterior third of the retina after this age [126]. In 40 % of eyes from individuals less than 20 years old, scanning electron microscopy of vitreous cortex shows adherence to the macula, temporal arcades and peripapillary posterior pole with ultrastructural studies showing inner portions of Muller cells attached to the posterior internal limiting lamina [130]. These findings suggest the connection between Muller cells and the internal limiting lamina are weaker than adhesions between vitreous cortex and internal limiting lamina [130].

Sclera

Rigidity

The sclera is less rigid in childhood which results in "collapse" during intraocular procedures such as cataract extraction or trabeculectomy, although the consequences of theses intraoperative changes seem to be less severe than in adults [20]. Infant sclera has approximately one half the tensile strength and four times the pliability of adults [132]. The coefficient of stretching is 0.6 times that of an adult which gives the infant sclera more elasticity [106].

Thickness

The sclera is composed of three different proteoglycans including aggrecan, biglycan, and decorin, which undergo structural changes responsible for an increase in sclera thickness from 0.45 mm in neonates to 1.09 mm in adults [26].

Optic Nerve

Width

The number of axons increase rapidly during the first 10 weeks of embryonic life, peak at 3.7 million (double that of the average adult), then enter a 3 week period in which the number remains constant after which, a rapid decrease in the number of axons occurs [133]. Specifically, the number of axons peaks then drops to the adult value of to 1.1 million (average adult value) by 30 weeks gestation. While the initial number of axons may determine disc size, the number of axons lost may dictate cup size. Hellström and coworkers looked at optic nerves in healthy children ages 2.9–9.1 years old and found the median optic disc area was 2.87 mm^2 (range 2.04–4.02) with no increase in optic disc area with age [134]. This finding supports that reported by Mansour showing no change in optic disc area in normal children ages 2–10 years old [135]. Rimmer and coworkers looked at autopsy eyes from patients ages 4.8 months gestation to 21.9 years and found that 50 % of the growth in the optic disk is complete at 20 weeks of gestation, 75 % by birth and 95 % before 1 year of age [136]. Optic nerve vertical diameter was found to be greater than horizontal diameter in all age groups [136]. Table 1.6 illustrates mean vertical and horizontal diameters and area of the optic disc by age group [136, 137]. One important note is that the autopsy eyes were fixed in

Table 1.6 Mean vertical and horizontal diameters and area of both the optic disc by age group [136, 137]

	Term to 6 months old	6 months to 2 years old	2–10 years old	>10 years old	42.7 (±19.6) years old
Mean vertical diameter optic disc (mm ± SD)	1.37 ± 0.21	1.57 ± 0.15	1.64 ± 0.20	1.73 ± 0.23	1.92 ± 0.29
Mean horizontal diameter optic disc (mm ± SD)	1.13 ± 0.19	1.40 ± 0.17	1.43 ± 0.19	1.59 ± 0.21	1.76 ± 0.31
Mean area of optic disc (mm^2 ± SD)	1.25 ± 0.40	1.73 ± 0.32	1.87 ± 0.44	2.19 ± 0.54	2.69 ± 0.70

formalin which, based on prior studies, may cause approximately 12–13 % optic nerve shrinkage. After adjusting for this fixation artifact, the measurements match those of clinical studies [136, 138].

Imaging of newborn optic nerve heads using Optical Coherence Tomography (OCT) found a mean optic disc area of 1.26 ± 0.23 mm^2 with a mean vertical diameter of 1.37 ± 0.15 mm and a mean horizontal diameter of 1.14 ± 0.12 mm [139]. The vertical diameter of the optic disc was significantly longer than the horizontal diameter ($p < 0.0001$). Birth weight and sex did not influence the size of the optic disc [139].

The Sydney Childhood Eye Study provided measurements for optic nerve head dimensions based on OCT and digital photographic planimetry in healthy 6 year olds and found mean planimetric optic disc area was 2.29 mm^2 (CI 2.27 to 2.32), mean cup area 0.48 mm^2 (CI 0.47 to 0.50), mean vertical disc diameter 1.81 mm (CI 1.80 to 1.82) and mean vertical cup diameter 0.72 mm (CI 0.71 to 0.73), resulting in a mean vertical cup/disc ratio of 0.40 (CI 0.39 to 0.40) [140]. This finding is similar to another study in slightly older children (9.16 ± 1.7 years) using OCT that found an average cup/disc ratio of 0.43 (SD 0.19) [141]. Richardson utilized direct ophthalmoscopy to evaluate the incidence of cup to disc asymmetry in 483 normal newborn infants and found an incidence of 0.6 % with only 2.6 % of the infants having optic cups >1/3 the disc diameter [142].

Comparisons could be made between measurements made by planimetry and optical coherence tomography for vertical, horizontal and area cup/disc ratios ($p > 0.05$), but only for vertical disc diameters between 1.75 and 1.96 mm. They also reported prevalence of various optic nerve findings including visible lamina cribrosa pores in 4.9 % (associated with larger optic nerve parameters), optic disc tilt in 1.6 %, cyclotorsion in 8.7 %, and cilioretinal arteries in 27 % (with tendency for temporal location). After adjusting for age, sex and ethnicity, neither α-peripapillary atrophy nor β-peripapillary atrophy was associated with myopia, although eyes with b-peripapillary atrophy had a longer mean axial length ($p < 0.04$).

NFL Thickness

Various studies have evaluated the average retinal nerve fiber layer in different races and ages (Table 1.7) [114, 115, 126, 143–145].

El-Dairi and coworkers found that measurements of RNFL thickness were not dependent on age in children younger than 18 years which is compatible with other published studies in children [114]. These measurements remained stable in adults [114]. In a study of 357 Caucasian children aged 9.16 ± 1.7 years, Elía and colleagues also found no difference in any of the parameters tested including mean RNFL thickness (98.46 ± 10.79 mm) with regard to weight, height and gender [141]. They noted the temporal quandrant contained the thinnest RNFL (69.35 ± 11.28 mm), followed by the nasal (71.30 ± 13.45 mm), superior (123.65 ± 19.49 mm) and inferior (130.18 ± 18.13 mm) quadrants [141]. The authors also failed to demonstrate any statistically significant change in the RNFL or optic nerve head parameters with increasing age, a finding also reported by others [114, 140, 143, 144]. Other considerations in children include a proven variation in optic nerve head parameters based on ethnicity as well as variations in measurements among different commercially available imaging devices [144].

Optic Nerve Sheath

Ballantyne and coworkers evaluated optic nerve sheath diameter measurements in 102 normal children and found the range was 2.1–4.3 mm with a mean of 3.1 (SD 0.36) mm [145]. By adulthood, the retro-orbital optic nerve sheath width reaches 5.5 ± 0.8 mm just behind the globe and 4.2 ± 0.6 at its midsection in the orbit [146]. A relation between increasing age and increasing optic nerve sheath diameter ($r^2 = 0.48$) was noted, with the greatest increase in the first year of life [145]. Under 1 year old the mean optic nerve sheath diameter was 2.9 mm (range 2.2–3.4 mm, SD 0.4) and over 1 year old 3.1 mm (range 2.3–4.0 mm, SD 0.3, $p = 0.01$). Based on this data, the upper limit of normal was defined as 4.0 mm for those under 1 year old and 4.5 mm for older children [145].

Table 1.7 Studies of retinal nerve fiber layer thickness by optical coherence tomography [114, 115, 126, 143–145]

Source	El-Dairi et al.	Salchow et al.	Huyhn et al.	Ahn et al.	Parikh et al.
Race/ethnicity	Black	92 % Hispanic	White	Korean	Asian Indian
	White		East Asian		
Age mean (range)	8.5 (3–17) All	9.7 (4–17)	6.7 (6, 7) White	12.6 (9–18)	11.1 (5–20)
	8.6 (3–17) Black		6.7 (6, 7) East Asian		
	8.5 (3–17) White				
Mean average RNFL in μm (SD)	108.27 (98.8) All	107 (11.1)	102.7 White	105.53 (10.33)	100.15 (10.8)
	110.7 (8.84) Black		107.7 East Asian		
	105.9 (10.18) White				

RNFL retinal nerve fiber layer

Blood Flow

Flow Supine Vs. Sitting

There has been very little research into ocular blood flow during childhood. Ravalico and coworkers measured pulsatile ocular blood flow in the second decade of life and found that there was a significantly higher rate of flow and pulsatile amplitude as compared to later decades of life [75]. They measured the flow to be 819 ± 212 and 654 ± 176 μL/min in the sitting and supine positions respectively between 10 and 20 years with adult values showing on average a much smaller difference between sitting and supine (age 71–80 sitting 630 ± 194 and supine 560 ± 147). This suggests immature autoregulation in childhood [75].

Extraocular Muscles

Anatomy

Tenon Capsule

As is evident at surgery on infants and children, Tenon capsule is thicker and more abundant. This appears as a sonolucent zone around the sclera on B-scan ultrasound of newborns up to 44 weeks gestation but is particularly evident in low birth weight infants and those babies with shorter axial lengths [122]. This finding on ultrasonography is consistent with the work of Shauly and coworkers who found that Tenon's capsule in children has thicker collagen fibrils and a greater mean number of collagen fibrils when compared to older age groups [147]. They studied children ages 1 month to 12 years old (mean 5.9 years old) and found a mean collagen fibril diameter of 86 ± 5 nm and mean area of 5299 ± 561 nm^2 [147].

Muscle Width

The normal adult muscle measurements have been generated based on CT scan imaging [146]. Nugent and coworkers measured the width of the horizontal recti on axial and the vertical recti on coronal cuts (Table 1.8) [146]. Adult muscle diameter measurements along with width of muscle insertion measurements throughout childhood can be found in Table 1.8 [19, 146]. Muscle width values may differ between CT scan and ultrasound measurements [148]. Comparatively, infant medial rectus muscles measure 7.9 mm in width and the lateral rectus muscle measures 6.9 mm in width [149]. Swan and Wilkins reported on the change in rectus muscles in childhood and noted there was great variation in size between individual children with the average muscle 2.5–3 mm narrower than adults [19]. Growth continued throughout the first years of life with adult-like dimensions being reached by 20 months old [19].

Muscle Length

The four rectus muscle all arise from the annulus of Zinn, at the apex of the orbit [150]. Their tendon lengths measure 3.0 mm (1.0–7.0), 4.7 mm (3.0–7.0), 7.2 mm (4.0–11.0) and 4.3 mm (2.0–6.0) for the medial, inferior, lateral and superior rectus muscles respectively. The rectus muscles show prominent growth throughout childhood (Fig. 1.7) [151].

The Oblique Muscles

The superior oblique arises superiomedial to the annulus of Zinn at the frontoethmoidal suture at the orbital apex and courses anteriorly where it is redirected at a 54° angle posteriorly at the trochlea, a 6 mm by 4 mm curved plate of hyaline cartilage affixed to the trochlear fossa of the frontal bone. The muscle is divided into the length from its origin to the trochlea which in adulthood is 40 mm and the reflected part from trochlea to insertion which measures 20 mm. The muscle belly becomes tendenous approximately 10 mm prior to the trochlea and fans out at its insertion of variable width of 10–18 mm [63]. The shortest extraocular muscle is the inferior oblique measuring 37 mm in length with a short tendon measuring between 1 to 2 mm [149, 152]. While adult dimensions are available for the oblique muscles, little work on the growth of these muscles through childhood is available.

Muscle Insertions

The rectus muscles insert at various distances behind the limbus in a gradual progression, the spiral of Tillaux, which increases from the medial, inferior, lateral and superior rectus.

Table 1.8 CT scan extraocular muscle diameter and width of insertion by age (mm) [19, 146]

	Width of insertion neonatal (mm)	Width of insertion 2–3 month (mm)	Width of insertion 6 months (mm)	Width of insertion 9 months (mm)	Width of insertion 20 months (mm)	Width of insertion adult (mm)	Adult diameter ± SD (mm)
Medial rectus muscle	7.6	6.8	9.0	8.7	8.9	10.5	4.1 ± 0.5
Inferior rectus muscle	6.8	6.7	8.3	8.3	9.3	9.8	4.9 ± 0.8
Superior rectus muscle	7.5	7.3	8.9	8.8	10.2	10.8	3.8 ± 0.7[a]
Lateral rectus muscle	6.9	7.0	8.4	8.2	7.8	9.2	2.9 ± 0.6
Superior oblique muscle	N/A	N/A	N/A	N/A	N/A	N/A	2.4 ± 0.4

[a]Superior Rectus Muscle Group (combined superior rectus/levator palpebrae complex)
N/A not available

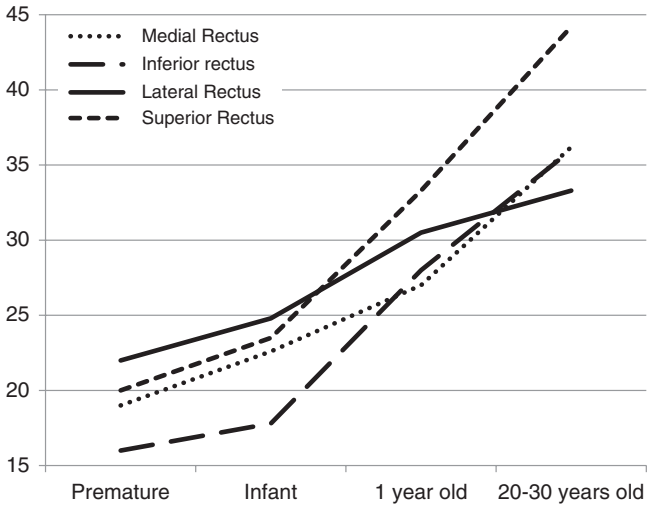

Fig. 1.7 Length (mm) of rectus muscles with age (mean) [151]

The average adult insertion points behind the limbus are 5.5 mm for the medial rectus, 6.5 mm for the inferior rectus, 6.9 mm for the lateral rectus and 7.7 mm for superior rectus. In infants, the corneal-limbal distance measures 5.0 mm, 6.3 mm, 6.1 mm and 6.5 mm for the medial, inferior, lateral and superior rectus respectively [150]. At birth, the rectus muscles insert approximately 2 mm closer to the limbus than in adults decreasing to 1 mm at age 6–9 months and reaching adult distances by 20 months old [19, 150].

The superior oblique muscle passes between the superior rectus and the globe inserting obliquely with the anterior insertion in adults 13.8 mm on average from the limbus and 3.0–4.5 mm behind the lateral end of the superior rectus muscle insertion. The posterior portion inserts 18.8 mm on average from the limbus and 13.6 mm behind the medial end of the superior rectus muscle insertion [152]. The width of the insertion varies widely from 7 to 18 mm but averages about 11 mm [149, 152].

The inferior oblique arises from the orbital plate of the maxilla anteriorly and courses below the inferior rectus muscle to insert on the posterio-lateral aspect of the globe. The anterior margin of the insertion is approximately 10 mm posterior to the inferior edge of the lateral rectus insertion. The posterior edge of the inferior oblique insertion is located 1 mm below and 1–2 mm anterior to the macula. to the lower edge of the insertion of the lateral rectus with the posterior insertion 3–6 mm anterior to the optic nerve and 1 mm below and 1–2 mm anterior to the macula [153]. The concavity of the insertion is towards the origin of the muscle and the width of the insertion point varies greatly from 5 to 14 mm with an average of 9 mm [153].

Ocular Alignment

Binocularity Development

Binocularity is not present at birth [154, 155]. It develops in the first 2–4 months of life only with binocularly coordinated visual stimulation such that the presence of ocular misalignment, media opacities (e.g. cataract), or large uncorrected refractive errors may preclude the proper development of normal stereopsis [154, 155]. It has been shown using individuals that have experienced esotropia through varying periods of their lives that several months after birth a sensitive period for binocularity begins and peaks between 1–3 years of age [156]. In addition, Molteno and coworkers extrapolated data gathered by photoscreening to estimate that simultaneous perception develops by 3–4 months, stereoscopic depth perception by 5 months, and the ability to converge and accommodate accurately by 6 months [6].

Phorias

Several very large studies have been done in which the ocular alignment of thousands of babies has been examined. Archer and coworkers reported that just over 75 % of normal infants of gestational age ≥36 weeks will have a constant or intermittent exotropia in the first 2 months of life [157]. In the first few days of life 33–66 % will have either constant or intermittent exotropia [158, 159] although Chace and coworkers (while examining the incidence of retinal hemorrhages) noted an incidence of only 1.8 % in babies who had been pharmacologically cyclopleged [160]. As the infant ages the frequency and size of the deviations decrease such that only 10 % of infants are exotropic by 4 months of age and none are constantly exotropic by 8 months [157]. There may be great day-to-day variability in ocular alignment in the first 4 months of life [157]. Sondhi and coworkers found that 2.6 % of babies showed swings between esotropia and exotropia [159]. Esodeviations are very unusual at birth (0.2–1.8 %) and when present are usually small and intermittent [157–160]. They are rare after 2 months of age [159]. However, brief episodes of "convergence spasm" with simultaneous adduction of both eyes, can often be seen in normal children up to 4 months old [159].

Normal Deviations of Infancy

Cranial nerve palsies causing strabismus in the neonatal period are extremely rare. The incidence of sixth cranial nerve palsy, which often resolves spontaneously, is less than 0.09 % [159]. Based on this data we would recommend observation of ocular misalignment in the first 4 months of life particularly if the deviation is small, intermittent, decreasing in size and frequency over time, and exotropic. Exotropic babies showing improvement through the fourth month may be observed until 7 or 8 months as long as visual

acuity appears to be unaffected and the trend for resolution continues. Esotropic babies should not be referred earlier as should any baby with a constant large angle strabismus. Children who are premature and those who demonstrate neurologic impairment, visual compromise, abnormalities of ocular movement, or signs of other strabismus syndromes may require more aggressive management.

Ocular Movement

Saccades

Normal neonates are capable of following large objects usually by making use of head and eye movements. Saccades develop at a faster rate than smooth pursuit [161]. Garbutt and coworkers studied saccades in infants ages 2–18 months old with adult comparison and found from the age of 2 months, the infants were able to generate saccades at speeds similar to or faster than the adult population and showed no statistical difference between peak velocity or duration [162]. Metz showed that prism induced shifts in fixation were equivalent to voluntary shifts in fixation in a cooperative population (age 10–79 years old) with an infant population showing good reproducibility [163].

Smooth Pursuit

Smooth pursuit develops rapidly in the first 3 months of life but has still not reached adult levels of gain by 6 months [161]. Asymmetry of smooth pursuit movements are normal in these first 6 months although more prominent in the first 3 months [161]. This lack of smooth pursuit has been attributed to the lack of foveal maturity [164]. Salman and coworker studied smooth pursuit in children ages 8–19 years old and found that smooth pursuit gains increased with age ($P < 0.01$), with vertical gains having large variability among participants and with horizontal gains reaching adult values by mid adolescence [165]. Table 1.9 illustrates ages of major milestones in the visual system [7, 166–171].

Table 1.9 Maturation of vision [7, 166–171]

Age	Description
34 weeks gestation	Vestibular eye rotations well developed
Birth	Visual fixation present
	Conjugate horizontal gaze well developed
	Optokinetic nystagmus well developed
1 month	Ocular alignment stable
2–3 months	Fixation well developed
	Conjugate vertical gaze well developed
	Demonstrate stereopsis
3 months	Visual following well developed
4 month	Accommodation well developed
6 months	Fusional convergence well developed

Tonic Downgaze

Variations in ocular movement may also be normal in infants. Tonic downgaze is occasionally seen (<1 %) with or without upper eyelid retraction especially in response to sudden dimming of the lights (eye popping reflex) [157]. Usually, one can determine that this is a normal variant by brightening the ambient lighting or attracting the infant's attention and fixation [157]. Benign paroxysmal tonic downgaze may rarely be associated with vertical nystagmus and resolves within the first year of life (usually in first 6 months) with persistence possibly indicating neurological disease [172, 173].

Craniofacial

Detailed studies have been conducted regarding the growth of the cranial vault, cranial base skull and face. As these factors influence the eye and orbit only by indirect means, the reader is referred elsewhere for further details [174, 175].

Eyelids

Palpebral Fissure Height and Length

Palpebral fissure length at 40 weeks gestation is 1.85 ± 0.13 cm [176]. Duke-Elder reported a progression of palpebral fissure length from 1.99 cm at 1–6 months of age to 2.84 cm at age 16–18 years old [177]. There have been studies showing that blacks have the longest palpebral fissures compared to Hispanic and white children [178]. The horizontal palpebral fissure length (PFL) may become shortened on forced lid closure. It has been suggested that the amount of shortening should not exceed 4 mm in normal children [179]. Abnormal PFL shortening may be due to defective insertion or absence of the lateral canthal tendon [179]. Paiva and coworkers studied palpebral changes in childhood and noted at birth, the upper eyelid was at its lowest position with the lower eyelid margin close to the pupil center [180]. After 3 months of age, the distance between the lower eyelid margin and pupil center increased linearly until 18 months when the position stabilized while the upper eyelid reaches maximum position between ages 3 and 6 months then declines linearly [180]. At birth, a single crease was the most common lower eyelid pattern with the proportion of patients showing a double crease increasing with age until 36 months when the double crease pattern becomes the most common [180]. Palpebral fissure length in caucasians can be calculated based upon work done by Chouke using the formula PFL = (Outer Canthal Distance – Inner Canthal Distance)/2.

Inner Canthal Distance

Inner canthal distance in the distance measured between the medial canthi of each eye. Normative values for inner canthal distance have been established by Feingold and Bossert using direct measurement [181]. These values were obtained through study of 2403 newborns to age 14 years old [181].

Outer Canthal Distance

Outer canthal distance is the distance measured between the lateral canthi of each eye. Feingold and Bossert adjust the OCD in girls between 1–4 years old by adding the value of 0.2 cm and normative values can be used for comparison [181].

Orbit

Measurements

At birth, the orbital cavity is 75 % of adult size and continues to grow passively in response to globe growth before reaching adult size by age 7 years old [182]. The volume of the orbit at birth is 10.3 mm^3, doubling by age 1 year old to 22.3 mm^3, enlarging further to 39.1 mm^3 by age 6–8 years old and measuring 52.4 and 59.2 mm^3 for the adult female and male respectively [63]. The orbital roof in infants is flatter and larger than in adults with the greater wing of the sphenoid contributing more significantly to the lateral orbital wall [63]. The changes in orbital opening with age can be found in Table 1.10 [183, 184]. The optic canal and bony orbit reach adult levels by age 10 years with the infant optic canal measuring 3.5 mm in diameter reaching adult diameter of 5.5 mm by 5 years old [182]. Nugent and coworkers determined the normal adult position of the globe by measuring the distance between the most posterior aspect of the sclera relative to a horizontal line joining the two zygoma (interzygomatic line) [146]. The normal position was 9.9 ± 1.7 mm posterior to this line [146]. The main structures affecting the change in interorbital dimensions are the ethmoid aircells [15].

Table 1.10 Changes in orbital opening by age [183, 184]

Age	Height (mm)	Width (mm)
Newborn (6 months)	27	27
Child (7 years)	28	33
Adult	Males: 32.44 ± 1.89	Males: 37.42 ± 2.44
	Females: 31.75 ± 2.44	Females: 36.60 ± 1.71

Superior Ophthalmic Vein

The superior ophthalmic vein in adulthood measures 1.8 ± 0.5 mm on axial CT cuts and 2.7 ± 1.0 mm on coronal views [146]. It appears larger and more readily visible on B-scan in neonates, particularly premature infants, up to 46 weeks [122]. This may due to the closer relationship to the superior rectus in this age group causing partial compression with secondary dilation [122].

Interorbital Distance

When assessing a child for hypertelorism or hypotelorism, one must measure the interorbital distance (IOD) which is the distance between the two anterior medial orbital walls measured radiographically. Morin and coworkers showed that IOD increases approximately 10 mm from birth to adulthood based on examinations of 600 cephalometrograms (Fig. 1.8) [15]. Fifty percent of this growth occurs in the first 3 years of life followed by a slower rate of growth, approximately 0.5 mm per year, until 12 years of age after which the growth slows but continues until adulthood [15]. They also noted that even though the range of variation in IOD around the mean was 9.0 mm at all ages, each child followed its own IOD growth curve such that reasonable predictions about eventual outcome could be made [15]. Hellman found values similar to Morin's based on measurements taken from a small series of native American Indian skulls measuring interorbital distance at the dacryon (juncture of frontal and lacrimal bones): early infancy mean 15.89 ± 1.10, late infancy mean 17.67 ± 0.94, childhood mean 18.0 ± 1.53, and puberty 21.40 ± 1.20 [175].

Interpupillary Distance

Interpupillary distance (IPD), although difficult to measures due to errors induced by accommodative convergence, has been studied in normal individuals. IPD can also be calculated using the Feingold and Bossert method formula: IPD = 0.7 + (0.59 × ICD) + (0.41 × OCD) [181]. The rate of change in IPD can be calculated using the linear regression formula y = 0.78x + 47.48 where y is the IPD and x the age [185]. However, the rate of change in females and in children below 5 years old are both significantly higher than males and children over 5 respectively [185]. The authors offer formulas for each subgroup [185]. The Mustardé Index defines the normal ratio of ICD/IPD as ≤0.55 [186].

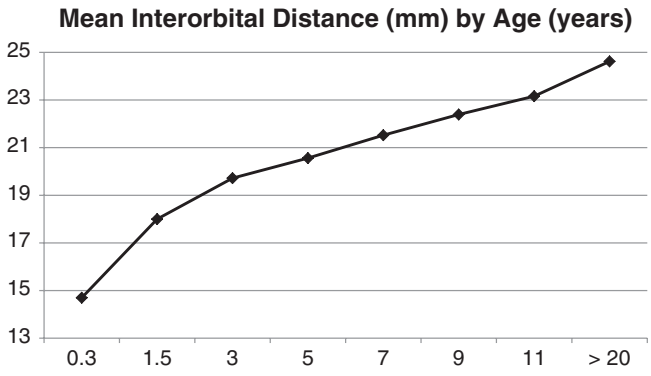

Fig. 1.8 Mean interorbital distance (mm) by age (years) [15]

Sinuses

Rate of Growth

At birth, the ethmoidal air cells occupy most of the medial orbital wall [15]. By 7 years of age the ethmoid air cells represent only half of the medial wall as the maxillary air cells have grown in the interim [15]. The frontal sinus is not present at birth and later develops from the anterior ethmoidal cells beginning at 6–12 months of age [15]. Thereafter, the frontal sinuses expand superolaterally rapidly until the third year of life after which slow growth continues well into adulthood [15]. The sphenoid sinus, present at birth, also continues growth until approximately 3 years old [15]. A rudimentary maxillary sinus is present at birth although the superior alveolar ridge lies in close proximity to the orbital floor [15]. The majority of maxillary sinus growth occurs between 3–4 years after which slow growth continues until 15 years [15]. Table 1.11 illustrates the development of each sinus by age group [187, 188].

Table 1.11 Development of paranasal sinuses by age [187, 188]

	Frontal	Sphenoid	Maxillary	Ethmoid
Newborn				
Length (mm)	–	–	10	10
Width (mm)	–	–	3	2
Height (mm)	–	–	4	2.5
1–4 year old				
Length	6	5	26	15.5
Width	5.5	7	15	8
Height	7.5	4	15	12
4–8 year old				
Length	8	12.5	36	21
Width	9	10	21	11
Height	15.5	9	24	12.5
16 year old				
Length (mm)	12.8 ± 5.0	23.0 ± 4.5	38.8 ± 3.5	
Width (mm)	21.9 ± 8.4	12.8 ± 3.1	27.5 ± 4.2	
Height (mm)	24.5 ± 13.3	22.6 ± 5.8	36.3 ± 6.2	

Visual Fields

Normative Values

Attempts have been made to establish normal standards for visual fields in children with variable success. Wilson and coworkers found a growth in the size of the visual field between the ages of 4 and 12 years [189]. Based on this data, by 11.6 years old the adult visual field size is obtained [189]. They established normative values in this age range although the accuracy of their values has been questioned based upon the difficulty of standardizing responses in children under 5 years old particularly using the double arc perimeter method [190]. Other studies have been variable in the reported progression of visual fields throughout childhood. Tomonaga used Goldmann perimetry in 4–10 year olds and found the adult size of visual field was reached by age 5 [191]. Conversly, Lakowski and Aspinall used Goldmann static perimetry found a constricted visual field to 15° at age 5–6 years old and adult size visual fields by age 12 years old [192].

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Ocular Manifestations of Prematurity

2

Edward W. Cheeseman, Jr., Brita S. Deacon, and Dorothea Jenkins

Introduction

Advances in medical technology and understanding over the last several decades have resulted in significant improvements in the survival of premature infants. Common ocular manifestations of prematurity include retinopathy of prematurity (ROP), strabismus, myopia of prematurity (MOP), and congenital or acquired infections. Ophthalmologists are most commonly consulted to do examinations for ROP which can lead to retinal detachment and blindness if not detected and treated in a timely manner. However, ocular examinations of the premature infant may also contribute to the diagnosis of developmental syndromes, chromosomal anomalies, sepsis, and coagulopathies. The immature eye differs in many respects from that of a child born at term and certainly can be much different than the adult eye. An understanding of these differences is important to the ophthalmologist, pediatrician, primary care provider, and the parents. This chapter will look at the differences in the structure and function of the immature eye, new evaluation techniques to identify these differences, and discuss the historical and current treatment considerations for ROP and other pathologies seen in the immature eye.

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Physical Characteristics

Definition

The physical characteristics of the developing eye and adnexal structures have been determined. These normal values may be helpful in the diagnosis of conditions such as hyper or hypotelorism, microphthalmia, or blepharophimosis. Awareness of the normal parameters is critical in the evaluation of infants with suspected birth anomalies.

Anterior Segment

External

The eyelids develop as a fused fold initially in the seventh week of gestational development. A number of very low birthbirthweight (VLBW) premature infants are born with the eyelids either partially or completely fused. The critical time for eyelid opening has been cited to occur between 25.5 and 26.5 weeks gestational age. If the lids are fused at birth, studies have shown the average time to opening is 5.5 days [1]. There is generally no need to try to forcibly pry open the fused lids as they normally will open spontaneously, and without trauma, on their own. The fact that the lids were fused was previously considered a marker of non-viability for life and may have influenced some to apply more conservative resuscitation efforts for the child [2]. This is clearly no longer the case with more modern resuscitation techniques and standards.

Parents will often question the ophthalmologist regarding tear production in the premature infant, often citing that they have not noticed any tears when the baby cries. A study comparing the tear functions in premature versus term babies showed a statistically significant decrease in tearing and corneal sensitivity in the preterm infants. The authors urged that premature infants should be checked for the presence of dry eye complications [3].

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Cornea and Intraocular Pressure

Corneal diameter and thickness are important determinants in the diagnosis of congenital glaucoma, with diameter being most important in the diagnosis of megalocornea, or microphthalmia. The infant's gestational age must be considered before considering a cornea to be abnormally large or small. A number of studies have been performed to determine corneal diameter in the preterm infant and its progression with advancing age [4–6]. Tucker et al. found corneal diameters between 6.2 and 9.0 mm in 70 infants of 25–37 weeks gestational age examined during the first week of life. The increases in corneal diameter with age were shown to parallel the linear increases in axial length of the eye [5]. Al-Umran et al. examined 127 premature infants between 27 and 36 weeks gestational age. The corneal diameters ranged from 7.75 mm in the youngest child to 10 mm in 34–35 week infants. They noted a positive correlation of corneal diameter to gestational age and birth weight [6]. Kirwan et al. in a study of 70 eyes of babies born at 31 weeks of gestation demonstrated an inverse relationship between corneal diameter and corneal thickness with advancing age. Horizontal diameter shows a progressive increase in size as the baby approaches term age and corneal thickness shows a progressive decrease (Table 2.1) [4]. Along with this remodeling process the corneal curvature of the infant eye is reduced. This has been reported to change from 65.83 diopters at 28 weeks post conception to 49.38 diopters at 42 weeks [7].

Central corneal thickness measured with an ultrasound pachymeter has been shown to be significantly greater in the premature newborn than in full term infants in the absence of any other ocular abnormalities. In a study of 33 patients with central corneal thickness (CCT) measurements taken between 30 and 32 weeks and again at 39–41 weeks post conception, the CCT decreased from a mean of 691 μm to a mean of 564 μm [4]. Other studies have also shown the CCT to be thicker in the premature infant with a linear decrease as the child matures. Explanations offered for this remodeling process include better control of corneal hydration after the infant begins to open the eyes after birth. The hydration of the central cornea and the increased corneal thickness have also been suggested as the reasons premature corneas are often quite cloudy until the child approaches roughly 31 weeks post conceptual age [8].

Another important feature associated with central corneal thickness in premature infants relates to the accuracy of intraocular pressure measurements (IOP). Common devices used to measure IOP in premature eyes are the Tonopen (Reichert Technologies, Buffalo, NY, USA), the Icare tonometer (Kansas City, KS, USA and Helsinki, Finland), and the Perkins Tonometer (Haag-Streit USA and Reliance Medical products, Mason, Ohio). In a study of premature and term infants correlating IOP and central corneal thickness, Karahan et al. found that CCT did not affect IOP significantly in preterm infants and was only moderately correlated in full term infants [9]. In contrast, Uva et al. found that IOP measurements in premature infants using the Tonopen XL were slightly greater than in full term infants because of an increased CCT. They found the mean IOP in premature babies was 18.9 ± 3.7 mmHg with a mean CCT of 599 =/− 36 μm. In full term infants the IOP was 17 ± 2.6 mmHg with a mean CCT of 576 ± 26 μm [8].

Table 2.1 Gestational age, central cornel thickness and horizontal corneal diameter at 30–32, 34–35, 37–38 and 39–41 weeks gestational age

Gestational age (weeks)	Central comeal thickness (μm)	Horizonta corneal diameter (mm)
30–32		
Mean	691	8.0
SD	87	0.2
34–35		
Mean	648*	8.5*
SD	72	0.3
37–38		
Mean	605*	8.9*
SD	59	0.3
39–41		
Mean	564*	9.6*
SD	34	0.5

*Statistically significantly at $p < 0.05$

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Anterior Chamber

The uses of ultrasound biomicroscopic measurements (UBM) have greatly enhanced the understanding of anterior chamber development in the preterm infant. This technology allows for accurate imaging and measurements of the anterior segment to be taken in premature eyes. This is particularly valuable when the media are not clear or a child is confined to an incubator and access with a portable slit lamp is nearly impossible. Anterior chamber depth can be measured as the axial distance from the corneal endothelial surface to the anterior surface of the lens. Also measurable are the trabecular-iris angle and iris thickness. In a study of 39 premature infants born from 25 to 39 weeks gestational age, Kobayashi et al. established normative values related to postconceptional age and birth weight for these measurements [10]. They found that each value showed a linear relationship with post conceptual age and birth weight. Therefore, the younger the child, the more shallow the anterior chamber depth, the narrower the trabecular-iris angle, and the thinner the iris tissue.

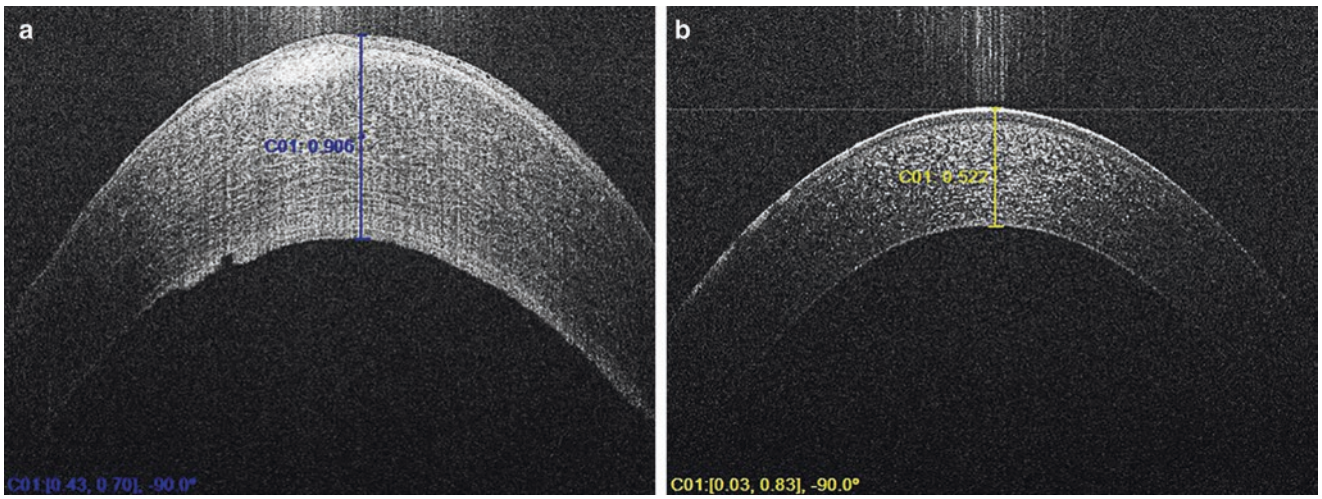

Fig. 2.1 (**a**) Hand-held spectral domain ocular coherence tomography (SD-OCT) (Bioptigen, Inc, Morrisville, NC) image of a premature infant with a markedly thickened central cornea. (**b**) The normal cornea of the fellow eye is shown next to it

UBM has also been used to evaluate angle closure glaucoma in premature infants which has been noted to occur in the advanced stages of retinopathy of prematurity (ROP). In a report of three infants, high resolution UBM confirmed angle closure in the setting of advanced ROP with a retrolental membrane. After peripheral iridectomy, repeat UBM showed an open angle in each of these infants. The authors concluded that a pupillary block mechanism was the cause of the angle closure in these infants [11].

More recently, hand-held spectral domain ocular coherence tomography (SD-OCT) (Bioptigen, Inc, Morrisville, NC) has been used to provide excellent quality images of the anterior segment in infants. As with UBM, this technology is particularly helpful when the cornea is cloudy and the direct view is compromised (see Fig. 2.1a, b).

Lens

Transient lens opacities can occur in premature infants. These were initially reported by McCormick and have later been confirmed by others [12]. Alden found 2.7 % of infants examined with a birth weight of less than 2500 g had opacities present. These transient opacities were distinguishable from neonatal cataracts by their appearance and clinical course. The lens changes were symmetrical, bilateral, and consisted of clear fluid vacuoles just anterior to the posterior lens capsule. The vacuoles were initially found in clusters corresponding to the apices of the posterior inverted Y suture of the lens. These progressed in varying degrees up to a total vacuolar opacification of the posterior subcapsular space. The onset of the lens opacities was estimated to be 16 ± 4 days post-partum and had a mean duration of 25 ± 30 days until clearing. Resolution occurred in a manner opposite to the initial formation, with initial clearing centrally and the most prolonged retention of vacuoles at the lens apices [13].

The tunica vasculosa lentis may be a prominent feature in the examination of the preterm infant. It can be a contributory factor to the hazy view of the posterior pole seen in these patients. This represents a branching capillary network on the posterior lens capsule that extends anteriorly around the lens capsule. It has been suggested by Hittner et al. that the presence of this network between 27 and 34 weeks is a useful adjunct in accurately estimating the gestational age of a preterm infant [14]. Another consideration with persistence of the tunica is whether it may compromise transpupillary laser treatment for threshold ROP or perhaps predispose the child to cataract development. Paysse et al. reported a very low incidence of acquired cataract following diode laser treatment for threshold ROP. They indicated the mechanism for this cataract formation is unclear, but postulated it is more likely the result of thermal damage from absorption of laser energy by lens proteins or hemoglobin contained in a persistent anterior tunica vasculosa lentis. They reported an incidence of acquired cataract of only 0.003 % using diode laser therapy and suggested the incidence should be lower with diode than argon because of the reduced absorption of diode laser energy by hemoglobin [15]. In support of this hypothesis, other reports have shown an incidence of 1–6 % of cataract development after transpupillary argon laser photocoagulation in the setting of a persistent anterior tunica [16, 17]. Of note, there have been several reports of rapid resolution of the tunica vasculosa lentis after injection with bevacizumab, an anti-vascular endothelial growth factor medication that has been introduced into use for threshold ROP which will be discussed later in the chapter [18, 19].

Posterior Segment

Vitreous

The vitreous in the premature infant is often hazy, providing a less than optimal view of the peripheral retina. This is particularly true in infants less than 34 weeks gestational age, and is compounded by the premature corneal haze and the persistent tunica vasculosa lentis that have been discussed previously. By the end of the sixth to seventh month of gestation, the primary vitreous and hyaloid vasculature tend to atrophy and regress leaving a clearer secondary and tertiary vitreous gel. If this regression fails to occur, either partially or completely, this results in persistence of the fetal vasculature (PFV). In PFV, a fibrovascular stalk connects between the optic nerve head and the posterior lens capsule. A whitish fibrovascular membrane covers the posterior lens capsule to varying degrees and the eye may be microphthalmic with cataract development. If the membrane is large enough, it may result in traction on the ciliary processes and will pull them centrally toward the pupil. Angle closure glaucoma is a potential risk of this process.

Retina

In 1986, Isenberg described the ophthalmoscopic appearance of the developing macula in a series of 129 premature infants [20]. He correlated the developmental changes in this region to the gestational age of the infant. At 34 weeks, pigment was first noted in the macular area. By 36 weeks, a complete annular reflex was present, and by 42 weeks in normal infants the macula appeared adult-like. The 37 infants in the study who developed retinopathy of prematurity showed a delay of 2 weeks in macular development in the later stages.

A number of studies have suggested that the presence of ROP, or premature birth alone, alters the development of the central retina. Through the use of hand-held spectral domain ocular coherence tomography (SD-OCT), it has been shown the central retinal thickness is significantly increased in preterm infants than in age matched full term controls [21]. The thickest central retinal area was found in infants treated with laser for ROP (Table 2.2). More recent SD-OCT studies have documented the development of the human fovea after premature birth. The technology has evolved to the point that all retinal layers that in the past were only observed by histologic study, can now be seen in vivo with dramatic detail (see Fig. 2.2) [22]. At 31–33 weeks post conceptual age, the foveal thickness is greater than that found in the adult fovea. In the center of the fovea at this stage, ganglion cell, inner plexiform, and inner nuclear layers can be seen. As the retina matures in ensuing weeks, the inner retinal layers migrate in a centrifugal fashion toward the periphery and the foveal pit forms more succinctly. In conjunction with this migration, parafoveal inner retinal layers increase in thickness in contrast to the more peripheral retina. The majority of this migration of the inner retinal layers occurs between 31 and 42 weeks gestational age [22]. This increase in thickness is thought to result in the observation of a macular annular reflex by 36 weeks post conception, but the characteristic foveal light reflex generally is not visible until 42 weeks post conceptual age [20].

An interesting finding that has arisen from SD-OCT studies in premature eyes has been the presence of cystoid macular changes. These are generally not visible on examination of the retina by indirect ophthalmoscopy. Vinekar et al. in a study of 54 premature infants with ROP and 20 controls, demonstrated that no control eyes or eyes with stage 1 ROP showed any foveal edema or disruption of architecture in that region. In contrast, 29.1 % of eyes with stage 2 ROP showed cystoid foveal changes. When these eyes were re-imaged by SD-OCT at 52 weeks post conceptual age, 100 % of the eyes had normalized by this visit.

Table 2.2 Mean of OCT parameters

	Group I	Group II	Group III	Group IV	*P*
Total macular volume (mm^3)	7.1 ± 0.3 (6.47–7.55)	6.9 ± 0.4 (6.2–7.52)	6.7 ± 0.33 (6.22–6.99)	7.1 ± 0.3 (6.29–7.39)	0.095
Foveal thickness (μm)	220.4 ± 39.1 (165–284)	198.6 ± 23.6 (176–248)	190.7 ± 28.9 (160–231)	164.7 ± 16.7 (136–191)	*0.002*
Central retinal thickness (μm)	240.6 ± 28.9 (201–286)	223.3 ± 14.7 (208–253)	218.9 ± 19 (191–248)	199.6 ± 14.5 (171–221)	*0.002*
Inner retinal thickness (μm)	272.7 ± 23.5 (210–291)	269.4 ± 15.9 (244–295)	269.9 ± 14.7 (249–291)	273.1 ± 13.5 (256–295)	0.65
Outer retinal thickness (μm)	243.4 ± 18.6 (198–267)	239.9 ± 17.8 (210–264)	239.7 ± 18.5 (217–279)	249.9 ± 9.8 (235–262)	0.252

Data are expressed as the mean ± SD (range). Results of Kruskal-Wallis H test, asymptomatic significance level for the four groups. All groups were compared with each other (10 eyes and 10 children/group). Significant differences (*P*) are italic

Group 1 = Patients treated with laser for threshold ROP

Group 2 = Patients with stage 1 or 2 ROP

Group 3 = Patients with no ROP

Group 4 = Age matched full term controls

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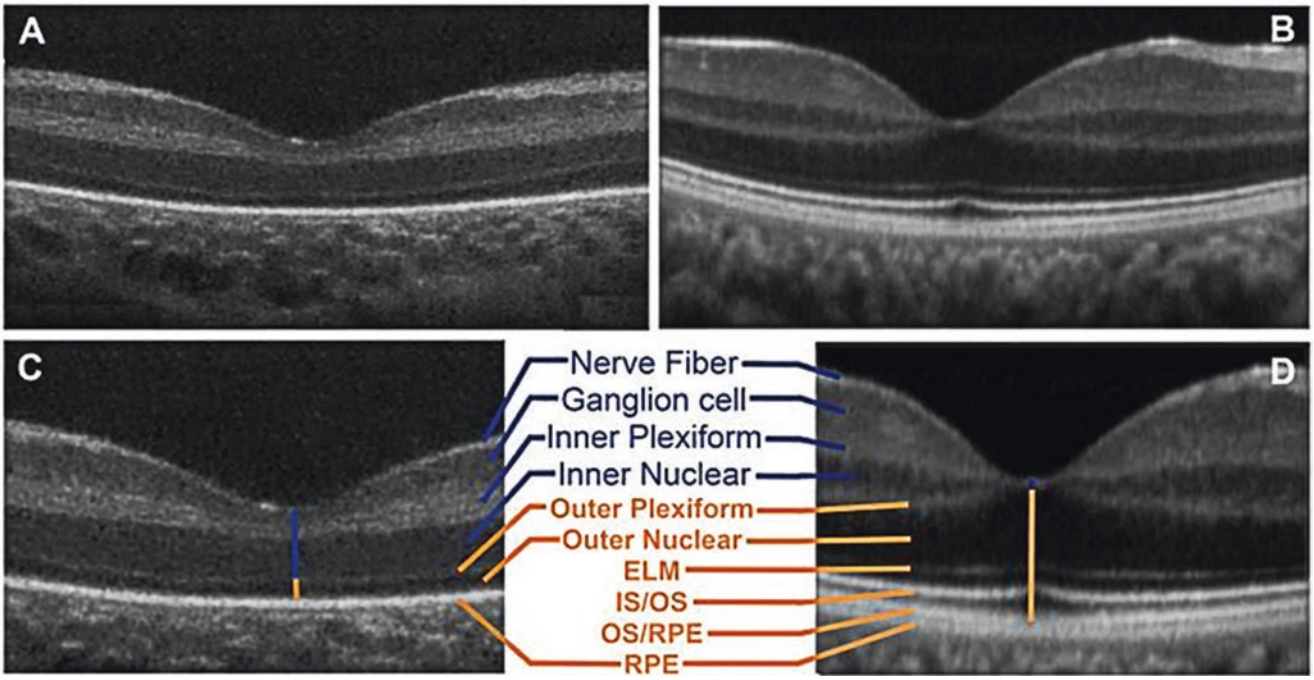

Fig. 2.2 Hand-held spectral domain ocular coherence tomography (SD-OCT) (Bioptigen, Inc, Morrisville, NC) cross sectional images of immature and mature retinas. On the left is the retina of a 31 week post conceptual age neonate born at 27 weeks and 1205 g. On the right is a 23 year old adult born at term. (Reprinted from Maldonado RS, O'Connell RV, Sarin N, Freedman SF, Wallace DK, Cotten CM, et al. Dynamics of human foveal development after premature birth. Ophthalmology. 2011;118(12):2315–25 [22]. With permission from Elsevier.)

The authors postulate that the macular edema noted in the more severe ROP could be due to several causes. The first is an increase in VEGF levels in this setting and the second is mechanical traction exerted on the macular by the more peripheral acting ROP process. They considered it less likely that the ridge found in stage 2 ROP exerted significant tractional forces on the macula [23].

Other studies done to assess the retina of formerly preterm children with ROP include fluorescein angiogram (FA) and electroretinogram (ERG). A smaller than normal foveal avascular zone has been documented in formerly preterm children. In children born before 30 weeks of post conceptual age, the normal remodeling of the avascular zone from a densely vascular area does not appear to occur fully. Of note, this smaller avascular zone does not correlate with visual acuity [24]. It should also be noted that the increased central macular thickness found in formerly premature infants discussed previously also did not correlate with visual acuity. Multifocal ERG studies have documented a significant reduction in amplitude and implicit time in children with a history of ROP as compared to age-matched controls. This is postulated to occur due to the impairment of the normal centrifugal movement of foveal cone nuclei and inner retinal cells in children with ROP. This arrest can result in the bipolar and amacrine cells remaining more central and causing the ERG findings [25].

Optic Nerve

During the second trimester of fetal development, the optic nerve contains about 3 million nerve fibers. During the third trimester, a number of the fibers are eliminated during the segmentation of inputs to the ipsilateral and contralateral lateral geniculate nuclei. An adult optic nerve is left with about 1 million nerve fibers. The optic nerve and optic tract are not completely myelinated at term birth and this process continues until roughly 2 years of age. The appearance of the optic disc is different in preterm infants, assuming initially an ovoid shape and over a period of several months normally becoming more round in shape. The optic nerve of a preterm infant often appears paler than that of an older child, regardless of racial or ethnic origins [26].

Optic Nerve Hypoplasia

Definition

An abnormally small optic nerve head that may appear pale or gray in color that may be surrounded by a peripapillary halo and bordered by a ring of either increased or decreased pigmentation. This process can be either unilateral or bilateral and may occur as an isolated event or be associated with midline brain defects.

History

The first case of optic nerve hypoplasia was described in 1877 by Briere. The first schematic drawing of the condition is attributed to Schwarz in 1915. The association of optic nerve hypoplasia with absence of the midline septum pellucidum was first described by Reeves in 1941. Dr. William Hoyt described in 1970 the association between optic nerve hypoplasia and growth hormone deficiency [27].

Epidemiology

Optic nerve hypoplasia is a common cause of congenital legal blindness. In 2007 the Babies Count Registry listed optic nerve hypoplasia as the third most common cause of blindness in infants. The first two were retinopathy of prematurity and cortical visual impairment. It was also attributed to be the most likely cause of blindness in children under the age of 3 years in the United States [28].

Systemic Manifestations

The most significant potential association with optic nerve hypoplasia is hypopituitarism. Infants manifesting this condition should be monitored carefully for associated endocrine abnormalities [29]. More recently, associations have also been established with hypothalamic dysfunction, developmental delay, and autism. Of note, these are all independent of septum pellucidum development. It is important to monitor these children carefully from an early age [30, 31].

Ophthalmic Manifestations

In a study of RetCam image analysis of the optic nerve in premature infants, Mcloone et al. sought to examine children with and without ischemic brain injury. These images were combined with serial cranial ultrasonography in order to date the brain injury in children with periventricular white matter damage. There is a well-established increased incidence of intraventricular hemorrhage (IVH) with decreasing gestational age. In the above study, 61 % of the 109 premature infants with birth between 24 and 33 weeks gestation demonstrated IVH. In this population, only the infants with grade 4 IVH had significantly more hypoplastic discs than the normal control group. The median age of injury for the patients in the Grade 4 IVH group was 26 weeks post conceptual age and this group represented 8.3 % of the study population. 44 % of infants in this group were noted to have hypoplastic discs [29]. The authors recommend that given the potential association of neurologic and visual complications, preterm infants with Grade 4 IVH be referred for eye evaluation even if they fall outside of normal ROP screening criteria. Jacobsen et al. have postulated that if early prenatal damage occurs to the periventricular white matter, prior to development of the supporting tissues around the optic nerve, then a smaller optic disc size may result. They also reported that a small optic disc area in a child with periventricular leukomalacia or periventricular hemorrhage could predict the timing of the brain injury. A small optic disc area was only seen in children with white matter damage estimated to occur prior to 28 weeks of post conceptual gestational age. If the injury occurred after 28 weeks, they suggest that a normal sized optic disc would develop but it would have a large cup area and thin neuroretinal rim [32].

In a study by De Silva et al., optic nerve head dimensions were measured in 51 infants during routine ROP screening using the Retcam with either an 80 or 130° lens. Past studies were done using postmortem specimens and were subject to fixation and shrinkage artifact. The mean values obtained were horizontal disc diameter 1.05 mm ± 0.13, vertical disc diameter 1.41 mm ± 0.19, and mean disc area 1.17 mm^2 ± 0.26. The infants studied ranged from 32 to 50 weeks post conceptual age and the authors found that the optic nerve head dimensions did not change significantly over this age range [33]. Other studies have also reported the optic disc parameters of premature infants such as optic disc area and cup-to-disc ratio did not correlate with birth weight or gestational age [30, 31]. The measurements taken of optic disc height and width were found to be larger than the values previously obtained from postmortem studies. Of note, De Silva et al. also reported a high proportion of eyes (23 %) to have a double ring sign classically ascribed to optic nerve hypoplasia. They suggest this may be a normal stage of disc development since their measurements would indicate the optic nerve enlarges by 50 % after birth to reach adult proportions. This growth largely abolishes the double ring sign in most and those that do not grow retain the double ring and are left with a hypoplastic nerve [33].

Refraction and the Premature Eye

History

Children with a history of prematurity, and particularly those that have had retinopathy of prematurity (ROP), have a higher incidence of myopia than their age matched counterparts. Another interesting finding that has been reported is that premature infants tend to have a higher degree of astigmatism, particularly in more severe cases of ROP [34, 35]. It remains a subject for debate as to which element(s) of the determination of refractive status are most responsible for the development of both myopia and astigmatism. A number of studies have been published over the last several years proposing several possible answers. These studies address axial length, corneal curvature, anterior chamber depth, lens thickness, and the impact of either laser or cryotherapy induced treatment changes as causative factors [36–41]. Other factors that have been implicated are bone mineral deficiency, temperature, lighting, and visual deprivation [42, 43].

Epidemiology

Quinn et al. have reported that in eyes with any stage of untreated ROP, and eyes treated with cryotherapy for threshold stages of the disease, the incidence of myopia increases during the first year of life [34]. Others have reported that myopia in preterm infants begins at about 6 months of age and severity increases between 6 months and 3 years of age [41]. The severity of the myopia is often linked to the severity and stage of the ROP that was present. Cross sectional and longitudinal studies have reported the rates of myopia in the pre-term population to be anywhere from 5 % to in excess of 80 % varying with the age at the time the examination was performed [44–46]. Choi et al. found in a study of 125 eyes that premature infants tend to initially develop myopia at the age of 6 months and progresses to the age of 3 years. The highest levels of myopia tend to develop in children that had cicatricial retinopathy, regardless of whether they received treatment with cryotherapy or not [41]. One common theme that emerges from most of these studies is that the myopia is not due to an increase in the axial length of the eye, but rather to factors related to the anterior segment of the eye such as the cornea, anterior chamber depth, and lens.

Ophthalmic Manifestations

The normative refractive status of full term infants is generally a moderate state of hypermetropia. This tends to persist for the first several years of life with a steady decline in hyperopic refraction through the childhood years as the emmetropization process proceeds. In premature eyes, there are several factors that may contribute to the development of myopia, which may be mild to severe. In a study comparing highly myopic eyes in preterm children with a history of ROP to an age matched group of patients with high myopia born at term without any ROP, Garcia–Valenzuela et al. found that increases in lens thickness and attendant power are the primary factors causing high myopia in ROP eyes. This finding was not related to stage of ROP attained or treatment of threshold ROP [47]. This finding led them to support a theory of altered anterior segment development for the resultant high myopia. They also found only a minimal increase in axial length as compared to age matched norms (mean of 23.36 ± 1.71 mm vs. 22.21 ± 0.80 mm). In the full term group with high myopia, the cause was primarily axial length with the mean value measured at 27.02 ± 1.87 mm. They advocate comparing the ratio of lens thickness/anterior chamber depth between ROP and full term highly myopic eyes to highlight the difference in anterior structures between the two groups. The eyes with ROP had a ratio 50 % higher than full term or normative eyes [47].

Fielder et al. proposed that myopia associated with prematurity was a result of the preterm cornea not appropriately flattening in the setting of the cooler environment outside of the womb [42]. Hittner et al. reported decreased anterior chamber depth in myopic eyes that had cicatricial changes secondary to ROP [48]. Laws et al. found that axial length was inversely related to increasing stage of ROP with the higher the stage reached, the lower the axial length recorded. This remained true after correction for gestational age, sex, birth weight, and head circumference. They also found that infants reaching threshold stage 3 disease had a shorter axial length than stage 3 infants not receiving treatment. In both cases, the growth in axial length was found to be linear [49]. Yang et al. found that laser treated eyes for threshold ROP showed a significantly thicker lens and shallower anterior chamber depth than full term control infants [50]. A reasonable conclusion is that the myopia associated with prematurity has an arrested development of the anterior segment structure as its root cause and is nonaxial in nature. Its cause seems to be more related to a steeper cornea and a thicker lens with associated shallower anterior chamber depth. Findings from the Early Treatment of Retinopathy of Prematurity Study (ETROP) would also indicate that the increased myopia in patients treated with laser is not due to any direct effect of the laser on the retinal periphery, but rather due to the severity of the ROP [51]. In a follow on report regarding the progression of myopia to ages 4–6 years, the ETROP group found that approximately 2/3 of eyes of children that had high risk pre-threshold ROP will likely be myopic into the early school-age years. The proportional increase in high myopia noted in earlier age groups was not noted to continue between ages 3 and 6 years [52].

Another potential refractive outcome in the premature infant with ROP is the development of astigmatism. In a cross-sectional study of 24 consecutive preterm children treated with diode laser for threshold disease at age 9 years, Yang et al. sought to assess the prevalence of astigmatism in this group. They matched their results with 1021 full term controls from a national survey in Taiwan, Republic of China. They found that the laser treated eyes had a mean astigmatism of 3.47 ± 1.92 diopters, with a mean spherical equivalent of −4.49 ± 3.76 diopters. Age matched controls showed a mean of 0.08 ± 0.9 diopters, with a mean spherical equivalent of −0.44 ± 1.48 diopters. 98 % of the eyes studied showed astigmatic changes, the majority of which were with- the- rule with greater steepening in the vertical meridian. They found the astigmatism to be corneal in origin and reported a statistically significant steeper vertical corneal meridian and flatter corneal meridian than those found in the control group. Their hypothesis was that there is an incomplete postnatal development of the cornea, anterior sclera, and anterior segment in this population at the age of 9 years [53]. In an ETROP study report,

Davitt et al. reported that by age 3 years, over 40 % of eyes with high-risk pre-threshold ROP will develop astigmatism of greater than or equal to 1.00 diopter and 10–20 % of these eyes will develop more than 2.00 diopters. There was no evidence that earlier treatment of this population, or the presence of stage 1 disease or plus disease significantly influenced the development of astigmatism. The majority of the astigmatism was with the rule in nature [51].

Ocular Infections in the Premature Infant

Definition

An ocular infection can be considered to be located anywhere on the surface of the eye, on the surrounding ocular adnexa, such as the lids or periocular skin, or inside the eye in the form of endophthalmitis. A series of infections with the collective acronym TORCH infections can have potentially devastating clinical and ocular manifestations. This acronym stands for Toxoplasmosis, Other (syphilis, Varicella Zoster), Rubella, Cytomegalovirus, and Herpes Simplex Virus. These infections, with the exception of Herpes Simplex, will be addressed in another chapter of this text.

History

Ophthalmia neonatorm or conjunctivitis of the newborn has been a public health concern that has been recognized for over 100 years. In late nineteenth century Europe, the prevalence of this condition exceeded 10 %, with blindness occurring in about 3 % of affected infants. About 50 % of the children in schools for the blind during this era were there due to ophthalmia neonatorum infection. In an 1881 paper, Crede' published the impact of using a 2 % silver nitrate solution in reducing the number of cases of this disease dramatically. He realized that the majority of infections resulted from transmission of Neisseria gonnorhea as the child passed through the vagina at birth. His discovery led to a dramatic reduction in the disease throughout Europe [54]. In the modern era, silver nitrate has been largely supplanted in developing countries by erythromycin or tetracycline ointment. These antibiotics are far less irritating, seldom produce a chemical conjunctivitis, and also provide better coverage for Chlamydia trachomatis, the number one cause of ophthalmia neonatorum in developed countries today. Prophylaxis is recommended by the American Academy of Pediatrics and required by state law in many states, but is not being done automatically in other developed nations such as the United Kingdom [55]. Another option for prophylaxis worldwide, but not CDC approved in the United States, and one which is highly cost effective, is the use of povidone iodine 2.5 %. The cost of a 5 cm^3 container of this substance is $0.10, as compared to erythromycin ointment at $0.74 [54]. Drug shortages of erythromycin in the United States in 2009 led to the use of alternative, unproven antibiotic substitutes [56].

Epidemiology

The duration of hospitalization for a newborn infant is inversely related to the gestational age at birth. The average length of stay for newborn infants born at 26 weeks is roughly 2 months. This population of extremely low birth weight infants generally undergoes a number of invasive procedures and is commonly exposed to mechanical ventilation, including high frequency jet and oscillation, continuous positive airway pressure devices (CPAP), endotracheal suctioning, prolonged use of central venous lines, and nasogastric tube feedings. This places them at high risk for the development of infections, a number of which can affect the eyes from either exogenous or endogenous sources. In a study of two Neonatal Intensive Care Units (NICU) over a 2 year period and involving almost 3000 premature infants, conjunctivitis was found in 5 % of patients. An association was established between low birth weight, the performance of an eye examination, and respiratory support measures as a predictor for the development of conjunctivitis. The respiratory support measures implicated included nasal cannula delivered CPAP, endotracheal intubation, and mechanical ventilation [57]. Common pathogens isolated are identified in Table 2.3 with

Table 2.3 Organisms causing conjunctivitis in neonatal intensive care unit patients

Organism	Total no. of isolates[a]
Coagulase-negative *Staphylococcus*	38 (25)[b]
Staphylococsus aureus	29 (19)
Klebsiella spp.	16 (10)
Pseudomonas aeruginosa	13 (8)
Enterococcus spp.	13 (8)
Escherichia coli	12 (8)
Serratia marcescens	12 (8)
Enterobacter spp.	10 (6)
Streptococcus spp.	9 (6)
Other Gram-negative bacilli	11 (7)
Diphtheroids	3 (2)
Yeast	4 (3)
Culture not obtained	33 (21)
Total	203 (131)[a]

[a]Includes 44 cases with >1 organism isolated
[b]Numbers in parentheses, percent of cases
Reprinted from Haas J, Larson E, Ross B, See B, Saiman L. Epidemiology and diagnosis of hospital-acquired conjunctivitis among neonatal intensive care unit patients. The Pediatric infectious disease journal. 2005;24(7):586–9 [57]. With permission from Lippincott, Williams & Wilkins

the most common pathogen being coagulase negative Staphylococcus Aureus. These results are consistent with previous studies published in the literature [58–60]. Another important factor to consider is the potential colonization of bacteria among mothers and infants which could contribute to the development of ocular infection in vulnerable preterm infants. Studies have shown that between 1–4 % of mothers and infants are colonized with the potentially serious Methicillin Resistant Staphylococcus Aureus (MRSA). This organism may be vertically transmitted from mother to child during vaginal birth [61]. An important consideration is that in some cases of conjunctivitis in a premature infant, the causative organism may lead to a significant keratitis or endophthalmitis, and may also result in a life threatening systemic infection. Conjunctivitis in a preterm infant warrants a thorough evaluation with cultures and bloodwork.

Ophthalmic Manifestations

Bacterial conjunctivitis in the preterm infant is generally heralded by a purulent discharge from one or both eyes accompanied by ocular redness and possible lid swelling. The discharge may be less copious than that observed in an older child with a similar infection due to the immature immune system. Gonococcal conjunctivitis is a notable exception and normally presents with a hyperpurulent discharge even in the preterm infant. The most frequent cause found in the United States and other developed countries is Chlamydia trachomatis. This is a sexually transmitted pathogen normally acquired by the child during the delivery process. The incubation period is generally 5–14 days after delivery and it may present either unilaterally or bilateral. Children born to infected mothers have a 30–40 % chance of developing conjunctivitis [62]. Unfortunately, according to the 2012 Red Book, there is no effective agent to date to prevent the vertical transmission of Chlamydia from infected mother to her infant. Infections can range from mild to severe with the mildest forms presenting with a clear discharge with thickening and erythema of the palpebral conjunctiva. More serious infections can result in a thicker discharge with pseudomembrane development or corneal involvement in the form of clouding or pannus [63].

Gonococcal conjunctivitis is also a sexually transmitted pathogen acquired by the infant during vaginal delivery. Classically this presents as bilateral hyperpurulent conjunctivitis with significant lid edema, chemosis, and potential formation of membranes or pseudomembranes. Its ocular consequences may be more severe with progression to corneal ulceration or perforation if not treated promptly. The organism is able to penetrate intact epithelial cells and multiply rapidly inside of them. The onset of the infection is usually within 48 h of vaginal delivery. In the modern era, this organism represents less than 1 % of the cases of neonatal conjunctivitis [59].

Another potentially serious bacterial pathogen in the preterm infant is Pseudomonas aeruginosa, which tends to colonize in water saturated respiratory equipment Although Pseudomonas is a less common cause of conjunctivitis, it is capable of progressing rapidly to corneal ulceration or perforation if not treated promptly. An outbreak in seven ventilated infants at a NICU in Brazil suggests that the conjunctivitis may have occurred from spread from endotracheal tube aspirates. The same strain of pseudomonas was isolated from the respiratory tract of two of the infected infants [64]. In an outbreak of this organism in a pediatric hospital involving 30 patients, 70 % of the patients were preterm infants in the NICU. All of the patients except one had respiratory care interventions prior to the onset of conjunctivitis. These included endotracheal tube, tracheostomy placement or suctioning of the respiratory tract. The authors stressed the need for caution and protection around the eyes when performing these measures [65].

Other organisms, both gram positive and negative, have been identified as causative agents in conjunctivitis in the preterm infant. Common gram positive organisms are Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumonia, and Streptococcus viridens. These collectively make up 30–50 % of the reported cases [66]. Common gram negative organisms isolated, in addition to the previously mentioned Pseudomonas aeruginosa, are Eschericia coli, Klebsiella pneumonia, Serratia marcesans, and Haemophilus influenzae. Very low birth weight infants with commensurate early gestational age in the NICU with signs of conjunctivitis should generate immediate concern for a possible gram negative etiology. Chen et al. reported the incidence of gram negative isolates causing conjunctivitis as 38 % in a NICU setting [67].

Viral conjunctivitis is another potential issue for the preterm infant. Most herpetic infections in the preterm infant are secondary to vertical transmission of HSV-2 transmitted to the infant during birth. This infection generally occurs within the first 2 weeks after birth and may affect one or both eyes. Clinical signs may be subtle and include lid edema, bulbar conjunctival injection, and a watery discharge. Typical dendrites are seldom noted but geographic ulceration of the cornea may be seen. Herpetic infection may also result in a retinopathy causing necrosis, vasculitis, and hemorrhage. Those with retinitis will often develop a cataract and the virus can often be isolated from these lenses [68]. Ocular signs may be the initial or only manifestation of herpetic infection although serious systemic disease can result, as will be discussed in the next section. If a mother with an active genital herpetic infection delivers vaginally, there is a 40–60 % chance the child will be infected [69]. In about 60 % of infections in the preterm infant, the mother will show no signs of active herpetic infection [70].

Another potential viral pathogen of the preterm infant is adenovirus. In an outbreak in a NICU in Israel, the virus was found in seven premature infants who had undergone an eye examination 4–7 days previously. Three of the infected infants went on the manifest systemic respiratory symptoms. The temporal relationship of the eye exams to the outbreak suggests direct inoculation of the infants by ophthalmic instruments or transmission by the involved personnel. Several of the affected children had underlying pulmonary disease and were being treated with steroids which likely exacerbated the course of the illness [71]. Respiratory related pathology is a very common finding in the preterm infant. The need for aseptic techniques using separate sterile instruments for each child in the NICU during exams cannot be overemphasized.

More serious ocular infections are also a very real threat in the premature infant. Endophthalmitis may result from both exogenous and endogenous sources. It has been reported that 80 % of neonatal endophthalmitis comes from endogenous sources [72]. In the cases of exogenous spread, conjunctivitis was the initial presenting sign. These infections are generally nosocomially acquired, often from contaminants from suction devices, nasal CPAP devices, or respirators. Typical exam features in the NICU are a red eye, a compromised red reflex, and corneal clouding. Pseudomonas aeruginosa has been identified as an exogenous source agent of neonatal endophthalmitis and has been reported to be the causative agent in more than 75 % of invasive eye infections in this population. Preterm infants are particularly vulnerable to infection by this organism [73]. Gaili and Woodruff reported a case of a preterm infant who initially became ill on day 12 of life and intravenous antibiotic treatment was begun, but there were no signs of ocular infection at that time. She was started on nasal CPAP. By day 21, the eye became "sticky", and by day 22 there was a frank purulent discharge coming from one eye and the cornea became cloudy. A culture of the conjunctiva was positive for pseudomonas aeruginosa. Despite intensive intravenous and topical therapy, the eye perforated and was lost. They postulate an initial corneal epithelial injury that likely occurred via the CPAP apparatus and progressed rapidly [74]. Figueirdo et al. describe a similar case of pseudomonas aeruginosa endophthalmitis in a preterm infant born by caesarean section. In this instance, the infant initially developed septicemia and shortly thereafter developed a red eye with discharge, a cloudy cornea and hypopyon. Blood cultures subsequently revealed pseudomonas aeruginosa, but conjunctival cultures were negative. The mother's wound cultured positive for the same organism. As in the first case, despite aggressive intravenous and topical therapy, the ocular infection progressed and the eye perforated and was lost [75]. These cases underscore the importance of aggressive treatment of ocular infections in the preterm infant. If the organism is fulminant, as in the case of pseudomonas, morbidity is very high and the infection can be life threatening.

Other forms of endophthalmitis can also occur in the preterm infant. Group B streptococci (GBS) are a major pathogen causing bacterial infection in this age group. Endophthalmitis from this pathogen is unusual in the neonate, but has been reported [76]. Most of the cases are associated with both sepsis and meningitis from the organism and tend to occur weeks later than the onset of the systemic infection, even with appropriate intravenous antibiotic therapy. Group B streptococcal meningitis interferes with the normal blood flow autoregulation to the eye and may contribute to an increased risk of retinal pathology in this group [77].

Another form of endophthalmitis to which the preterm infant is susceptible is *Candida*. This is also a rare occurrence but the visual consequences are often devastating. It is almost always associated with a septicemia due to the *Candida* organism and is spread to the eye endogenously. Systemic candida infection has been reported to occur in 1.6–12.9 % of premature births, particularly in very low birthweight children [78–80]. Of note, there are a number of reported cases of endogenous *Candida* endophthalmitis in premature infants secondary to the organism remaining sequestered in the lens [81–83]. The endophthalmitis often presents after resolution of the systemic candidemia and is thought to be potentially due to the regression of the fetal hyaloid artery between 24 and 32 weeks post conceptual age. This permits the transmission of the fungus to the lens initially with subsequent sequestration. A cataract that may develop in this setting may actually represent a fungal abscess within the lens [84]. Fungal endophthalmitis may lead to necrotic retinal detachment and glaucoma, in addition to cataract.

Systemic Manifestations

A number of ocular infections in the preterm infant can be associated with serious systemic illness and may result in serious morbidity or mortality. Premature infants who contract a *Chlamydia* infection during the birth process have a 10–20 % chance of developing pneumonia related to this organism [85]. This generally results from an infection in the nasopharynx or aspiration of infected secretions from the mother during birth. The presentation is generally a respiratory distress with low grade fever and cough that may progress to apnea requiring ventilator support. The infection typically occurs around 3–6 weeks after birth but has been reported between 1 and 19 weeks of chronologic age [86].

Sepsis of early or late onset is not an uncommon occurrence in the preterm infant. Infant birth weight is inversely related to the risk of developing sepsis. Organisms that can

cause ocular infection that can also result in sepsis include Group B streptococcus, Staphylococcus aureus, Coagulase negative staphylococcus, Klebsiella pneumonia, Haemophilus Influenza, Candida albicans, Pseudomonas aeruginosa, Serratia marcesans, and Neisseria gonorrhea [87].

Although intrapartum prophylaxis has significantly reduced early onset of GBS infection, late onset GBS sepsis is still common in the preterm infant. Most reported cases of associated endophthalmitis are associated with later onset disease and generally occur 1 week to 3 months after birth [76, 88]. The early onset infections are generally vertically transmitted from an infected or colonized mother during the birth process. The later onset infections are either acquired from colonized mothers, staff, or equipment in the NICU. With the increased survival rates of preterm infants, the burden of potential infection remains higher than ever. If a preterm child becomes septic, pediatricians often recommend a daily eye exam for early identification of ocular disease, and prompt ophthalmology consultation for any ocular signs [87].

Candida is a major cause of sepsis in the NICU in infants born less than 1500 g. Rates have been reported between 1.6 to 12.9 % in this population of infants, and morbidity and mortality rates approach 25 % [80]. The sources of systemic candidiasis are mostly endogenous, and infections are associated with total parenteral nutrition solutions and indwelling intravenous lines [89, 90]. Some authors suggest that candida sepsis should be strongly suspected after the third week of NICU admission in infants on mechanical ventilation and who have undergone treatments with multiple classes of antibiotics for other infections [91]. The general colonization rate for candida in infants who have been in the NICU environment for 1–3 months may be as high as 50 %, with the GI tract often being an early area affected [92]. Once the empiric or confirmed treatment for candida sepsis is begun, the ophthalmologist is often consulted to check the eyes for evidence of candida endophthalmitis.

Meningitis is another potential systemic complication of infections in the preterm infant that can also affect the eye. The potential organisms involved are those previously described that may result in sepsis. Meningitis is usually of later onset in this population, between 1 week and 3 months after birth. The most commonly identified organism causing meningitis in the premature infant is GBS, which is involved in about 50 % of cases. E-coli is the next most common pathogen, implicated in 20 % of cases, with Listeria monocytogenes next at 5–10 % [93, 94]. Another potential causative organism in neonatal meningitis worthy of mention is the *Herpes simplex* virus. The impact of a meningitis infection in these infants is significant. In a large study of 1500 babies with neonatal meningitis, 8 % had motor deficits, to include cerebral palsy, 7.5 % had learning difficulties, 7.3 % suffered from seizures, and 25.8 % had hearing impairments [95].

Diagnosis

The diagnosis of ocular infection in the premature infant may be more challenging than in the adult patient. Due to the increased susceptibility of the immature immune system, a healthy suspicion of a possible coincident systemic infection must be kept in mind. For a suspected conjunctivitis, the suggested evaluation would include a conjunctival swab for culture and sensitivity, a conjunctival scraping for gram and giemsa stain, polymerase chain reaction (PCR) testing for *Chlamydia*, chocolate agar plating for *Gonococcus* or *Haemophilus*, blood agar for other bacterial species, and PCR for suspected Herpes infection. In the setting of any associated illness, blood cultures should also be performed immediately. Blood cultures should include both aerobic and anaerobic varieties, with results usually available within 36–48 h.

In the setting of a suspected endophthalmitis, organisms may be identified through vitreous culture, either from a biopsy or retrieval from a vitrectomy specimen. Most commonly the diagnosis is established by blood cultures. In a review of endogenous bacterial endophthalmitis, blood cultures were positive with the offending organism in 94 % of cases, and vitreous samples were positive in only 56 % [76]. To evaluate for fungal etiology, routine cultures can be ordered but are often low yield. More recently, the use of pan-fungal PCR testing has improved the yields on these cultures [96].

Management

In treating conjunctivitis in the preterm infant, initial treatment should be presumptive based upon initial gram stain or giemsa stain results. Consideration should be given to the potential for maternal infection and potential transmission of *N. gonorrhea*, *Chlamydia*, *Herpes*, or Group *B streptococcus*. Examination and culture of the parents may be necessary if suspicion is present. Time honored initial treatment of the conjunctivitis is the use of erythromycin ointment for gram positive organisms or topical gentamicin or tobramycin for gram negative organisms. It is also important to initially start intravenous antibiotics to cover for potential Neisseria gonorrhea infection or Chlamydia infection pending the return of culture results. The use of topical antibiotics alone is inadequate for the treatment of either of these forms of conjunctivitis and generally should not be used once the diagnosis is confirmed. Typical intravenous regimens would include either penicillin G or ceftriaxone to cover the Neisseria gonorrhea and erythromycin to cover Chlamydia [97].

Longer duration of stay in the NICU may predispose the infant to other pathogens that may cause conjunctivitis. Gram positive organisms, to include Methicillin Sensitive *Staphylococcus Aureus* (MSSA) and Enterococcus have

been reported in higher frequency with greater duration of stay. Gram negative organisms such as *Pseudomonas aeruginosa* and *Serratia marcesans* were more frequently cultured after the first 10 days of admission, presumably from nosocomial transmission [98]. These organisms, with the potential exception of MRSA (see next paragraph), can be effectively treated with topical fourth generation fluoroquinolone preparations. These medications have shown very low resistance patterns to most gram positive and gram negative isolates to date. This potent class of antibiotics tends to kill the organisms quickly, thus reducing the potential for bacterial mutation [99].

Bacterial conjunctivitis caused by Methicillin Resistant *Staphylococcus Aureus* (MRSA) has also been reported in the neonate. A common practice in a number of NICU's is to take weekly pharyngeal and skin swabs to test for colonization of MRSA. These infants are typically not symptomatic, but colonization may be associated with a nasolacrimal duct obstruction. In these cases, it is possible that the parents or staff is also colonized and they should be checked accordingly [100, 101]. Current guidelines suggest treating MRSA infections with agents other than fluoroquinolones when possible. This is due to the high in-vitro resistance rates that MRSA have shown to these agents [102]. Other options in this setting would be topical vancomycin, a topical polymixin B- trimethoprim combination, and topical chloramphenicol, although the latter is seldom used in the United States and carries with it the potential complications of bone marrow hypoplasia and aplastic anemia.

The treatment of endophthalmitis, in the immature infant needs to be aggressive in nature. It is usually endogenous in origin, associated with sepsis, and often has a poor visual outcome. The diagnosis may be established from blood culture results or vitreous sampling. Treatment is generally with intravenous antibiotics and possibly intravitreal antibiotics. The normal blood ocular barrier is usually broken down in the setting of endophthalmitis, allowing reasonable absorption of intravenous antibiotics into the eye. Initial treatment involves empiric broad spectrum antibiotics for presumed bacterial infections. These generally include vancomycin and ceftazidime or amikacin, and arguably decadron. Some favor the administration of steroids and others do not. The dosage of vancomycin for a preterm infant is a 15 mg/kg loading dose, followed by 10 mg/kg/day. The infusion is generally given over a 1 hour period and dosing can be effectively adjusted using serum creatinine concentration and desired trough levels as a guide [103]. The dosage of ceftazadime in this age group is 25–100 mg/kg/day in two divided doses.

Some preterm infants may have a persistent endophthalmitis or even develop endophthalmitis while on appropriate intravenous therapy with blood levels in the therapeutic range. This has led to the recommendation to combine intravitral antibiotic injection with intravenous antibiotic use. Vitreous biopsy can be achieved at the time of injection of intravitreal vancomycin and ceftazadime. This provides excellent initial gram positive and gram negative coverage and can be modified accordingly dependent upon gram stain and culture results. The normal dose of intravitreal vancomycin is 1.0 mg/0.1 mL and for ceftazadime 2.25 mg/0.1 mL [104, 105].

Vitrectomy is another treatment option in this age group but remains controversial. While it can relieve the bacterial burden in the vitreous, these children are often very ill and may not be well enough to undergo the surgical procedure [76]. It may be best advised for those infants who are not as ill systemically, those who may have developed a retinal detachment in the process, those with infections with particularly aggressive organisms, or in cases where the fundus cannot be visualized. Modern 25 gauge vitrectomy instruments may make this challenging surgery marginally safer.

The treatment of fungal endophthalmitis can often be initiated based upon the characteristic white appearance of the retinochoroiditis with overlying white vitreous condensations. This is a rare infection but accounts for many ocular consultations in the NICU in children with systemic involvement. Intravenous therapy with amphotericin B is a common approach, but this medication has relatively poor ocular penetration and can be toxic to the renal system. Less toxic alternative include fluconazole with a usual dose of 200–400 mg/day for Candida species [106]. Intravitreal injection of amphotericin B or voriconazole are a possible adjunctive treatment approach, and vitrectomy may need to be considered if the infection remains unresponsive to treatment [107]. Recommended intravitreal dosage of amphotericin B is 5–10 μg/0.1 mL and Voriconazole 50–100 μg/0.1 mL.

Retinopathy of Prematurity

History of ROP

In 1941, Dr. Paul Chandler encountered the first two cases of retrolental fibroplasia in Boston, Massachusetts. These two cases were the forerunners of the epidemic now referred to as retinopathy of prematurity (ROP) [108]. Between 1942 and 1945, Dr. Theodore L. Terry collected 117 additional cases of ROP and determined that the pathology occurred in premature infants who initially had normal eyes. The changes associated with retrolental fibroplasia occurred a number of weeks after birth [109]. Husband and wife ophthalmologists, William and Ella Owens concluded that postnatal development of the vascular abnormality seen in ROP was caused by neovascularization beginning 2.5–3.5 months after birth [108, 110]. Secondary to these findings, weekly examinations of the interior of the eye soon became routine for ophthalmologists at large research institutions around the world.

Initially, multiple factors were considered in the pathogenesis of ROP including infection, anemia, vitamin deficiency, and oxygen supplementation. In the 1950s, Patz and colleagues reported an association between supplemental oxygen use and the exponential increase of ROP and resulting blindness worldwide [111, 112]. As a result of the Cooperative Study undertaken to determine the effect of oxygen on ROP, neonatal units started limiting the use of oxygen delivered to pre-term newborns and the morbidity and mortality of these infants exponentially increased [113–115]. In the 1970s, advances in medical technology improved the ability to save the most premature and low birth weight infants, and the incidence of ROP again increased exponentially [116]. Over the years, numerous multi-center trials have been performed to study the treatment outcomes and pathogenesis of ROP.

Pathogenesis of ROP

Understanding of the pathogenesis of ROP requires a basic understanding of ocular embryology. The retinal vasculature begins its development around 16 weeks post conception. The vessels begin at the optic nerve and spread circumferentially, reaching the nasal ora serrata around the eighth month of gestation and is completed at the temporal ora serrata at 40 weeks gestation. In full term infants, the retinal vasculature is mature; however, in pre-term infants, the amount of mature retina is highly dependent on how prematurely the infant is born. The risk of normal development of the retinal vasculature depends on the gestational age of the infant: the younger the infant, the higher the risk.

The relationship between ROP and oxygen exposure has been well elucidated over the years. Researchers are now able to explain the relationship of oxygen and ROP on a molecular level. It is known that angiogenesis is controlled by oxygen tension in many tissues; however, the retina appears to be more at risk when a breakdown of oxygen control occurs. The relationship between retinal and choroidal circulations is suspected to be the reason behind this vulnerability [117]. When a premature infant is placed on supplemental oxygen, a rise in oxygen tension occurs, which in turn reduces the level of cytokines, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1), required for blood vessel formation [118]. Therefore, the formation of normal retinal vasculature stops. Secondary to the inner retina's interaction with the choroidal circulation, which continuously maintains a high level of oxygen, the retinal vessels constrict and irreversibly close [119]. This is referred to as the hyperoxic stage. The next stage, hypoxia, occurs when the premature infant is taken off supplemental oxygen. Because of the fall in oxygen levels in the retina, anigogenic factors (VEGF and Erythropoietin) are up-regulated and neovascularization occurs [119]. These new vessels may resolve spontaneously with adequate oxygenation; however, in severe cases, contraction of the new vessels places traction on the retina leading to retinal detachment and permanent vision loss.

The angiogenic factors most notable for their role in the pathogenesis of ROP include VEGF and IGF-1. As mentioned previously, VEGF is down regulated during hyperoxia causing retinal blood vessels to become irreversibly obliterated. VEGF is then up-regulated during hypoxia and promotes the formation of new blood vessels that contribute to the pathology seen in ROP [120]. With this knowledge, it is not surprising that anti-VEGF agents, such as bevacizumab, have been used with success in the treatment of ROP [18, 121–123]. This topic is discussed further in the section titled Treatment of ROP.

IGF-1 is also an important player in the development of normal retinal vasculature and in the pathogenesis of ROP. A deficiency of IGF-1 early in life causes abnormal retinal vascular development and contributes to the development of ROP. IGF-1 appears to contribute to ROP independent of oxygen related factors, such as VEGF [124].

Other factors such as Hypoxia-inducible factor 1α (HIF-1α), Placental growth factor (PlGF), and Erythropoietin (Epo) have also been implicated in the pathogenesis of ROP, although their roles are not as well understood. HIF-1α is responsible for controlling the formation of VEGF. It is down regulated during hyperoxia and increased production occurs when oxygen levels return to normal. Therefore, HIF-1α is important in both phases of ROP [120]. PlGF is similar to VEGF and shares many of the same biochemical properties; however, it has not been sufficiently studied in the pathogeneis of ROP and normal angiogenesis [120]. Epo is released during hypoxia and increases angiogenesis, as well as the number of erythrocytes. Studies have shown that a deficiency of Epo contributes to the first phase of ROP [125]. Current studies are evaluating the role of genetic factors, nitric oxide, apelin, adenosine, β-adrenergic receptors, inositol, and omega-3 fatty acids in the prevention and treatment of ROP [120, 126, 127]. Additionally, studies conducted in mice and several infants in utero suggest that increased light exposure decreases the risk of severe ROP [128]. Additional studies are underway to determine role of light exposure in ROP.

Oxygen Therapy and ROP

As mentioned previously, the role of oxygen therapy in the pathogenesis of ROP is well known. Michelson, Ashton et al., and Patz were the first to describe the effects of oxygen therapy on the developing retina in animal models [111, 112, 129, 130]. At that time, high oxygen levels alone were

believed to be responsible for the vascular attenuation seen in the developing retina. Since then, further studies have revealed that the duration of supplemental oxygenation is most strongly responsible for the development of ROP [115]. The incidence of ROP has remained high over the years and this can be attributed in large part to advancing technology that has enabled neonatologists to save extremely low birth weight infants. The availability of these advanced technologies varies throughout the world and accounts for the variability reported on the incidence of blinding ROP, reported as 10 % in the United States and 20 % or more in developing countries [131, 132].

After evidence that high levels of oxygen therapy were responsible for the epidemic of blinding ROP, neonatologists began to limit oxygen therapy for preterm infants. It quickly became apparent that insufficient oxygen therapy was devastating to the survival of preterm infants [113]. Studies in animal models suggested that oxygen therapy later in the course may reduce severe ROP by reducing the release of angiogenic factors responsible for the disease. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial studied this hypothesis. STOP-ROP tested whether higher oxygen saturation levels (96–99 % S_pO_2) as compared to lower levels (89–94 %) would decrease the progression to threshold ROP [133]. The study found that the group with higher oxygen saturations did not significantly reduce the number of infants requiring treatment for threshold ROP, nor did it increase the number of infants progressing from prethreshold to threshold disease [133].

Owen and Hartnett reviewed the recent studies published on the current role of oxygen therapy in ROP. They found these studies show no agreement in the appropriate target range for oxygen levels in premature infants [134]. The reasons cited for the inconsistencies found between the studies include differences in neonatal populations enrolled, as well as potential differences in NICU technology to monitor oxygen saturations. Some studies included infants from areas outside the United States, which strongly add to the potential variability in neonatal care and technology [164]

Classification of ROP

The classification of ROP follows criterion set forth by the International Classification of ROP (ICROP), a consensus statement published by a group of international ROP experts in 1984. The criterion was expanded in 1987. This system classifies ROP in regards to the location, extent, and severity of disease based on retinal landmarks, clock hours of diseased retina, and stage of neovascular response, respectively.

Location of disease is defined by three concentric zones surrounding the optic disc. Zone I is the innermost zone and its radius is twice the distance from the optic disc to the center of the macula, with the optic disc being the center of the circle. Zone II extends from Zone I to the nasal ora serrata (3 o'clock in the right eye and 9 o'clock in the left eye) and along the same line of curvature temporally. Zone III is the temporal crescent of retina anterior to Zone II [135] (see Fig. 2.3).

The extent of disease is recorded as clock hours of diseased retina. Each clock hour, for example from 12 o'clock to 1 o'clock, subtends 30° [135]. When the examiner is looking at the patient, the 3 o'clock position is nasal in the right eye and temporal in the left eye. The 9 o'clock position is temporal in the right eye and nasal in the left eye. The more clock hours of retina involved, the worse the retinal disease.

The severity of disease is classified in stages of abnormal retinal vasculature. In premature infants without ROP, the junction between vascular and avascular retina is very discrete. As ROP begins and advances, this junction becomes more apparent, and the observer can assign the pathology seen into one of the five stages of ROP. The highest stage seen in the eye is the stage assigned to that eye. This is an important distinction because different stages can be seen in different locations within the same eye.

Stage 1, the vascular-avascular junction is described as a white demarcation line. Often times, abnormal branching of vessels can be seen leading up to the demarcation line [136]. In stage 2, the demarcation line develops height and width and becomes a ridge extending above the retina. Tufts of neovascularization may be seen posterior to the ridge and on the

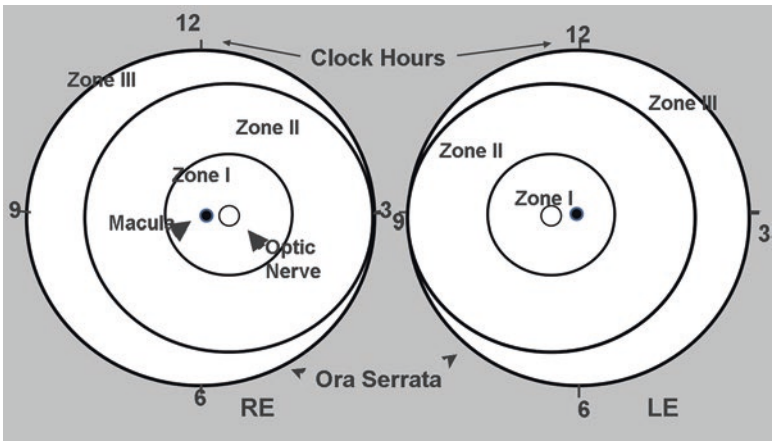

Fig. 2.3 Standard retinopathy of prematurity (ROP) classification zones and their location relative to the optic nerve head. (Reprinted from International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991–9 [136]. With permission from the American Medical Association.)

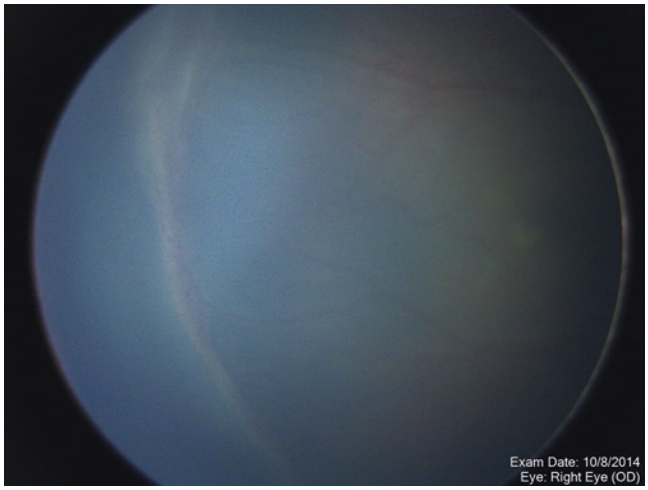

Fig. 2.4 Stage 3 retinopathy with prematurity (ROP) demonstrating an elevated ridge with neovascularization posterior to the ridge in zone 2

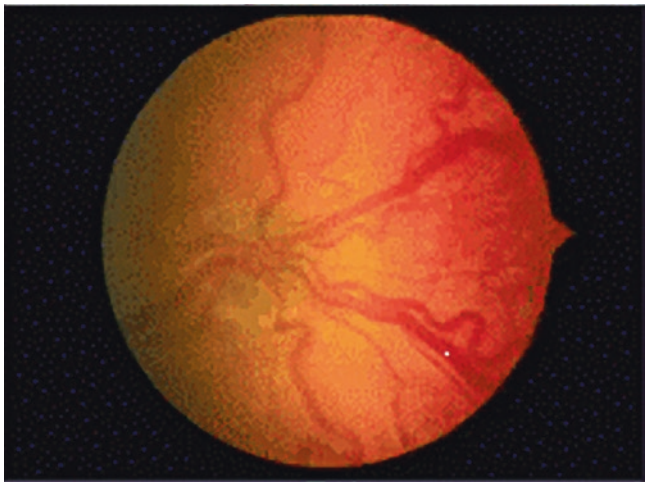

Fig. 2.5 Standard photograph of Plus Disease. (Reprinted from International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991–9 [136]. With permission from the American Medical Association.)

surface of the retina. This vascular tissue, called "popcorn", is not consistent with stage 3 neovascularization. Stage 3 refers to fibrovascular proliferation involving the ridge that extends into the vitreous. The severity of stage 3 can be classified into mild, moderate, or severe disease, depending on the extent of fibrovascular tissue extending into the vitreous [135]. Contraction of the neovascular tissue can lead to retinal detachment, which is diagnostic for stage 4 ROP. Stage 4 is divided into two groups: extrafoveal (stage 4A) and foveal (stage 4B) retinal detachment [135]. If there is a total retinal detachment, this is classified as stage 5. As mentioned previously, retinal detachments in the setting of ROP are tractional and usually funnel shaped. Stage 5 can be divided into groups based on the appearance of funnel (see Fig. 2.4).

In addition to changes at the vascular-avascular junction, changes in the posterior pole vessels can aide in determining the severity of ROP. Plus disease refers to venous dilation and arterial tortuosity of the posterior pole vessels. Additionally, plus disease can worsen to include findings such as poor pupillary dilation, iris vascular engorgement, and vitreous haze [135]. A standard photograph depicting the minimum amount of venous dilation and arterial tortuosity to diagnose plus disease is used commonly in practice and has also been evaluated in several multi-center ROP trials [133, 137, 138]. If qualifying vascular dilation and tortuosity is present in two or more quadrants, the diagnosis of plus disease is made (see Fig. 2.5).

In 2005, the ICROP criteria were revised. Several important additions were made during this revision to include descriptions of pre-plus disease and aggressive, posterior ROP (AP-ROP) [136]. Pre-plus disease is defined as the observation of venous dilation and tortuosity that does not meet the criteria of the standard photograph for plus disease. These findings indicate a risk for progression to plus disease

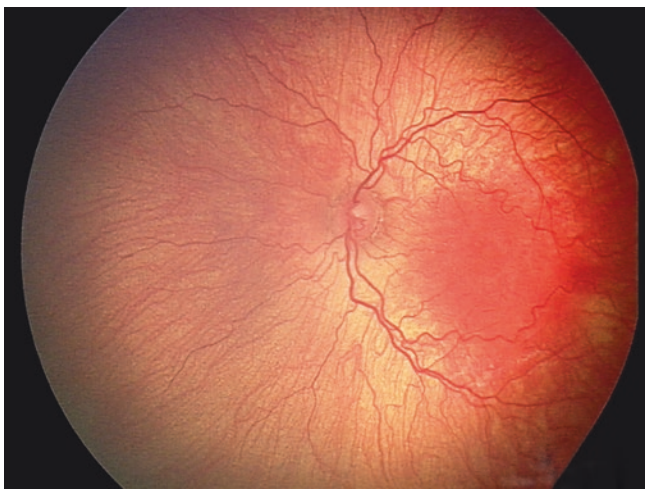

Fig. 2.6 Aggressive posterior retinopathy of prematurity (APROP) in zone 1 prior to laser treatment

and treatable ROP. AP-ROP (previously called rush disease) is a severe, rapidly progressive form of ROP that is seen in a very posterior location, usually zone I, and displays a prominence of plus disease and ill-defined extraretinal fibrovascular pattern. Plus disease is seen in all four quadrants, and it is often difficult to distinguish between the retinal veins and arteries secondary to significant dilation and tortuosity of both [136]. APROP may be easily overlooked by an inexperienced observer because the vascular-avascular junction may be relatively featureless, displaying only a flat neovascular network. APROP extends circumferentially and a circumferential vessel is often seen [136]. If left untreated, APROP often leads to stage 5 ROP (see Figs. 2.6 and 2.7).

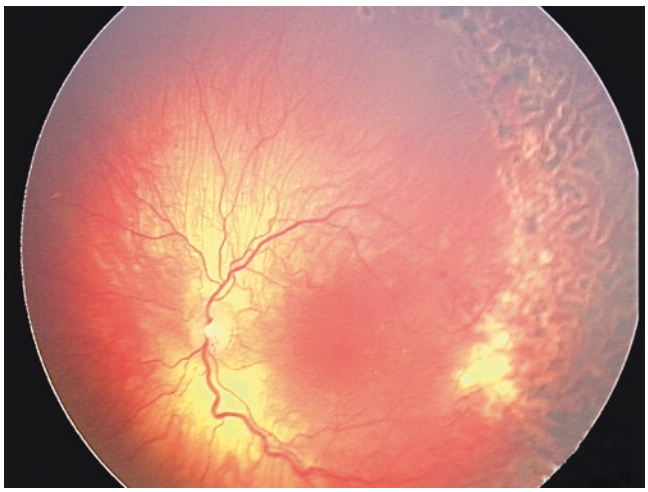

Fig. 2.7 Aggressive posterior retinopathy of prematurity (APROP) in zone 1 after laser treatment

Table 2.4 Recommendations for timing of first eye exam in premature infants

Gestational age at birth (weeks)	Age at examination (weeks)	
	Postmenstrual	Chronological
22[a]	31	9
23[a]	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4

[a]This guideline should be considered tentative rather than evidence-based for infants with a gestational age of 22–23 weeks because of the small number of survivors in these gestational age categories
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The proper documentation of ROP follows a standardized format for describing the zone and stage of disease. The zone is documented using Roman numerals I, II, or III. The stage uses numerical notation, stages 0–5. If plus disease is noted, a "+" can be placed next to the stage or plus disease can be written instead. If pre-plus disease is noted, this distinction can be written next to the ROP stage. For example, zone two, stage three with plus disease is written zone II, stage 3+.

In addition to describing the zone and stage of ROP above, a standardized drawing method is also used. The extent and stage of disease is drawn on a standard cartoon of the posterior pole depicting zones I, II, and III. For stage 0, the posterior pole vessels are drawn extending from the optic nerve and ending at the clinically observed vascular-avascular zone. Stage 1 is drawn as a single line for the amount of clock hours it is observed. Stage 2 is drawn as double lines and stage 3 is drawn as three lines with "x" depicting the area of neovascularization.

Screening Guidelines

The American Academy of Pediatrics, American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus have published standard guidelines for American hospitals to follow regarding the screening of immature infants for ROP. The confidence of these guidelines in detecting severe ROP is 99 % [139]. The goal of a hospital screening program is to identify the few premature infants that will require treatment for ROP from the larger number of at risk infants. In following these parameters, the goal is to decrease the amount of exams required to diagnose treatable ROP and to minimize the hospital resources required to examine a larger number of infants. This is also important because ROP examinations can be stressful and potentially harmful for the premature, sick infants [139].

The current guidelines recommend screening of all infants born at 30 weeks estimated gestational age (EGA) or earlier or infants weighing <1500 grams (g) at birth. Additionally, infants with EGA of more than 30 weeks or those with a birth weight between 1500 and 2000 g with an unstable clinical course as determined by the attending neonatologist should also be screened. Screening should be performed with indirect ophthalmoscopy after pupillary dilation and topical anesthesia to reduce any discomfort the exam may cause. One retinal examination is sufficient only if it unequivocally shows full vascularization of the retina in both eyes. Many ophthalmologists that screen for ROP prefer a second exam confirming the presence of full vascularization before discharging the patient from examinations.

The guidelines for initiating screening examinations for ROP was developed by the evidence gathered in the Cryotherapy for Retinopathy of Prematurity study (CRYO-ROP) and later confirmed by the Light Reduction in ROP study [137, 140]. Because the onset of severe ROP correlates better with postmenstrual age (gestational age at birth plus chronologic age), this is used over postnatal age when determining the appropriate time for initiating screening examinations. In other words, the youngest infants at birth take the longest to develop serious ROP [141]. The initial eye examination should take place at 31 weeks postmenstrual age or 4 weeks chronological age, whichever is later (see Table 2.4).

Follow-up examinations should be recommended based on retinal findings encountered on examination. Follow-up of 1 week or less is normally recommended for the following findings: (1) zone I, stage 1 or 2 or (2) zone II, stage 3.

Table 2.5 Recommended follow up intervals for premature infants with or at-risk for Retinopathy of Prematurity

ROP severity	Recommended follow-up
Stage 1 or 2 ROP: zone I	1-week or less follow-up
Stage 3 ROP: zone II	
Immature vascularization: zone I—no ROP	1- to 2-week follow-up
Stage 2 ROP: zone II	
Regressing ROP: zone I	
Stage 1 ROP: zone II	2-week follow-up
Regressing ROP: zone II	
Immature vascularization: zone II—no ROP	2- to 3-week follow-up
Stage 1 or 2 ROP: zone III	
Regressing ROP: zone III	
Plus disease zone I or II	The presence of plus disease in zones I or II suggests that peripheral ablation, rather than observation, is appropriate

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The patient should be re-examined in 1–2 weeks with the following findings: (1) zone I, no ROP (immature vascularization); (2) zone II, stage 2; or (3) zone I with regressing ROP. Two week follow-up is recommended for the following: (1) zone II, stage 1 or (2) zone II with regressing ROP. Follow-up of 2–3 weeks is recommended for the following: (1) zone II, no ROP (immature); (2) zone III, stage 1 or 2; or (3) zone III with regressing ROP. The parameters for treatment of ROP are discussed later in the chapter [141] (see Table 2.5).

It should be noted that there are several factors that can make the ROP examination difficult and may require further examination for better visualization. These factors include poor dilation, normal haze of the premature cornea, persistent tunica vasculosa lentis (most often related to early postconceptional age), vitreous flare or vitreous hemorrhage. It is important to document these findings as they often prevent an adequate screening examination and may warrant repeat examination sooner than otherwise necessary. It is also important to consider that some of these findings, including poor pupillary dilation, persistent tunica vasculosa lentis, vitreous haze, and vitreous hemorrhage, can be associated with active, severe ROP.

Age and retinal findings guide the decision regarding cessation of ROP examinations. Findings that suggest that the examinations can be stopped include the following: (1) zone III retinal vascularization without previous zone I or II disease; (2) full vascularization; (3) postmenstrual age of 45 weeks and no prethreshold disease (zone II, stage 3 or any zone 1 ROP) or worse ROP is present; (4) regression of ROP with absence of abnormal vascular tissue capable of progression or reactivation. If the infant is less than 35 weeks postmenstrual age, confirmatory exams, even in the presence of the above findings, may be warranted [139, 142].

Most ROP screening programs arrange for the examining ophthalmologist to examine infants in the neonatal unit once weekly [143]. The neonatologist and neonatal nurses are responsible for identifying infants meeting the screening guidelines outlined above and communicating this with the ophthalmologist and his/her staff. Many large ROP screening programs have a specific ophthalmology nurse or technician responsible for maintaining this list in the ophthalmology office. This person often accompanies the ophthalmologist during weekly ROP exams, as well. It is equally important that the neonatal and ophthalmology staffs communicate regarding which infants need continuing examinations. This can become problematic if the infant is discharged home or transferred before the follow-up examination date [143]. If either of these events occurs, it is the responsibility of the neonatologist and ophthalmologist to ensure that the baby is screened either as an inpatient at the new facility or as an outpatient in the ophthalmology office and for communicating previous findings and appropriate timing of repeat examination.

It is crucial to ensure that parents are informed of scheduled ROP examinations and to keep them updated regarding their child's ROP status. Ensuring that the parents understand the basics of ROP and the potential consequences, if left untreated, often helps in maintaining appropriate follow-up, especially when the patient is discharged from the hospital. Providing this information both verbally and in writing is helpful, and all encounters with the parents should be documented in the patient's medical record. However, parents of premature infants often feel quite overwhelmed and come into contact with many providers. Special family situations in which multiple caregivers are responsible for the child's care and in the setting of multiple births, it is difficult for parents and caregivers to remember to schedule and keep follow-up appointments for ROP screenings [143]. Often, significant follow-up efforts on the part of the ophthalmology staff are required to ensure that screening and treatment is occurring as necessary. In some cases, when multiple appointments are missed or are not occurring at timely intervals despite the staff's efforts to arrange for the patient to come to clinic, social services or even law enforcement may be required to become involved to ensure the appropriate care is received.

The medicolegal risk for those who examine and treat ROP is high. Even with the best of screening programs as described above, ROP can still be a blinding disease [144]. These risks can be minimized with good training, diligent screening programs, and effective communication with the families of at risk patients.

Treatment of ROP

The CRYO-ROP study defined the criteria for threshold, or treatable, ROP, which is defined as five or more contiguous or eight cumulative clock hours of neovascularization (stage 3) in zones I or II with plus disease. Prethreshold disease is a term used for ROP that has a high risk for meeting threshold criteria. With the revision of the ICROP criteria, the number of clock hours involved became less important and plus disease became a requirement for treatment (except for zone 1, stage 3 disease) [145]. The terms threshold and prethreshold are not commonly used today and have been replaced with the terms type I and type II ROP [109]. Type 1 ROP (high-risk prethreshold) is defined as any one of the following: (1) zone I, stage 3 without plus disease; (2) zone I, any stage with plus disease; or (3) zone II, stage 2 or 3 with plus disease. Type II ROP (low-risk prethreshold) includes any one of the following: (1) zone I, stage 1 or 2 without plus disease or (2) zone II, stage 3 without plus disease. The ET-ROP study found that patients have a more favorable outcome if treated prior to developing threshold disease. The recommendation now is that patients with type I ROP be treated within 48–72 h of diagnosis [138, 143]. If AP-ROP is detected, treatment may be warranted emergently.

Traditionally, cryotherapy was the preferred treatment for type I ROP. However in recent years, laser photocoagulation has replaced cryotherapy as the treatment of choice. The proposed mechanism of action for laser photocoagulation is that ablation of the peripheral retina decreases the stimulation for neovascularization by destroying the retinal tissue responsible for cytokine production that induces neovascularization. Treatment of the peripheral avascular retina is accomplished with transpupillary diode or argon laser. Spots are typically placed in a nearly continuous pattern, 1–1.5 spot sized widths apart [146]. Each laser technique is associated with complications many of which are undesirable, including decreased peripheral vision, intraocular bleeding, high myopia, macular dragging, cataract formation, and/or retinal detachment. It has been established that cataract formation is more common with argon laser [15, 17]. Laser photocoagulation can be performed in the neonatal intensive care unit or in the operating room with sedation or general anesthesia. Often times, general anesthesia with intubation is required for precise laser treatment, which is a major disadvantage in the eyes of neonatologists, ophthalmologists, and parents. The decision regarding anesthesia and location of treatment ultimately depends on the medical status of the infant, preferences of the treating ophthalmologist and neonatologist, and hospital protocols. Another major disadvantage of laser is that ROP may continue to progress for at least a week following successful laser treatment. The reason for this is that VEGF is already present in the vitreous prior to laser, thus it continues to stimulate neovascularization [121]. Only the formation of additional VEGF is halted with laser treatment.

Secondary to the lasting side effects and undesirable outcomes of laser photocoagulation, there have been many efforts to find a less destructive and more effective treatment. This is especially important in cases of zone I, posterior zone II, and AP-ROP, when laser treatment causes permanent damage to the posterior retina [121]. Recently, the use of anti-VEGF agents, popular in the treatment of other retinal disorders including wet macular degeneration and diabetic retinopathy, have been used as an off label treatment for type I ROP. The appeal of treatment with anti-VEGF agents is that it inactivates VEGF already present in the vitreous. The most widely used anti-VEGF agents include bevacizumab (Avastin®) and ranibizumab (Lucentis®). Bevacizumab is a complete antibody, rather than an antibody fragment like ranibizumab, giving it less ability to penetrate retinal tissue and less potential to escape the eye [121]. Additionally, the newest anti-VEGF agents, known as VEGF traps (Eyelea®), have been used with some success in animal models [147].

The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) study demonstrated that bevacizumab was a successful intervention for eyes with zone I and posterior zone II, stage 3+ disease, and potentially superior to laser therapy for zone I retinopathy [121]. However, the BEAT-ROP trial was not powered to evaluate safety, and few studies have investigated the global effects of bevacizumab in the pediatric population, so the effects of a VEGF-antagonist on the developing child remain largely unknown.

One of the major advantages of anti-VEGF therapy is that it is delivered directly to the vitreous through intravitreal injection at the bedside without sedation or anesthesia. Often, only a single injection is required to stop angoiogenesis. As mentioned previously, the use of this less destructive treatment is desirable when severe posterior disease is present and in cases of AP-ROP [122]. Studies have shown that even after treatment with anti-VEGF, vascularization of the peripheral retina continues, which is vastly different from the ablative effects of laser treatment. Additionally, myopia is not a common side effect of anti-VEGF therapy. Lastly, earlier treatment may be justifiable with anti-VEGF therapy as opposed to laser because of its lack of irreversible damage to the retina [121, 148].

There are also controversies regarding the disadvantages of anti-VEGF therapy. As mentioned previously, the major concern is potential ocular and systemic complications when using these drugs in neonates. With multiple centers of rapid blood vessel growth, such as the brain, lungs, and kidneys, premature infants may be more vulnerable to the systemic effects of anti-angiogenic therapy. It is known that anti-VEGF causes serious systemic side effects when used in repeated, large doses in cancer patients; however, the drug is given as a single, low dose intravitreal injection to premature infants with ROP [121]. Recent evidence suggests that bevacizumab may enter the systemic circulation after intravitreal injection; adults treated with intravitreal bevacizumab dem-

onstrated significantly lower blood VEGF levels than those not treated with the medication even 1 month after injection [149]. In a study of infants previously treated with laser, bevacizumab levels were measured in the serum 2 weeks after intravitreal administration, and reported that the serum concentration of bevacizumab increased from 946 to 1214 ng/mL from 1 to 2 weeks after a 0.5 mg intravitreal injection. Additionally, a significant negative correlation between serum concentration of bevacizumab and VEGF was found [150]. A recent case study of 13 patients suggested that systemic development up to age five is preserved after intravitreal bevacizumab, but the authors noted that their study was limited by its small patient number and lack of a control group [151]. The Pan-VEGF Blockade for the Treatment of Retinopathy of Prematurity study (BLOCK-ROP) attempted to evaluate the safety and tolerability of bevacizumab in newborns with APROP by assessing two doses of anti-VEGF therapy. However, the study was cancelled in first phase secondary to lack of patient enrollment. A randomized, controlled trial evaluating the safety of anti-VEGF therapy is warranted to answer these lingering questions regarding long-term safety and systemic outcomes in neonates.

Another potential disadvantage of anti-VEGF therapy is that it is not beneficial for stage 4 or 5 ROP. While anti-VEGF is quite beneficial for decreasing angiogenesis, it has no effect on fibrosis and may accelerate retinal detachment by triggering contraction of the fibrovascular tissue [152]. Local complications of intravitreal injections include infectious and traumatic events. If the injection is given too anteriorly, there is risk of injuring the lens which may lead to cataract formation. Additionally, retinal tears and detachments may occur, but the risk is decreased by using a smaller gauge, shorter length needle [152]. Good sterile technique and administration of topical antibiotics for 1 week following the procedure decrease the risk of infection. Lastly, there are concerns that retinal development may be adversely affected in eyes treated with bevacizumab. Histopathology on a pair of premature, infant eyes that were examined 20 weeks following intravitreal injection revealed that all layers of the retina had developed normally and inner retinal vessels had advanced beyond the vascular-avascular junction noted at the time of injection [153].

Recurrence of disease can be seen with any of the aforementioned treatments. After laser treatment, recurrent disease has been noted to occur as soon as 1 week following the procedure and up to 55 weeks post menstrual age [152]. Treatment for recurrence after laser includes repeat laser treatment with or without vitrectomy and/or anti-VEGF injection. It is important to note that there is a risk that the anti-VEGF agent may escape the eye more rapidly in an eye previously treated with laser, thus necessitating multiple injections. Recurrence of disease after anti-VEGF tends to occur later than that seen with laser treatment, usually between 1 month after injection and up to 70 weeks post-menstrual age [152]. Therefore, it is very important for infants treated with anti-VEGF agents to be followed for a longer period of time. Treatment for recurrence after anti-VEGF injection includes additional injections, if discovered prior to the development of fibrovascular traction, or laser therapy with or without vitrectomy.

The treatment of late-stage ROP (stages 4 or 5) differs from that of acute phase disease. As mentioned previously, in late-stage ROP tractional disease is present making laser and anti-VEGF injection unsuitable for treatment. Surgery for stage 4 and 5 retinal detachments includes vitrectomy with or without scleral buckle. Many retina specialists advocate the treatment of stage 4a ROP; however, there are concerns that intervention may cause more harm in addition to the potential medicolegal consequences. It is well known that stage 5 detachments have universally poor outcomes; therefore, earlier intervention is often desired for stage 4a and 4b ROP [154]. Several studies have shown success with vitreoretinal surgery for stage 4a ROP in regards to stopping detachment progression and visual outcomes [155, 156].

Evaluation Modalities

The standard evaluation modality for ROP screening still remains binocular, indirect evaluation and treatment of ROP [157]. However, advancements in imaging technology, along with a shortage of trained or willing ophthalmologists in both the United States and the developing world, have employed the use of telemedicine in ROP screening. The photographic screening for retinopathy of prematurity (photo-ROP) determined that remote use of digital fundus images is a useful adjunct to standard indirect ophthalmoscopic exams of the retina [158]. Since then, various digital photographic systems have been studied as screening tools for the documentation of ROP for telemedicine purposes and have been found to be useful in the detection of clinically significant ROP [158–171]. Additional studies evaluating software providing analysis of posterior pole vessel diameter and tortuosity have also shown promising results in diagnosing plus disease and reducing interexaminer variability of this diagnosis [160, 172–175]. This technology may also prove to be beneficial in predicting the need for treatment of severe ROP prior to the clinical diagnosis of plus disease [176].

One of the primary limitations for broad implementation digital imaging for ROP is cost of the imaging system, especially in the developing world [177]. However, considering the alternative cost of employing additional medical staff, this alternative may be more cost effective. Additionally, the technology is portable, so it could be used for multiple regional hospitals, making this option more cost effective [177]. Other barriers to widespread implementation include limited internet access, parental and staff acceptance, liability, and lack of insurance coverage and reimbursement [178].

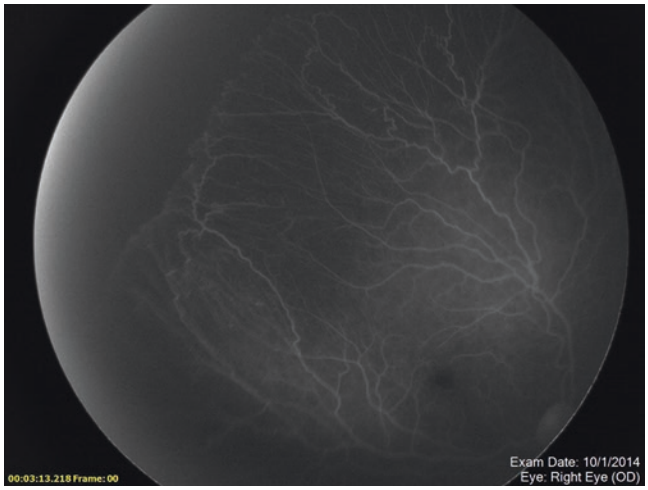

Fig. 2.8 Intravenous fluorescein angiogram in a premature infant at 37 weeks post conceptual age 7 days after treatment with intravitreal Bevacizumab for threshold retinopathy of prematurity

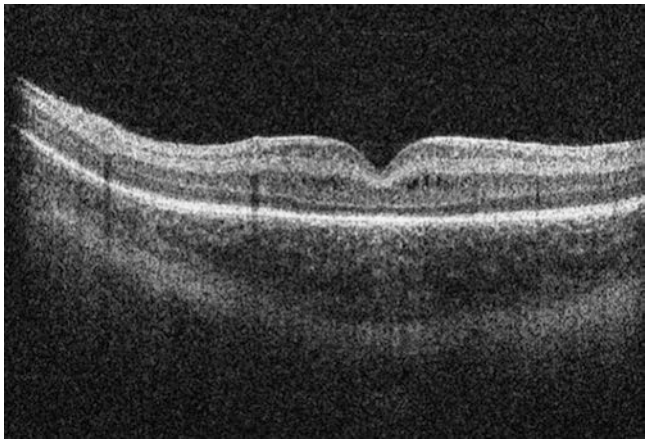

Fig. 2.9 Spectral domain ocular coherence tomography (SD-OCT) of the foveal region (Bioptigen, Inc, Morrisville, NC) in a premature infant at 35 weeks post conceptual age

Similar to ROP programs within a single institution, it is equally, if not more important to have designated office staff to manage the telemedicine program and to ensure examinations and referrals are occurring as needed. Communication between neonatologists, ophthalmologist, and patient caregivers remains of utmost importance.

Advancements in imaging technology have provided additional modalities to allow ophthalmologists to monitor changes in the retina over time. These modalities include intravenous fluorescein angiography (IVFA), spectral domain optical coherence tomography (SD-OCT), and ultrasonography. IVFA has allowed researchers to compare the extent of retinal vascularization in eyes treated with laser compared to those treated with anti-VEGF therapy. We know that laser therapy permanently ablates the peripheral retina but little is known about the effects of anti-VEGF on the peripheral vasculature. The BEAT-ROP trial concluded that peripheral vascular development continued after injection with intravitreal anti-VEGF agents. However, further research following IVFA studies after anti-VEGF therapy suggest that while the peripheral retinal pathology does resolve, the peripheral retina may remain incompletely vascularized with leakage at the vascular-avascular junction [179–181] (see Fig. 2.8).

Ultrasonography can be used as an adjunct screening tool in ROP to document changes overtime. Several investigators successfully documented all stages of ROP with ultrasonography; however, earlier stages are difficult to detect [182]. This technology may be useful in patients with poor pupillary dilation or hazy media, and as well as an initial screening tool in telemedicine programs or developing countries with a shortage of qualified examiners [182–184]. Recent studies have determined the utility of SD-OCT in demonstrating subclinical retinal pathology in ROP [184]. Changes documented in foveal architecture are felt to represent foveal pathology seen in older ROP survivors [23]. These changes include retention of inner retinal layers and absent foveal depression, although these changes may not correlate with visual acuity. Instead, photoreceptor maturation may be a better indicator of final visual outcome in these patients [185] (see Fig. 2.9).

Additional ROP Studies

In addition to the ROP studies previously mentioned in the text, there are other ROP studies worthy of mention and reference. The use of beta blockers in treatment of ROP was evaluated by the safety and efficacy of propranolol in newborns with Retinopathy of Prematurity study (PROP-ROP). Newborns receiving systemic propranolol showed less progression to stage 3 ROP and required fewer laser and anti-VEGF treatments. However, serious adverse effects including hypotension and bradycardia were encountered in these infants [186]. The PINT ROP, WIN-ROP, and CHOP ROP studies evaluated and validated clinical prediction models, including postnatal weight gain to determine the risk of severe ROP. Future implications of the algorithms developed by these studies may allow ophthalmologists to reduce the number of ROP screening examinations on preterm infants [187–189].

Cataracts Unique to Premature Babies

Since the establishment of routine ophthalmologic examination in premature infants in 1996, it became apparent that a significant number of the smaller premature babies develop transient lens opacities [12, 13]. Described first by Dr. McCormick, the cataracts always exhibited bilateral symmetry and appeared to consist of vacuoles in the poste-

rior cortex near the lens capsule and to lie in relation to the posterior inverted Y suture. McCormick described seven infants born with clear lenses on the first, second, and third day of life who developed cataracts between the eighth and fourteenth days of age and persisted for between 10 and 18 days. McCormick attributed the lens vacuoles to a non-specific metabolic disturbance since they appeared to be completely reversible [12]. Alden, Kalina and Hodson noted transient cataracts in 2.7 % (19 of 692) babies examined in a single NICU neonatal intensive care unit from January 1, 1969 and August 1, 1971. The lens opacities which were observed were similar to those described by McCormick and according to these authors were sufficiently characteristic to prevent confusion with any other type of cataract. They noted that the resolution occurred in a manner opposite to formation, with initial clearing centrally and most prolonged retention of the vacuoles at the apices of the posterior lens suture. Interestingly, after a case-control analysis the authors concluded that the time taken to regain birth weight was longer in the patients with cataracts (18 ± 7 days) than in the control infants (12 ± 6 days) ($p < 0.05$) These authors suggested an osmotic factor as the most likely etiologic agent [13].

Another unique category of cataracts infants is the development of *Candida* lens abscesses in premature infants with history of neonatal candida sepsis. Isolated infections of the neonatal lens can occur in the absence of endophthalmitis. It has been hypothesized that these lens abscesses are initiated when fungal organisms spread hematogenously to the neonatal lens via a patent tunica vasculosa during episodes of candidemia. After regression of the tunica vasculosa lentis, the fungal organisms become effectively sequestered from the immune system surveillance and exposure to systemically administered anti-fungal agents. The lenticular opacity may be evident at variable times after neonatal *Candida* sepsis/fungemia and onset can be delayed for months. Treatment regimens for lens abscesses have consisted of lensectomy, anterior vitrectomy, and intravitreal injection of antifungals in addition to systemic treatment. Cultures should be obtained of the aqueous, the lens/vitreous aspirate or any associated anterior chamber membranes. The prognosis for functional vision is poor in these eyes [81, 83, 190–192].

Endogenous bacterial endophthalmitis in preterm babies can also present with leukocoria. This can be confusing for the treating pediatrician or neonatologist but should be readily recognized by the examining ophthalmologist because of the location of the opacity behind the lens. In these cases, vitreous inflammation can results in dense white vitreous opacities that produce the grey-white reflex. Endogenous endophthalmititis can be initially misdiagnosed and can result in poor visual prognosis if the treatment is delayed. Treatment generally involves vitreous biopsy and culture with intravitreal administration of antibiotics. Vitrectomy may be required to clear the visual axis. Secondary cataract formation is common post-vitrectomy and also secondary to the significant intraocular infection and inflammation. Early systemic antibiotic therapy remains the cornerstone of treatment. Vitrectomy can be therapeutic [76, 88, 105].

Bilateral transient cataracts have been reported in a preterm newborn during treatment with linezolid therapy and relieved 1 week after the discontinuation of the therapy. Linezolid is the first member of the oxazolidinone antibiotic therapy, indicated for serious infections caused by resistent organisms (vancomycin resistent enterococcus (VRE), methicillin resistant. *S. aureus* (MRSA), methincillin resistent coagulase negative staphylocci and penicillin resistent *S. pneumonia*) in infants and child. Treatment with linezolid had been associated with reversible thrombocytopenia developing after the second week of therapy as a side effect reported in children. A premature baby born at 26 weeks gestation had a screening ROP exam that revealed avascular zone 2 without plus disease at 31 weeks of corrected age. This baby was diagnosed with late onset sepsis on day 40 because of apnea and fever. Although treated with vancomycin and meropenem, VRE was isolated on blood culture on day 47. Thereafter, vancomycin was discontinued and linezolid (10 mg/kg/day, twice daily) was started. Routine ROP examination was performed on day 50, and vacuoles located in the peripheral portion of the lens close to the posterior capsule were observed, on the third day of linezolid treatment. The cataracts were also evident on day 13 of linezolid therapy. Follow-up blood cultures were negative on Day 18 of therapy and thereafter linezolid was discontinued. There was regression of the cataracts, with no sign of cataract on the eye examination performed 1 week later [193].

As described earlier, laser ablation remains effective therapy for proliferative retinopathy of prematurity. However, phthisis bulbi secondary to anterior segment ischemia following laser photoablation for threshold ROP has been reported [194, 195].

Cataracts have been reportedly consistently among infants treated for threshold ROP with laser photoablation [16, 196–198]. Cataract formation was not common in the earlier era when threshold ROP was treated with cryotherapy [199].

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Ocular Manifestations of Allergic and Immunologic Diseases

3

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Introduction

The immune response is a highly intricate system that serves as the primary defense against infection and/or foreign body intrusion into the human body. Without a strong immune system, individuals would be vulnerable to numerous different types of infections. This defense system works by both innate and adaptive immune responses. The innate immune system responds immediately to an antigen by using circulating leukocytes and humoral elements. The adaptive immune system serves as a long-term defense with T and B cells that are antigen specific and have the benefit of memory. Immunologic and allergic diseases result from a malfunctioning immune system.

As the eye contains many components of this complex immune system, many systemic diseases can manifest in the eye. The eye is unique in that it does not contain any lymphatic tissue. Lymphocytes, however, reside in the lacrimal gland and in the substantia propia of the conjunctiva. This in combination with the tear film, sclera, uvea, and retina, all serve as part of the immune system of the eye. The purpose of this chapter is the review the ocular findings in relation to the allergic and immunologic diseases.

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Allergy

Definition

Allergy and other hypersensitivity disorders are an exaggerated or inappropriate response of the immune system. These disorders can lead to numerous diseases that are both immune and autoimmune. Hypersensitivity reactions can be classified into four types, as described by Gell and Coombs [1].

Type I: This hypersensitivity type reaction is Immunoglobulin E (IgE)-mediated. An antigen binds to IgE, which is already bound onto tissue mast cells triggering degranulation and release of histamine, leukotrienes, and other chemotactic factors. These mediators cause vasodilatation, increase in capillary permeability, smooth muscle spasm, mucus hypersecretion, and tissue infiltration with eosinophils, type 2 hyper cells, and other inflammatory cells. This type of reaction includes the atopy disorders (allergic asthma and rhinitis), urticaria, anaphylaxis, and conjunctivitis.

Type II: Type II hypersensivity reaction is the result of an antigen-antibody complex on a cell surface. This cell-mediated cytotoxic response leads to a cascade of cytotoxic mediators (natural killer cells, eosinophils, macrophages, and complement factors) to result in cell tissue damage, including lysis of the affected cell.

Type III: This type of hypersensitivity reaction is an immune complex disease. The inflammation results from an antigen-antibody complex that circulates and deposits within the vasculature and tissue. These complexes can activate the complement system and lead to the release of inflammatory mediators.

Type IV: Type IV hypersensitivity reactions are a delayed T-cell mediated response. T cells are sensitized to an antigen after contact. These T cells are activated in response to a

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re-exposure to the antigen. This causes the release of cytokines and other factors to cause a direct toxic effect to tissue.

Allergy is a disorder of the immune system; it can affect multiple systems in the body. Allergy in childhood is common and its effects can hinder the patient's school performance, social and physical activities. Allergic diseases are classically characterized by an ability to create an immunoglobulin E (IgE) antibody response to a specific allergen, which is a Type I hypersensitivity reaction. This can manifest in many ways, such as itchy, watery eyes, stuffy nose, wheezing, hives, and anaphylaxis. Atopic disorders include asthma, allergic rhinitis, urticaria ("hives") and atopic dermatitis. The development of these atopic disorders is strongly influenced by genetic and environmental factors [2].

History

In the early 1900s in Vienna, Austria, Clemens von Pirquet and Bela Schick proposed the term *allergy* to describe an inappropriate reaction to an *allergen*, a protein that causes hypersensitivity [3]. Allergy comes from the ancient Greek words *allos*, meaning "other", and *ergon*, meaning, "reaction" [4]. Initially, all forms of hypersensitivity were classified as allergies. Later, Philip Gell and Robin Coombs described four types of hypersensitivity reactions that had a common link to a disorder in the immune system [3]. These are now known as the hypersensitivity reactions I–IV. Another major breakthrough in allergy was the discovery of immunoglobulin E by Ishizaka and Ishizaka [5], and the laboratory means to measure IgE by Wide and et al. [6].

Epidemiology

Allergies are a widespread disease that affect many people. Atopic diseases, including atopic dermatitis, allergic rhinitis, and asthma, affect approximately 20 % of the population worldwide [2]. Atopic diseases have been a major and increasing problem in industrialized countries. The International Study of Asthma and Allergies in Childhood (ISAAC) reports a prevalence of approximately 1.2 million children, in 98 countries have allergic rhinoconjunctivitis, asthma and eczema [7]. Prevalence of atopic dermatitis in children ages 13–14 varies from 0.3 to 20.5 %, allergic rhinoconjunctivitis 1.4–39.7 %, and asthma 1.6–36.8 % in 56 countries [8].

The prevalence of atopic dermatitis in the English population has been about 20 %, with the age of onset ranging from 3 to 11 years of age without a gender preference. Another study by Illi et al. done in Germany showed that approximately 55 % of patients with atopic dermatitis will develop it in the first year of life, and 50–80 % of these patients will develop another aspect of the atopic march such as respiratory disease later in life [9].

Allergic rhinitis (AR) affects 30–60 million people per year in the United States, of which 40 % are children. The risk factors for AR are a family history of atopy, serum IgE levels > 100 IU/mL before 6 years of age, higher socioeconomic class, and presence of a positive allergy skin prick test (SPT) [10].

The higher socioeconomic class seems to correlate with the children being washed and kept "clean" more than children who are allowed to play, crawl, etc. on the ground. Children who have more exposure to possible infectious agents presumably keep their immune system occupied in fighting those microbes, and their immune cells develop along a pathway called the Th-1 pathway. Children whose immune systems are not so preoccupied have their immune cells develop along the "allergic", or Th-2 pathway. This explanation is known as the "Hygeine Hypothesis," initially proposed by Strachan, in 1989, and further refined by Graham Rook, in 2000 [11, 12].

Asthma affects up to an estimated 300 million people worldwide [13]. About 80 % of patients report symptoms of asthma before 6 years of age [14]. The worldwide prevalence rates of wheezing, according to the ISAAC phase III study, was 11.6 % for 6–7 year old children and 13.7 % for 13–14 year old children [15].

The incidence of anaphylaxis is approximately between 50–112 episodes per 100,000 person-years. An estimated prevalence is 0.3–5.1 %. These numbers are about 3 times higher for children ages 0–4 years than that of other groups. The recurrence rate of anaphylaxis associated with atopic disease is higher than those without atopic disease [16].

Allergic conjunctivitis affects up to 20 % of the population. Of patients who have allergic rhinitis, 60 % will have associated allergic conjunctivitis [17]. The prevalence of asthma was 10.7 % in patients with rhinoconjunctivitis [18].

Systemic Manifestations

Allergy can present in many different forms. Allergy, as mentioned before, is a Type I hypersensitivity reaction. The two main components of allergy are the atopic diseases and anaphylaxis. Each one of these entities presents with specific signs and symptoms.

Atopic Dermatitis

Atopic dermatitis (AD) tends to be the first step in the atopic march. Atopic dermatitis is a Type I hypersensitivity reaction. It is a chronic pruritic skin condition. Its onset ranges from 3 to 11 years of age but can occur as early as 1 month of age. Risk factors for poor prognosis of the AD are a parental history of this disease or concomitant early respiratory symptoms like wheezing. Triggers of AD include stress, food allergens, microorganisms like *S. aureus*, and chemical irritants [19]. AD however has more an endogenous source, whereas allergic contact dermatitis has an exogenous source.

Infants present with erythematous and pruritic papules and vesicles on the face and scalp. AD in childhood (from age 2 onwards) have more chronic skin involvement that includes lichenified papules and plaques involving the hands, feet, antecubital and popliteal regions. As AD progresses into adulthood starting at puberty, the skin becomes dry and scaly. These patients develop erythematous, lichenified papules and plaques on the flexural folds, face, neck, arms, back, hands, fingers, and toes [19].

Contact allergic dermatitis (CAD) due to an allergen is a Type IV hypersensitivity reaction. The etiology of CAD is by direct damage to keratinocytes and does not require prior sensitization. Symptomatically it is similar to AD, however, patients with CAD are typically refractory to standard treatments for AD. These patients will develop new sites of dermatitis such as the eyelids and hands. If a patient is suspicious for CAD, a work up including allergy skin testing, possible patch skin testing, should be done [20].

Allergic Rhinitis

Allergic Rhinitis (AR) is a chronic IgE-dependent respiratory disease of the upper airway. AR can begin as early as 2 years of age and increase in prevalence over time [21]. Patients with AR have symptoms of rhinorrhea, sneezing, nasal congestion, and/or naso-ocular pruritis. Other common symptoms include irritability, cough, postnasal drainage, and fatigue. Children, however, may have different symptoms of sniffing, snorting, throat clearing, and coughing as they usually do not blow their noses. Children with AR can also have facial abnormalities, dental malocclusions and snoring due to chronic mouth breathing from nasal obstruction [22]. These symptoms of AR can occur during specific seasons or be perennial with or without seasonal exacerbations. AR is caused by an allergic reaction causing mucosal inflammation by infiltrating inflammatory cells and pro-inflammatory mediators [10]. AR is associated with asthma, sinusitis, and allergic conjunctivitis.

The nasal mucosa can exhibit edema with pallor or bluish hue. Clear nasal and posterior pharynx drainage can be observed. There may be a serous effusion behind the tympanic membrane when significant nasal mucosal edema and eustachian tube dysfunction exist. Patients can develop the "allergic salute", rubbing the nose in a vertical fashion in an attempt to open the nasal passages. This very frequently leads to a transverse nasal crease across the nose. Allergic shiners, infraorbital discoloration from venous stasis, and Dennie-Morgan lines, creases in the lower lids, can also be seen [22].

Allergic Asthma

Asthma is a chronic inflammatory disease of the airway that is associated with an eosinophilic response. The mucosa is characterized by infiltration with eosinophils, CD4+ cells, mast cells, and expression of IgE receptors [23]. Following an allergen exposure, there is an increased presence of Th2-driven inflammation [24]. It usually starts in childhood and may be associated with allergic rhinitis and/or atopic dermatitis. Risk factors for asthma include atopic dermatitis, allergic rhinitis, and elevated serum IgE levels in the first year of life, peripheral blood eosinophilia, and family history of atopy.

The symptoms include recurrent attacks of coughing, wheezing, chest tightness, and airflow obstruction. These patients may also have shortness of breath. On examination, wheezing (expiratory greater than inspiratory) can be heard on auscultation. Diagnostic testing would show abnormal pulmonary function tests.

Anaphylaxis

Anaphylaxis is a serious and pronounced IgE-mediated allergic reaction with rapid onset that occurs after an exposure to an allergen. Common allergens can include food substances, insect stings, medications, vaccines, and inhaled particles of latex in a previously sensitized individual. There is involvement of the skin and/or mucosal tissue that results in varying degrees of hives, pruritis, edema, and angiodema of the lips, tongue, and uvula. This can be accompanied by at least one other category of symptoms such as dyspnea, wheezing, bronchospasm, stridor, hypoxemia, hypotension, hypotonia, syncope, or incontinence. Patients may also have crampy abdominal pain or vomiting [25]. If left untreated, anaphylaxis can lead to death.

Ophthalmic Manifestations

Allergic diseases in the eye can manifest with a myriad of symptoms including conjunctival injection, itchy eyes, burning, stinging, tearing, and photophobia. These symptoms can be seasonal, recurrent, and/or chronic. Ocular allergy is a Type I (IgE mediated) hypersensitivity reaction. The interaction between the allergen and IgE specific antibody occurs on the surface of Mast cells in the conjunctiva. This reaction creates a cascade of events leading to the release of histamine. The histamine release causes the symptoms of itching, redness by vasodilation of conjunctival vessels, and edema. Ocular allergy can vary in severity.

Seasonal and Perennial Allergic Conjunctivitis

Seasonal Allergic Conjunctivitis (SAC) is the most common form of ocular allergic disease. About 70 % of these patients will have associated atopic findings. This most often occurs in the Spring and Fall seasons as it is triggered by airborne environmental factors such as pollen. Perennial Allergic Conjunctivitis (PAC) is a less severe form of allergic conjunctivitis. This is typically encountered all year long and can be associated with other environmental allergens such as dust or pet dander. Approximately 79 % of patients with PAC

do have seasonal exacerbations [26]. Both SAC and PAC can be associated with allergic rhinitis.

SAC and PAC are mast cell-mediated hypersensitivity reactions resulting from allergens reacting with IgE antibodies. The IgE antibodies bound to conjunctival Mast cells release histamine, leukotrienes, prostaglandins, and other mediators. The acute response can occur as rapid as 5–30 min. Next, an upregulation of adhesion molecules leads to an increase in inflammatory cells in the conjunctiva. In the conjunctival late phase, additional Mast cell activation occurs [27].

Patients with SAC and PAC typically present with an acute onset of bilateral itchy red eyes. This can also be associated with tearing and burning. Signs of Seasonal Allergic Conjunctivitis include conjunctival injection and papillary reaction. This can occasionally be severe enough to lead to conjunctival chemosis and edema. Patients may also present with eyelid erythema, edema, and allergic shiners. Rarely can these patients have cornea symptoms such as blurry vision or photophobia. SAC and PAC rarely result in significant vision loss.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is a chronic Type I hypersensitivity reaction that is perennial. This type of conjunctivitis typically starts in the late teenage years, and can persist well into adulthood. AKC has been reported to occur as early as 7 years of age [28]. AKC tends to be more severe than SAC and PAC, and can result in disabling vision loss. A family history of atopy (asthma and eczema) is common with greater than 95% of patients having eczema and 87% of patients having asthma [26].

These patients will complain of itching, burning, tearing, foreign body sensation, redness, photophobia, and blurry vision. On examination, patients with AKC will have signs of chronic inflammation of the eyelids such as eczematous erythema, scaling, and edema. Infraorbital skin creases, called Dennie-Morgan lines, are caused by this eyelid edema and thickening [26]. Allergic shiners, dark circles underneath the eyes from venous congestion, can also be seen [29]. De Hertoghe's sign, absence of lateral eyebrow, can be present in older individuals from chronic eye rubbing [30]. Blepharitis can also be seen when atopic dermatitis affects the anterior (from staphyloccoal disease) and posterior eyelids (from meibomian gland involvement) [28]. The conjunctiva of the lower lids can have papillae and scarring. This scarring can become severe and result in subepithelial fibrosis, fornix shortening, and symblepharon formation [31]. The involvement of meibomian glands can lead to an inadequacy of the tear film. From this, patients can also demonstrate symptoms and signs of dry eye, including foreign body sensation and punctate epithelial erosions of the cornea. In severe AKC, the cornea surface can become very irregular, desiccated and eventually lead to neovascularization [32]. This significant cornea involvement can lead to blindness. Other associated ocular findings with AKC include keratoconus, anterior and posterior subcapsular cataracts, and predisposition to herpes simplex virus [33].

Vernal Keratoconjunctivitis

Vernal Keratoconjunctivitis (VKC) is a combination of an IgE-mediated, T-cell mediated response, eosinophilic infiltration and activation, and non-specific hyperactivity [34]. It affects mostly males, especially those with a history of atopy, in the first two decades of life and tends to decrease or resolve by the third decade of life. VKC is more common in patients of Asian or African origin. It is predominant in warm climates and can occur all year long; however, it can have exacerbations in the Spring and Fall [26]. Symptoms of VKC present with intense bilateral pruritis that is induced by wind, dust, bright light, warm climate, and physical exertion associated with sweating [29].

There are two clinical subtypes of VKC: palpebral form and limbal form. These can occur alone or in combination. The palpebral form is characterized by the upper tarsal conjunctiva involvement: injection, discharge, papillae, and cobblestoning. The papillae are pathognomonic for VKC. The palpebral form of VKC is more common in temperate climates. These patients complain of intense photophobia and itching. The limbal form is characterized by thickening and opacification of the conjunctiva near the limbus. This form of VKC is more common in hotter climates and in patients of Asian and African descent. These patients are less likely to have a history of atopy [35]. Limbal VKC can have vision threatening sequelae. The superior cornea can become involved by the presence of Horner-Trantas dots. These are limbal nodules that look like gelatinous mounds on the superior cornea and are histopathologically filled with eosinophils and epitheloid cells. These can increase over time and become confluent. In the late stages, punctate epithelial erosions develop on the superior cornea and can coalesce to form a shield ulcer. This is a sterile cornea ulcer with underlying stromal opacification. Left untreated, a plaque containing mucus and fibrin deposits on the cornea epithelium. This can permanently impair visual acuity [36]. Patients with VKC can also develop an involutional ptosis, either from chronic inflammation of the tarsal conjunctiva and/or frequent rubbing of the eyelids [37]. Other ocular findings such as keratoconus and limbal stem cell deficiency have also been seen in patients with VKC [38]. Treatments of VKC by corticosteroid therapy can lead to ocular complications, such as steroid induced cataracts and glaucoma.

Giant Papillary Conjunctivitis

Giant Papillary Conjunctivitis (GPC) is a chronic inflammatory disorder that is caused by the irritation of the conjunctiva, usually superior) by an exogenous material. It has been

observed to occur in reaction to contact lenses [39], ocular prostheses [40], exposed nylon sutures [41], scleral buckles [42], cyanoacrylate glue [43], filtering blebs, band keratopathy [44] and limbal dermoid [45]. The etiology of this allergic reaction is a mixed mast cell and lymphocytic-mediated response to antibodies on the surface of these exogenous materials. Histologically, there is an accumulation of mast cells, basophils, and eosinophils in the conjunctival epithelium and substantia propia [26].

Patients with GPC present with symptoms of recurrent itching, tearing, discomfort, discharge, and blurry vision. The conjunctiva is injected. GPC due to contact lens intolerance, may also present with frequent contact lens decentration [46]. Signs on examination include thickened and hyperemic conjunctiva. There may be white or clear exudates on awakening. The superior tarsal conjunctiva will develop large papillae. Ptosis can also result due to chronic inflammation of the conjunctiva.

Contact Dermatoblepharitis

Contact dermatoblepharitis is dermatitis of the eyelids in reaction to a contact with an allergen such as medications or cosmetics, causing a local allergic reaction. This can present in either an acute or subacute fashion. An acute reaction is a Type I hypersensitivity reaction that can occur minutes after exposure. The symptoms are typically itching, eyelid erythema and edema, conjunctival injection and chemosis. Rarely can systemic anaphylaxis occur. It has been associated with medications such as bacitracin [47], cephalosporins, penicillin, sulfacetamide, and tetracyclines [48]. The subacute reaction is a Type IV delayed hypersensitivity reaction that occurs about 24–72 h after the use of the offending agent. There is typically previous exposure to the offending agent. The symptoms include eczema, erythema, stinging, burning, scaling and thickening of the eyelid skin. In long term contact with the allergen, the skin can become hyperpigmented and scarred. If significant scarring occurs, a cicatricial ectropion can develop. These patients can also develop corneal changes with punctate epithelial erosions and papillary conjunctivitis. Agents that can cause this type of reaction include phenylephrine [49], cycloplegics, atropine, aminoglycosides, glaucoma medications, thimoersol, EDTA [48], and benzalkonium alkalide [50]. In rare incidences, an ocular pseudopemphigoid reaction can occur from topical medications, which can lead to significant scarring [51].

Diagnosis

The diagnosis of any of the allergic diseases is multifold. For many patients, the allergens that exacerbate their allergic symptoms are already known when initially visiting a physician. The diagnosis of most allergic diseases is made mostly on clinical history and examination. This is certainly the case in allergic diseases of the eye. An ophthalmologist's exam in combination with a good history will pinpoint the type of ocular allergy. In some cases, especially for the systemic allergic diseases, further testing is required to determine and confirm the inciting allergen, presence of atopy, and/or diagnosis. There are several different *in vivo* and *in vitro* diagnostic tests available. The benefits of the *in vivo* response are that one can elicit an immediate reaction, however the patient will endure more symptoms. These symptoms, when created by skin prick testing, by an Allergist, are in almost all instances minor, self limited, and transient.

The skin prick-puncture test and the intradermal test are both ways for identifying type I hypersensivity reactions. In the prick-puncture test, a small droplet of each text extract (and a control) via a small gauge hypodermic needle is placed in the epidermis of the back or volar surface of the arm. In the intradermal skin test, allergen extract is injected intracutaneously via a tuberculin syringe so a small bleb is formed. This test can elicit more pain than the prick test. Systemic reactions have been reported with the use of both skin prick and intradermal testing, therefore in vivo testing should be done under physician supervision. The skin prick test is quick, induces less pain, and has less risk compared to the intradermal test. However, the skin prick test is also less sensitive, less reproducible, and more specific than the intradermal test. The intradermal skin test is used in the rare instance when increased sensitivity is the main goal of testing and the prick test was negative, in the presence of a strongly suspicious history. Given these findings, the prick test is the best initial test to perform [52].

Patch testing is an important diagnostic procedure for identifying causes of type IV hypersensitivity reactions, especially in conditions like allergic contact dermatitis. This testing methodology involves exposing a patch of allergen to the skin, typically the back, and evaluating the localized response. The patch remains on the skin for 48 h for the first reading, and then 72 h to a week for the second reading. The patch test must remain in place, and kept dry, until it is removed at 48 h. This test is relatively simple to perform, however patient selection is important. The skin needs to be hairless and without any other known skin conditions. It is best to not use this test on someone who already has known eczema as this can result in false positives. It is also important to not use this test on a patient who is being treated with systemic or topical steroids, as that can result in false negatives. The test reader should also be experienced in evaluating the reaction at both readings [53].

An atopy patch test (APT) is a type of skin patch test with known allergens to elicit an IgE-mediated reaction. These tests sites are then evaluated for delayed hypersensitivity skin reaction approximately 48–72 h later. This type of test uses intact protein allergens instead of haptens.

A positive APT test correlates with a lymphocytic transformation and allergen-specific Th2 cells in the peripheral circulation [54].

Other organ provocative challenges similar to the skin test can also be done to look for an allergic response. One could do a challenge on the conjunctiva, bronchi, and nasopharynx with specific allergens. A conjunctival challenge can confirm an allergen for both allergic conjunctivitis and rhinitis. With the advent of newer skin test antigens, and better in vitro testing methodology, conjunctival testing is performed exceedingly rarely. A food challenge can also be helpful in determining a food allergy by introducing a new food item into the diet every few days [52]. All organ challenges should be done with caution and always in the presence of a clinician, especially in situations where the reaction has a potential, however remote, to cause anaphylaxis.

Total serum IgE measures the amount of circulating IgE. Normal values of this antibody vary with age and gender. Since Type I hypersensitivity allergic reactions are IgE-mediated, an elevated Total serum IgE may help with the diagnosis of clinical allergic diseases. Serum IgE can also be elevated in conditions of parasitic infections or in hypergammaglobulinemia E syndrome. An elevated IgE can overlap among atopic and nonatopic patients, therefore the clinical history and physical exam also play a role in the diagnosis [55].

In certain situations, skin testing cannot be performed to diagnoses a specific allergy. In individuals with eczema, on medication for allergies, or children who are not cooperative, skin testing can become unreliable and difficult to perform. Total serum IgE can help determine if an allergy response exists, but not the specific response. An allergen specific IgE antibody assay can help distinguish specific allergens to which an individual has already become sensitized. The radioallergosorbent test (RAST) is the first serological immunoassay developed for allergen-specific IgE antibody. While the patient may not have experienced allergy symptoms, there is an increased likelihood of a response with continued exposure to that allergen. The severity of the response does not necessarily correlate with the quantity of the serum IgE antibody specific for any particular antigen [55]. Serum specific IgE antibody tests measure the serum quantity of IgE specific for a particular antigen. The presence of that specific IgE does not mean that it is clinically functional. The skin prick test, however, is a functional test by evaluating the presence of the antibody and its ability to bridge IgE molecules on a Mast cell causing histamine release.

Treatment

There are many different options for managing and treating allergic diseases. Some of these treatments are specific for the organ system affected, while the systemic medications treat the overall disease of allergy. The primary initial treatment for any allergy is avoidance of the allergen if possible. Once an allergen is identified to precipitate a response, avoiding that allergen will help eliminate the symptoms. This works well in instances of an external factor such as foods and contact related allergies. In dust mite allergic patients, covering pillows and mattresses with a dust mite impermeable covers is extremely important in preventing repeated, daily exposures to the offending antigen.

With ocular allergies, the initial treatment besides avoidance is the use of cold compresses and artificial tears. These medications help rinse the antigen and inflammatory mediators from the eye and provide temporary relief. Refrigerating ocular eye drops also helps with itching symptom. Abstaining from eye rubbing also helps reduce ocular pruritis. This works best for mild ocular allergic diseases, but not for moderate to severe reactions.

When non-pharmacology treatments fail, there are a variety of topical and systemic pharmacologic options available. Topical ocular medications include Mast cell stabilizers, anti-histamines, nonsteroidal anti-inflammatory agents (NSAIDs), corticosteroids, or a combination of these drops. Table 3.1 lists a few of the drops currently available. Topical ocular medications can also be refrigerated to add an added benefit to relieve temporary itching.

Topical decongestants act primarily as vasoconstrictors to reduce erythema and are used in combination with antihistamines [29]. Side effects of vasoconstrictors include burning, stinging, rebound hyperemia, and mydriasis. Topical antihistamines provide faster and better relief of ocular symptoms such as pruritis than systemic anti-histamines, however they are shorter acting but have less side effects of ocular dryness [27]. Mast cell stabilizers prevent degranulation of Mast cells and are effective in treating ocular pruritis [56]. NSAIDs have sometimes been used to relieve symptoms associated with the inflammatory cascade triggered by the ocular surface in all forms of ocular allergy [57]. Corticosteroids, similarly, have been used to relieve symptoms of ocular allergy from the inflammatory cascade [58]. Corticosteroids, however, should be used in shorter bursts for severe allergy symptoms compared to NSAIDs because of the higher likelihood of side effects of cataracts, glaucoma, and a higher predisposition to ocular infections inherent with steroid usage.

Newer topical medications are being used and studied for the potential to treat ocular allergies. The use of topical tacrolimus and cyclosporine-A has been used to treat forms of allergic conjunctivitis [58–61]. Cytokine antagonists and anti-IgE therapy are also currently being evaluated for their efficacy in ocular allergy [26].

Systemic medications, sometimes in combination, will help treat all symptoms of allergies. These medications include oral decongestants, antihistamines, steroids, and anti-leukotrienes. Oral antihistamines (loratadine, fexofenadine, and cetirizine)

Table 3.1 Topical ocular medications

Class	Medications
Mast cell stabilizers	Cromolyn sodium 4 % (Crolom, Opticrom)
	Lodoxamide tromethamine 0.1 % (Alomide)
	Nedocromil sodium 2 % (Alocril)
H1 receptor antagonists	Emedastine difumarate 0.05 % (Emadine)
	Levocabastine hydrochloride 0.05 % (Livostin)
	Azelastine hydrochloride 0.05 % (Optivar)
Vasoconstrictors/antihistamine combination	Naphazoline/pheniramine (Naphcon-A, Opcon-A)
	Naphazoline/antazoline (Vascon-A)
NSAIDs	Ketorolac 0.5 % (Acular)
Corticosteroids	Fluoromethalone 1 %/0.25 %(FML, FML-F)
	Prednisolone acetate 1 %/0.12 % (Pred Forte, Pred Mild)
	Rimexoloe 1 % (Vexol)
	Loteprednol etabonate 0.5 %/0.2 % (Lotemax, Alrex)
	Medryson 1 % (HMS)
Mast cell stabilizer/H1 antagonist	Ketotifen fumarate 0.025 % (Zaditor)
	Olopatadine hydrochloride 0.2 %/0.1 % (Pataday, Patanol)
	Epinastine hydrochloride 0.05 % (Elestat)

do have side effects such as dry eyes, which can worsen ocular allergy symptoms. These medications tend to have a longer biological half-life, thus longer symptomatic relief. Oral antihistamines also reduce rhinorrhea, sneezing, and itching. They have little effect on nasal congestion. The newer, non-sedating antihistamines are preferred over the older, sedating antihistamines, as they reduce the risk of daytime somnolence [62]. Systemic corticosteroids should rarely be used in children with allergic diseases as they pose several side effects on the eyes, growth, and mental changes. Montelukast, leukotriene modifiers approved in the United States are also helpful for treatment of allergic rhinitis and asthma. They have also been helpful in reducing ocular symptoms [63].

Intranasal corticosteroids can be used to treat the inflammatory manifestations of patients with allergic rhinitis and asthma [22]. Cromolyn sodium, ipatropium, and decongestants also come in an intranasal form to treat allergic rhinitis. Antihistamines and corticosteroids also come as topical creams and ointments for the skin.

Allergen immunotherapy (AIT) encompasses both subcutaneous immunotherapy and sublingual immunotherapy. It involves the supervised administration of increasing doses of therapeutic vaccines of aeroallergens to which an individual has allergen-specific IgE. The goal of AIT is achieving the appropriate maintenance dose to result in fewer symptoms upon subsequent exposure to an allergen [64]. This treatment has been shown to be helpful in asthma and allergic rhinitis, but there is low evidence of the treatment success in conjunctivitis [65].

Omazilumab, anti-IgE monoclonal antibody, has been efficacious in treatment patients with allergic asthma, allergic rhinitis, atopic dermatitis, and other allergic diseases with high levels of serum IgE. It acts by reducing free IgE levels. This may be particularly useful in patients with severe allergic responses refractory to other treatments [66]. This medication is delivered subcutaneously. The side effects are rare and usually mild with a localized injection site reaction [67]. However, there have been documented anaphylactic reactions to this modality of therapy. Accordingly, these injections must be administered in a medical setting, where professional practitioners are prepared to treat severe allergic reactions [68]. Since such reactions have occurred, occasionally, several hours after a patient has left the medical setting, in keeping with accepted treatment recommendations for patients at risk for anaphylaxis, each patient must be prepared, demonstrated, and practiced with constant immediate access to preloaded epinephrine auto-injectors, for several hours after receiving each injection.

In the setting of anaphylaxis, the treatment should begin with removing the allergen and assessing the airway, circulation, mental status, and skin. The first line treatment is with epinephrine, which acts as an antagonist to adrenergic receptors resulting in vasoconstriction. This decreases airway mucosal edema and increases venous return. Subsequently, once the patient is stable, the other therapies already mentioned can be initiated [69].

Severe Combined Immunodeficiency

Definition

Severe combined immunodeficiency (SCID) is a genetically heterogeneous group of diseases with a common clinical phenotype. SCID represents the most severe form of primary inherited immunodeficiency (PID). SCID is characterized by an absence of T lymphocytes, leading to a lack of cellular and humoral immune responses [70]. Some variations of

SCID also include B cell deficiency and/or natural killer cell deficiency. The severe lack in immunity leads to serious health consequences, mostly infectious in etiology, usually presenting in the first months of life. The variable clinical presentation seen with SCID is attributed to the multiple genetic loci that have been discovered to be related to SCID. Multiple genes have been associated with SCID, including Adenosine Deaminase and *IL-2RG* (X-linked recessive) [71].

History

SCID was first described in 1950 by Glanamann and Rinker, in a Swiss case series of children dying of infectious etiologies by their first birthdays [72]. The first enzyme found to be responsible for SCID, adenosine deaminase, was described in the literature in 1972. The gene for the most common form, X-linked, was described in the literature in 1993 [73].

Epidemiology

Various reports regarding the incidence and prevalence of SCID have been published. Most report a prevalence of 1:5000 to 1:100,000 per live births. Prevalence varies depending on the population, with reports of increased prevalence among the Hispanic population [74].

Systemic Manifestations

Infants generally appear well at the time of birth. The disease usually manifests during the first few months of life, commonly presenting due to inability to fight infection. Bacterial infections are less common in newborns, due to residual circulating maternal IgG antibodies. Recurrent respiratory and gastrointestinal infections are common. Progressive respiratory disease can also occur and hyperinflation and interstitial pneumonitis is frequently seen on chest x-rays due to *Pneumocytis jirovecii*. Eventually the patient demonstrates failure to thrive with an inability to gain weight due to intestinal villi atrophy, leading to malabsorption. Omenn syndrome, an autosomal recessive type of SCID, presents with thickening erythematous rash of a leathery consistency, commonly accompanied by eyebrow and eyelash loss [75].

Ophthalmic Manifestations

SCID patients have an increased susceptibility to opportunistic infections; most ocular manifestations are a direct result of this. The most common ocular manifestation of SCID, especially during immune reconstitution after a bone marrow transplant, is cytomegalovirus (CMV)[76]. CMV manifests in the eyes in many ways and results from a disseminated infection. Typically, CMV will involve the retina causing chorioretinitis. Patients may also present with optic neuritis [77] or viral endophthalmitis [78]. Patients with CMV retinitis can develop retinal necrosis, leading to retinal tears and detachments.

Pediatric patients with CMV retinitis or optic neuritis may have symptoms of flashes floaters and a decrease in vision. However, preverbal children may not be able to express these symptoms. For that reason, these patients should be screened if disseminated CMV is found. Findings on examination can be retinal whitening and edema, hemorrhages, vascular sheathing, or optic nerve pallor. Long term, these patients can have permanent decrease in vision, even with adequate treatment [79].

After immune reconstitution, patients with healed CMV retinitis who are no longer receiving CMV prophylaxis medication can develop immune recovery uveitis, an inflammatory response within the eye. This has complications of vitritis, macular edema, epiretinal membrane, macular hole, retinal detachment associated with proliferative vitreoretinopathy, and cataract [80, 81].

In addition to CMV, other opportunistic infectious could potentially affect the eyes in patients with SCID. These include toxoplasmosis, fungal keratitis and/or endophthalmitis, and *Pneumocystis jirovecii* presenting as conjunctivitis and chorioretinitis [82]. More details about these ocular infections—including diagnosis and treatment—can be found in the infectious disease chapter.

Diagnosis

SCID is diagnosed with flow cytometric immunophenotyping of lymphocyte subsets in peripheral blood. Lack of T cells is essential to the diagnosis. It is important to rule out HIV as a cause of the immunodeficiency. A few states, such as Wisconsin and California, have enacted universal screening for SCID as part of the routine newborn screening. Currently, this has been widely adopted.

Treatment

The treatment of choice for SCID is a stem cell transplant, preferably early in life. Survival is now reported at 92 % if the transplant is within first month of life. Patients should avoid live attenuated viral vaccines, which could cause illness in the child. Prophylactic antimicrobials are frequently given to avoid previously mentioned infectious manifestations, such as *Peumocystis jirovecii*. Breastfeeding should be discontinued if the mother is CMV positive to reduce risk of transmission and subsequent infection [75].

X-Linked Agammaglobulinemia

Definition

X-linked Agammaglobulinemia (XLA) is an X-linked recessive immunodeficiency characterized by a lack of B cells, plasma cells and all subtypes of antibodies. It is caused by a defect in the non-receptor Bruton tyrosine kinase (*BTK*) [83, 84]. The defect leads to a block in B cell development in the pre-B cell phase. This subsequently leads to the absence of plasma cells and the inability to form secondary lymphoid follicles [85]. Given the genetic inheritance, it is clinically seen almost exclusively in males and usually presents in early childhood with recurrent bacterial infections.

History

The disease was first described by Bruton in 1952. Bruton described the case of an 8 year old male with recurrent bacterial infections with agammaglobulinemia [86]. The *BTK* genetic etiology of the disease was described in 1993 [83, 84]. Even with antibiotics, the outcome of patients was very poor until the development of intravitreal immunoglobulin (IVIG) in the 1980s.

Epidemiology

Prevalence of XLA is reported to be between 5–10:100,000 [87]. No reported ethnic variability has been reported. Family history and consanguinity are risk factors that dramatically increase prevalence in certain populations.

Systemic Manifestations

XLA is characterized clinically with recurrent bacterial respiratory and cutaneous infections, commonly with encapsulated organisms. Patients can also develop serious parasitic and gastrointestinal viral infections [88]. 90 % of patients are symptomatic by 18 months [89] with a mean diagnosis around 3 years of age. Respiratory infections continue to be the main cause of mortality [88].

Ophthalmic Manifestations

X-linked agammaglobulinemia patients can have a myriad of ocular manifestations of infectious diseases since these patients lack mature B cells and plasma cells. Patients may present with bacterial conjunctivitis. One case report by Al Ghonaium, et al. discussed a patient who presented with bilateral chlamydial conjunctivitis confirmed with culture. Patients with XLA may not present with follicular conjunctivitis that is highly suggestive of *Chlamydia* since B cells are necessary for follicle formation [90]. Bilateral conjunctivitis from *Haemophilus influenza* can also occur patients with XLA [91]. These patients with severe bacterial conjunctivitis can have significant sequelae of profound cornea scarring that can lead to vision impairment [91]. There has also been a reported case of sectoral iris atrophy from presumed viral infection [92].

Patients with XLA can develop unusual malignancies in unusual places in the pediatric population, which can present as ocular symptoms. There is one case report of a patient who presented with epiphora secondary to a non-Hodgkin lymphoma mass at the inferior portion of the nasolacrimal duct [93].

Diagnosis

Laboratory tests that demonstrate a lack of circulating B cells (Cd-19+) along with a lack of all antibody classes are used to make a diagnosis. Classically, serum IgG levels are less than 200 mg/dL, IgM less than 10 mg/dL and complete lack of IgA. Circulating B cells are usually less than 0.5 % of lymphocytes. Confirmation of XLA occurs with western blot confirmation of BTK protein mutation.

Treatment

With the development of IVIG in the 1980s, improvement in the clinical outcomes has been seen. While there is still a high associated morbidity and mortality rate, survival has improved. Immunoglobulins have also been formulated to be given subcutaneously, though IVIG still remains the standard of care [94]. One case report of the development of neutropenia in a patient with XLA reports successful treatment with granulocyte colony stimulating factor Filgrastim [87].

Patients are to avoid live attenuated vaccines due to inability to mount proper immune response and increased probability of infection.

Combined Variable Immunodeficiency

Definition

Combined Variable Immunodeficiency (CVID) is the term used to describe a genetically and clinically heterogeneous group of diseases with similar characteristics of agammaglobulinemia. It is the most common symptomatic primary immunodeficiency in adults [95]. As opposed to X-linked recessive agammaglobulinemia, which is congenital and affects males, CVID affects males and females at an equal rate. This normally manifests in the second or third decade of life. CVID is similar to XLA in its characteristic

agammaglobulinemia and persistent bacterial infections. CVID does not have one genetic marker like XLA, but is a group of diseases characterized by hypogammaglobulinemia with IgG levels two standard deviations below the mean, impaired vaccine response, or absent isohemagglutinins without another identified etiology of the hypogammaglobulinemia [96]. It is thought to be due to defective T cell and B cell interaction with defective antibody formation, due to abnormal B lymphocyte differentiation commonly termed late-onset antibody failure.

History

CVID was first reported in 1953 by Janeway [97]. This study led to the differentiation of XLA and CVID due to its description to an immunodeficiency similar to XLA with a different onset and inheritance pattern.

Epidemiology

Prevalence is estimated to be 1:50,000 to 1:100,000 [98]. There appears to be ethnic variation, with a reported prevalence of 1:25,000 in Australia and lower prevalence rates in the North East Asia region [96].

Systemic Manifestations

Similar to other primary immunodeficiencies affecting humoral immunity, the clinical presentation of CVID commonly consists of recurrent pyogenic sinopulmonary infections. Severe enteroviral infections can also occur and lead to chronic meningo-encephalitis. GI infections with bacteria such as *Giardia lamblia* and *Cambylobacter jejuni* are also common. CVID can also present with granulomatous disease, not unlike sarcoid, with ocular and pulmonary manifestations.

In addition to the multiple infectious complications associated with CVID, there is a well-studied phenomenon of non-infectious comorbidities. There is an increased incidence of autoimmune disorders including colitis, Sjogren's, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, inflammatory bowel disease, celiac disease, and Guillan- Barre syndrome. 22% of patients have an autoimmune diagnosis at time of CVID diagnosis. This prevalence increases to 36% in patients followed over an extended period of time. The autoimmune relationship is more common in women and patients with granulomatous disease [99]. This association with immunodeficiency and autoimmune disease illustrates the complexity of the immune system.

The mechanism of autoimmunity of CVID is unclear. Hypotheses include lack of removal of autoimmune of B cells due to ineffective B cell receptor signaling, abnormal ligand interaction due to reduced CD40 expression on B cells, accelerated expansion of auto reactive B cells and increased levels of BAFF/April [99]. There is also a higher reported incidence of malignancies, specifically lymphoma and gastric adenocarcinoma, which are a significant contributor to mortality [100].

Ophthalmic Manifestations

Patients with CVID are susceptible to recurrent infections and autoimmune disorders, both of which can manifest in the eyes, although this is rare. Ocular infections can include all aspects of the eye. Patients with CVID can present with significant bacterial conjunctivitis with *S. pneumoniae, H. influenzae, Staphylococcus epidermidis, Staphylococcus aureus,* and other multidrug-resistant bacteria [101–103]. Cornea involvement in the form of keratitis has also been reported [103], and there have been reported cases of dacryocystitis, an infection within the lacrimal sac, in patients with CVID [104].

The ocular features of CVID-associated uveitis can include granulomatous inflammation, retinal vasculitis, choroiditis, and optic nerve involvement [105, 106]. The granulomatous uveitis in CVID can manifest as mutton-fat keratic precipitates on the corneal endothelium, snowball vitreous opacities, or optic disc granulomas. The granulomatous inflammation seen in CVID could also be due to the association with sarcoidosis or a sarcoid-like syndrome. Patients with CVID can have an anterior granulomatous or non-granulomatous uveitis [107, 108]. A case report of three patients with CVID developed retinal vasculitis with optic nerve and macular edema. Two of the three patients in this case report also developed neovascularization of the retina. No signs of retinal ischemia or infectious etiology were found, therefore the etiology was presumed to be CD4+ T-cell-mediated autoimmunity [104]. Patients can present with a multifocal choroiditis [109, 110] or birdshot-like chorioretinopathy [111, 112]. Bilateral optic neuritis has also been reported as an autoimmune complication of CVID [113].

Other rare ocular diseases have been reported as case reports in the setting of CVID. These ocular diseases are also thought to be secondary to some autoimmune response. One patient with CVID, who presented with proptosis and limitation of extraocular motility, developed orbital inflammation with a mass infiltrating the lacrimal gland. Biopsy of this mass revealed a non-granulomatous, lymphocytic infiltration. There was no evidence of infection. His condition improved significantly on oral steroids [114]. Another patient presented with sterile cornea thinning resulting in perforation [115]. An acquired Brown's syndrome with tenderness in the area of the superior oblique tendon resulting in diplopia has also been reported [116]. There has also been the suggestion of the link of CVID with retinitis pigmentosa based on a case series of three generations that carry both diseases. Retinitis pigmentosa is a retinal degeneration char-

acterized by night blindness and peripheral visual field constriction. On examination, these patients have a pigmentary retinopathy with bony spicules seen in the retina, vascular attenuation, and a waxy pallor to the optic nerve [117].

Diagnosis

CVID is a diagnosis of exclusion and thus can be difficult. There is current discussion in the field regarding the exact diagnostic criteria. The European Society of Immune deficiencies established criteria with the pan American group for Immune Deficiency in 1999 and gave an update in 2014. The updated diagnostic criteria includes marked decrease in IgG and IgA, poor response to vaccines with low switched memory B cells developed after 4 years of age, with no evidence of profound T cell deficiency and a lack of secondary cause of hypogammaglublinemia.

Patients also must have one of the following: increased susceptibility to infection, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation, or an affected family member with antibody deficiency. Ameratunga et al. propose a different criteria. Though similar, it puts more emphasis on clinical manifestations with recurrent infections combined with laboratory testing [96].

Treatment

The current gold standard is either IVIG of subcutaneous immunoglobulin to address the hypogammaglobulinemia. Antibiotics are used appropriately to treat infections. Corticosteroids and cyclosporine A can be used to treat granulomatous manifestations and concomitant autoimmune diseases.

Selective IgA-Deficiency

Definition

Selective IgA deficiency is the most common primary immunodeficiency. Though it is much more common than CVID, many patients remain asymptomatic. The defect is presumed to result from impaired switching or a maturational failure of IgA producing lymphocytes. The clinical course is widely heterogeneous as is the inheritance pattern [98].

History

IgA deficiency was first described in 1963 in children with ataxia-telangiectasia [118, 119]. The deficiency was soon found to be in the general asymptomatic population along with increased numbers in those with recurrent respiratory and gastrointestinal infections and those with autoimmune diseases.

Epidemiology

Selective IgA deficiency is the most common primary immunodeficiency. Studies vary on prevalence rates as there have been differing opinions on laboratory diagnostic values along with ethnic variability. Reported values range from 1:173 in a study in Sweden to 1:22,500 in a Japanese study [98, 120]. This is consistent with various studies that report higher numbers in Caucasian populations and lower prevalence rates in East Asian ethnicities [121].

Systemic Manifestations

IgA is the most abundant immunoglobulin in the body. It is found in tissues and secretions, specifically the respiratory and gastrointestinal tract. IgA has a role in mucosal immunity, defense against mucosal pathogens and development of immune tolerance. Clinically there is wide variability in clinical presentation for patients with IgA deficiency. The majority remain a symptomatic. Those with clinical presentation frequently have recurrent sinopulmonary infections. Recurrent respiratory and gastrointestinal infections are due to lack of IGA in serum and mucosal secretions [121].

IgA deficiency is more common in patients with chronic lung disease. Additionally, there is an association between IgA deficiency and the development of CVID, suggesting a similar underlying pathogenesis [121].

There is a well-established relationship between IgA deficiency and an increased incidence of autoimmune diseases. One study reports a 25 % incidence of autoimmune disease in patients with IgA deficiency [122]. Autoimmune diseases that have shown to have an association with IgA deficiency include: autoimmune hemolytic anemia, systemic lupus erythematosus, juvenile idiopathic arthritis, sclerosing cholangitis, celiac disease, vitiligo, psoriasis, ulcerative colitis, Sjogren's disease, polyarteritis nodosa, sarcoidosis, Kawasaki disease, and Behcet's disease [120]. The exact reason for the close association is unknown though Jacobs (2008) proposes a mechanism involving IgA and its receptor leading to a phosphorylation cascade that results in deactivating immune-activating pathway, furthering the idea that IgA has a role in protecting against autoimmunity [123].

Most vaccines are considered to still be effective, though with a muted immune response. The CDC currently considers the oral polio vaccine, Bacillus Calmette-Guérin (BCG), and yellow fever vaccines to be the only contraindicated vaccines for patients with IgA deficiency [124].

Ophthalmic Manifestations

The lacrimal gland and the conjunctiva are parts of the ocular immune system which produce IgA. In patients with IgA deficiency, not many ocular diseases have been reported. However, the disease has been reported to in the conjunctiva as conjunctivitis [125].

Given the association with autoimmune diseases, patients with IgA deficiency may develop an uveitide, though this is more likely due to the underlying autoimmune disease as opposed to a manifestation of the IgA deficiency.

Diagnosis

Prevalence studies have used varying cutoff, but the standard definition suggests using a 0.05 g/L of serum IgA as the upper limit for diagnosis in adults with a concomitant lack of secretory IgA. Values above this level, but lower than normal, should be considered partial IgA deficiency. During diagnosis, it is important to rule out secondary reasons for the selective hypogammaglobulinema and for specific medicines that have been found to be associated with IgA depletion, such as anti-rheumatic and anti-epileptic drugs [126].

Treatment

No treatment is needed for the majority of patients, as they are asymptomatic. Infections should be treated with appropriate antimicrobials, though prophylactic antibiotics are not considered standard of care.

Patients should be warned of the potential complications with blood transfusions. Some patients with IgA deficiency develop anti-IgA antibodies, which can react to IgA in blood products and produce an anaphylactic reaction.

Additionally, patients should be counseled on the increased risk of progression to CVID.

Selective IgM Deficiency

Definition

Selective IgM deficiency is a relatively uncommon selective primary agammaglobulinemia. It is characterized by a complete or partial lack of IgM circulating antibodies. IgM deficiency is characterized with heterogeneous lab and clinical findings. Lab results can range from complete absence to partial deficiency with normal to complete absence of circulating B cells. There can also be normal to severely impaired specific antibody responses against pneumococcal polysaccharides with a wide variety of chromosomal associations.

History

The first case of IgM deficiency was described by Hobbs in 1967 in a case report of two male children with fulminant meningococcal septicemia that were found to have low levels of IgM on lab work [127].

Epidemiology

The prevalence of primary selective IgM deficiency is reported to be 0.03 % in the general population. The prevalence of partial deficiency is reported to be from 0.1 to 3.8 % in hospitalized patients [128]. There does not seem to be a gender predilection.

Systemic Manifestations

80 % of patients with IgM deficiency present with recurrent infections [129]. Infections range from benign to life-threatening meningitis and sepsis. Reported recurrent infections from intracellular bacteria, protozoan, viruses and fungi have been reported. Patients commonly have recurrent upper respiratory infections. Atopic diseases are common with an association with allergic rhinitis and 25 % of patients have a concurrent diagnosis of asthma [130].

Similar to other antibody deficiencies, there is an association with autoimmune diseases. Reports have shown an association with systemic lupus erythematous, vitiligo, autoimmune glomerulonephritis, rheumatoid arthritis, and celiac disease [128]. It is thought that the association is due to IgM- autoantigen complex crosslinks with B -cell receptors to auto reactive B cells and trigger their deletion/anergy [128].

Patients with selective IgM deficiency also may present with a number of skin manifestations including recurrent abscesses, impetigo, pyoderma, molluscum contageosum, and epidermal dysplasia verrucifomis [129, 131–134].

Also similar to other select agammaglobulinemia deficiencies, there is an association with malignancies. In IgM deficiency, clear cell carcinoma is the most commonly associated malignancy [135], along with leukemia [136].

Ophthalmic Manifestations

Few ophthalmic manifestations of selective IgM deficiency have been reported. IgM deficient patients have been reported to have recurrent hordeola, conjunctivitis, and blepharitis due to *Staphalococcus aureus* [137].

Diagnosis

Diagnosis is confirmed with a lab test showing IgM levels <30 mg/dL in children, which is less than two standard deviations below adult values.

Treatment

Treatment includes appropriate antimicrobials for recurrent infections. Recent case reports suggest that immunoglobulin therapy is helpful and beneficial to patients, even if all other immunoglobulins are normal [128, 138, 139].

Chronic Granulomatous Disease

Definition

Chronic Granulomatous Disease (CGD) is an uncommon inherited immunodeficiency disorder. The disease is caused by an inability for phagocytic cells such as neutrophils and macrophages to kill catalase-positive organisms. Phagocytic cells use a respiratory burst, consisting of a rapid release of reactive oxygen species, to help degrade bacteria. Defects in the phagocyte NADPH oxidase results in low levels of NADPH activity and leads to CGD. More than two-thirds of the cases of CGD are X-linked recessive, though autosomal dominant and recessive patterns may occur [140].

History

CGD was first described by Janeway in 1954 [141]. Over the ensuing years, researchers learned that the disease was caused due to a lack of oxidative burst. In 1967, the use of reduction of nitroblue tetazolium by phagocytes from patients with CGD during phagocytosis was introduced as diagnostic testing, which helped distinguish the disease process from other immunodeficiencies [142].

Epidemiology

CGD prevalence is reported to be between 1:200,000 to 1:250,000 [143].

Systemic Manifestations

CGD is commonly associated with recurrent bacterial and fungal infections for which aggressive antibiotics are needed. Recurrent abscesses are common in early childhood, although presentation can be later. Patients with CGD are particularly susceptible to catalase-producing organisms, such as *S. aurea, E. coli, Serratia, Klebsiella, Pseudomonas aeruginosa*, and various fungi. Aspergillus infections are also a common cause of morbidity and mortality.

Patients can develop multiple granulomatous lesions in the lungs, liver, lymph nodes, and gastrointestinal and genitourinary tract, which can cause obstruction. Patients can also have suppurative lymphadenitis, hepatosplenomegaly, and colitis. Pneumonia is a common cause of mortality.

Ophthalmic Manifestations

As CGD affects the phagocytic cell function, these patients are susceptible to infections that can manifest within the eye. Anterior segment conditions such as blepharokeratoconjunctivitis, which includes inflammation or infection of the eyelid, cornea and conjunctiva, have been reported [144, 145]. These patients can develop severe keratitis [146] leading to ulceration [147] or thinning [148]. There is a case report of a patient presenting with anterior segment uveitis demonstrated by anterior synechiae, mutton fat keratic precipates, and anterior segment inflammation [149].

These patients can also have chorioretinal lesions, that have been described as being perivascular and sparing the macula [144, 150–152]. These lesions have also been described in female carriers [153]. There has been speculation that the cause of these scars may be from previous bacterial infections [154]. Some patients with CGD have chorioretinal lesions in the peripapillary region and associated with optic nerve pallor [155]. These lesions have been described as well-circumscribed scars in the retina and choroid with areas of atrophy involving the choroid, retinal pigment epithelium, and retina. The chorioretinal lesions are also sometimes associated with retina pigment clumping [156].

Chorioretinal lesions have been visualized in the absence of visual symptoms or signs of active uveitis. Some patients with these retinal findings can have severe visual impairment when associated with vitreous hemorrhage, neovascular membrane, peripheral retinal ischemia, and macular edema [156]. There have been reported cases of severe vision loss, pain and photophobia with presumed progression of chorioretinal lesions to anterior chamber inflammation, posterior synechiae, vitritis, vitreous hemorrhage, and exudative retinal detachment. These enucleated eyes showed multiple foci of granulomatous inflammation with an absence of an organism [157]. Exudative retinal detachment can also be associated with a granulomatous subretinal mass [158].

Diagnosis

Originally diagnosis of CGD was performed with reduction of nitroblue tetazolium by phagocytes. This has been replaced in clinical practice by the dihydrorhodamine-1,2,3 (DHR) oxidation test (a flow-cytometry study) due to its ease of use [159]. Confirmation of CGD is performed with a positive test with genetic testing of known mutations.

Treatment

The cornerstone of clinical care of CGD patients is lifelong preventative treatment. This includes prophylaxis of antibiotics, antifungals and immunomodulatory therapy [160]. Management of infection is also important which includes appropriate antimicrobials, excisions of liver abscesses, steroids for management of CGD colitis, and granulocyte transfusion in certain situations. Definitive treatment of CGD includes stem cell transplant. There is much research into gene therapy, but this is not currently approved [140, 160].

Chediak-Higashi Syndrome

Definition

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive immunodeficiency caused by an abnormal granule formation in neutrophils and melanocytes. The abnormal accumulation of granules causes a form of oculocutaneous albinism combined with immunodeficiency and recurrent infections. The alterations in neutrophils can lead to neutropenia, impaired chemotaxis and delayed phagolysosomal fusion resulting in decreased bactericidal activity. Lymphocytes can also contain large cytoplasmic granules and function poorly. Reduced natural killer cell activity can also be seen [161].

CHS is due to mutations in the lysosomal trafficking (*LYST*) regulator gene [162]. It is thought that defects of the lysosomal trafficking regulator protein lead to decrease MHC class II molecules reaching endosomes, inhibiting antigen presentation [163].

History

CHS was first described by Bequez-Cesar in 1943. Ultimately the disease was further characterized by Chediak (1952) and Higashi (1954), from which the disease's eponym originates [164].

Epidemiology

CHS is a very rare condition with approximately 500 cases reported in the literature [161].

Systemic Manifestations

CHS is accompanied by oculocutaneous albinism (OCA) due to melanosome dysfunction. CHS patients have all the findings that would be expected in OCA. This includes decreased pigmentation in skin, hair, choroid, and iris [165]. There have been reported cases of hyperpigmentation in sun-exposed areas [165].

Immunodeficiency due to neutrophil dysfunction leads to recurrent pyogenic infections, most commonly on the skin and in the gastrointestinal tract [166]. Coagulation defects are also seem to be due to platelet dysfunction. There are normal amounts of platelets, but due to the presence of dense platelet bodies, the platelets do not function properly, and bruising and bleeding times are increased [167].

If patients survive past the initial barrage of infections, approximately half will develop neurologic symptoms including progressive neuropathy, paresthesias, stroke, coma or convulsions [161]. Patients can also enter into an accelerated phase of the illness. This is characterized by lymphohistiocytic infiltration leading to a lymphoma-like infiltration of the major organs. There are various hypotheses related to the etiology of this accelerated phase, and there appears to be an association with the Epstein Barr Virus [166, 167]. Regardless of the exact etiology, this is a devastating stage with infiltration of visceral organs and a major cause of mortality [161].

Ophthalmic Manifestations

Similar to other forms of albinism, patients can have photophobia due to iris transillumination defects and fundus hypopigmentation [168]. Nystagmus can be present, thought to be a result of misrouting of optic fibers [169]. Exam can reveal a lack in pigmentation of iris, choroid, RPE and/or ciliary body. There have been case reports of hyperpigmentation of the iris with choroidal hyperpigmentation and concomitant RPE hypopigmentation [165]. Patients can experience foveal hypoplasia and papilledema [170]. Systemic manifestations and microscopic diagnostics are important for confirmed diagnosis given similar ocular findings to other the forms OCA. In addition to aforementioned ocular findings, HPS is associated with strabismus complications, cataract and posterior embryotoxon, which are generally not found with CHS [171].

Diagnosis

The diagnosis of CHS is definitively made with pathognomonic intracytoplasmic giant granules in leukocytes or gene testing [161].

Treatment

Prophylactic antibodies are frequently given due to the recurrent infections. A review of 25 patients with CHS showed a survival rate 62% at 5 years of HLA-matched allogeneic transplantation [172]. Survival was more likely if patients had no symptoms of the accelerated lymphoproliferative stage. Another review showed long-term neurocognitive sequelae in patients after stem cell transplants, presumably due to post-transplant chimerism [173].

Blau Syndrome

Definition

Blau Syndrome (BS) is a rare autoinflammatory, autosomal dominant disease characterized by the triad of granulomatous inflammation that affects joints, eyes and skin. The onset is almost always under 4 years of age. There is considerable overlap with juvenile sarcoidosis. Early onset sarcoidosis (EOS) and Blau Syndrome have defects from the same *CARD15/NOD2* gene mutation [174]. There is same uncertainty in the difference between the two, although it is generally accepted that Blau syndrome refers to the familial form and EOS refers to *de novo* mutations. The gene is a caspase recruitment gene involved in immune and inflammatory functions. The defects cause an overactivation that leads to increased inflammation, although how this specifically leads to Blau Syndrome remains unclear [175].

History

Blau Syndrome was first described by Blau in 1985. He describes granulomatous arthritis, iritis, and rash in 11 family members in four different generations [176].

Epidemiology

The disease is rare, with a review in 2012 noting 193 reported cases. This, however, is confounded by the incomplete distinction between diagnosis of BS and EOS [177]. There have been reported cases in the Caucasian, African-American, Spanish, and Asian populations. In a study of the Danish pediatric population, juvenile sarcoidosis in Denmark reported an incidence of 0.06 per 1,000,000, though that study did not distinguish between familial versus de novo presentations [178].

Systemic Manifestations

Presentation is usually in childhood with the majority of cases presenting between 3 and 4 years old [179]. Polyarthritis is the most common presenting symptoms, and can be commonly confused for juvenile idiopathic arthritis. Patients also have joint swelling and erythema. If the arthritis is severe, patients can develop camptodactyly. Skin manifestations are common with two distinct dermatologic presentations possible.

The first is a papulonodular tender brownish rash and the second is the multiple firm subcutaneous nodules [177]. Ocular inflammation is also common, which will be detailed in the next section. Various case reports have also described different cranial neuropathies [180, 181]. Granulomas of liver and kidneys along with large vessel vasculitis have also been described [181].

Ophthalmic Manifestations

Ophthalmic manifestation is extremely important in the diagnosis and management of Blau disease, given the high morbidity associated with its complications and sequelae. Anterior and posterior uveitides, frequently seen together in panuveitis, are the most common presenting features. In a review by Carreno, all patients developed anterior chamber inflammation and posterior segment involvement was present in 77% of patients [182]. An international review by Rose also showed anterior segment inflammation as the most common presentation [183]. Choroidal lesions have been reported, with one review reporting 94% of patients developed panuveitis with multifocal choroidal and were identified as the most common ocular presentation in that case series [184–186].

Other ocular complications include cataracts [180, 183, 186, 187], glaucoma [180, 183, 188], corneal opacities [187, 189], band keratopathy [183], peripheral retinitis [176], and retinal detachment [183]. In a review by Carreno, optic disc changes were common, specifically optic disc nodular excrescens at the margin and pallor [182]. Carreno argues that disc changes should be more closely analyzed as a common manifestation of BS.

Diagnosis

Diagnosis is initially made with a clinical exam with family history and confirmed with genetic testing demonstrating a NOD2 mutation. Electron microscopy can also be used, as

there can be characteristic common shaped bodies in epithelioid cells [181].

Treatment

Steroids are usually first line, especially for acute-phase inflammation. Immunomodulators can also be used to control inflammation long-term. There have been case reports of biologic anti-cytokine agents such as infliximab, TNF-alpha inhibitor and anakinra, Il-1 receptor antagonist [190, 191].

Neonatal Onset Multisystem Inflammatory Disorder

Definition

Neonatal onset multisystem inflammatory disorder (NOMID) or Chronic Infantile Neurologic Cutaneous and Articular syndrome (CINCA) is a rare autosomal dominant condition that is considered as part of the family of cryopyrin-associated periodic fever (CAP) syndromes. CAP includes a spectrum of diseases and includes familial cold autoinflammatory syndrome, Muckel-wells syndrome, and neonatal multisystem inflammatory disorder. All the CAP diseases are caused by a mutation in the *CIAS* gene on chromosome 1, which encodes NLRP3, an inflammasome and component of IL-1 beat and IL-18 activating platform. The genetic mutations lead to over-activation of NLRP3 leading to overexpression of inflammatory pathways [192, 193].

History

NOMID was first described by Prierur and Grischelli in 1981 with the report of three children with papilledema, arthritis and chronic rashes that flared with periodic fevers and lymphadenopathy [194].

Epidemiology

Formal studies have not been completed, but the estimated prevalence is 1–10:1,000,000 with Caucasians affected more than other racial groups. There does not appear to be any gender predilection [195].

Systemic Manifestations

NOMID, as the name implies, is a multisystem autoinflammatory disease that presents in the neonatal period. The most distinguishing characteristics include rash, arthropathy, hearing loss, ocular inflammation and CNS damage. The rash is usually a nonpruritic, neutrophilic, urticarial-like rash, which can progress to skin erythema and exuberant skin. The arthropathy affects large joints, can be severe, and is caused by bony overgrowth [196]. Progressive hearing loss results from chronic cochlear inflammation. CNS damage can occur from aseptic meningitis or increased intracranial pressure (ICP), and includes cognitive delays, seizures and strokes [192]. Patients generally have high inflammatory markers on laboratory work and can develop secondary sarcoidosis from prolonged systemic inflammation. However, this mechanism is not well understood [192]. Patients classically also have macrocephaly, saddle nose, and finger clubbing.

Ophthalmic Manifestations

Ophthalmic manifestations in NOMID can vary with a wide variety of ocular pathology presented in the literature. Dollfus et al. (2013) gave the most extensive review to date on ocular manifestations with a report of 31 patients. They reported 85 % with optic nerve head (ONH) changes, commonly pallor or swelling. 55 % had chronic non-granulomatous anterior uveitis and 42 % of patients suffered from chronic conjunctivitis [197]. Other manifestations reported include corneal abnormalities (42 %) such as stromal scarring, band keratopathy and corneal neovascularization [197]. Vitritis, retinal vasculitis, focal chorioretinitis, cystoid macular edema, and cataracts have also been reported [197, 198]. One report of retinal dystrophy in association with NOMID has been reported [199]. ONH appearance can vary with some reports of optic nerve head pallor and sheathing of peripappillary vessels [200]. There are also reports of pseudopapilledema thought to represent a neutrophil-based infiltrative etiology [201]. Other reports of papilledema and eventual pallor are thought to arise from increased ICP [202].

Diagnosis

The diagnosis of NOMID is confirmed with NLRP2 mutation detected by genetic testing.

Treatment

Historically, anti-inflammatory medicines, including steroids, have been the mainstay of therapy to decrease systemic inflammation. However, there are currently three IL-1 antagonists on the market, Anakinra, Rilonacept, and Canakumab, which are gaining popularity and usage in regards to NOMID treatment [195].

Ataxia-Telangiectasia

Definition

Ataxia-telangiectasia (A-T) is a rare autosomal recessive neurodegenerative disorder. It classically consists of cerebellar ataxia, progressive neurologic impairment, immunodeficiency, and oculocutaneous telangiectasia [203]. It has been shown to be associated with mutation in the *ATM* gene (11 q22-23). ATM encodes for protein kinase ataxia telangietctasia mutated (ATM), which responds to double-stranded DNA damage [204]. The ATM protein also assists with cell cycle checkpoint pathways [205].

History

The disease was first described in 1926, by Syllaba and Henner, with a report of three adolescent Czech siblings with progressive choreoatheotsis and ocular telangiectasias [206]. The disease is also known as Louis-Bar disease due a description of the disease by Louis-bar in 1941 [207]. The association with chromosome 11 was described in 1988 [208].

Epidemiology

The disease has an estimated prevalence of 1:88,000 live births in the USA [209].

Systemic Manifestations

Symptoms of A-T usually do not manifest until early childhood when the child is learning to walk (around 12 to 18 months of age). There is a persistent, unsteady gait with progressive development of hypotonia, intention tremor, and decreased deep tendon reflexes. This has been correlated to cerebellar atrophy on MRI and associated in pathology to a loss of Purkinje cells [203]. The disease is normally neurodegenerative with a decline in neurologic status with time. Patients frequently develop dysarthria and increased extrapyramidal symptoms with Parkinson-like symptoms.

Clinically, one-third of patients will have severe immune deficiency, one-third will have mild immunodeficiency, and one-third have no immune dysfunction [210]. The immunodeficiency frequently leads to sinopulmonary infections and chronic obstructive pulmonary disease. It is commonly associated with a lymphocytopenia.

There is an increased predisposition to malignancies, cells with increased radiosensitivity, sterility with poor secondary sex characteristics, and short stature [211]. There is commonly mild hepatic dysfunction with decreased excretion of 17-ketosteroids, likely related to the underlying hypogonadism [211].

In addition to ocular telangiectasias, which are discussed in the next section, patients frequently have cutaneous telangiectasia in sun-exposed areas such as the face.

Ophthalmic Manifestations

The most characteristic ocular finding in A-T is ocular telangiectasia. The telangiectasias can be found on both bulbar and palpebral conjunctiva, and reported to be most common in canthal regions. The telangiectasias do not extend past the limbus and have been confirmed to be of venous origin [211]. The vessels normally appear between 3 and 6 years of age and, in-and-of themselves, cause no ocular dysfunction.

There are numerous reports of eye motility abnormalities. Boder and Sedgwick report an 84 % prevalence of apraxic eye movements and 83 % prevalence of gaze nystagmus [212]. There is a reported 50 % prevalence of saccadic intrusions including square wave jerks and runs of back-to-back saccades without an intersaccadic interval [213]. Other studies report 100 % abnormal saccade movements including smooth pursuit and initiating saccades [214, 215].

Patients shows abnormal vestibular and optokinetic nystagmus fast phase. Approximately half of patients may have defective gaze holding. There is also a 95 % reported prevalence of extended interval of voluntary horizontal and vertical saccades [213]. Abnormal head thrust movements and strabismus, specifically esodeviations, have been reported [213, 216].

A large majority have abnormal convergence [214]. Farr et al. report mild decreased visual acuity in patients, likely secondary to the ocular motility abnormalities and abnormal convergence [217].

Diagnosis

Three laboratory findings frequently used to determine an A-T diagnosis include elevated alpha feto-protein, karyotyping of immune status of B and T cell compartments, along with assessing radiosensitivity of cells. Mutations in *ATM* can be sought [210].

Treatment

Treatment generally consists of medical management of complications including infection control. Neurorehabilitation is important to optimize the patient's neurologic capabilities. Neurologic medicines are commonly given to help improve neurologic symptoms, but there is no definitive treatment at this time [210].

Bloom Syndrome

Definition

Bloom syndrome is a rare autosomal recessive DNA breakage disorder that results in short stature, photosensitive rash, immunodeficiency, and malignancy. It is caused by disruption of the *BLM* gene, which encodes the protein RecQl3 helicase, an enzyme that restores malfunctioning replication forks during DNA replication. The protein binds to recombination intermediates and Holliday junctions, which normally assist with homologous DNA recombination [218]. The mutated gene causes a tenfold increase in DNA exchange between sister chromatids and prevents the removal of Holliday junctions, which results in elongated, segmented and entangled sister chromatids [219].

History

The syndrome was first described by Bloom in 1954 with a case series of three patients with short stature and systemic lupus erythematous–like facial rash [220].

Epidemiology

The syndrome is most common in Ashkenazi Jews in Eastern Europe and Israel, accounting for one-third of reported cases [221]. Over 170 cases have been reported in the literature in the USA with a male to female ration of 1.3:1 [222].

Systemic Manifestations

The systemic manifestations of Bloom Syndrome include short stature, erythematous facial skin with malar hypoplasia, beaked nose, micrognathia and dolichocephaly [223]. Patients can also have hyper and hypopigmented skin lesions. Immunodeficiency is common, leading to pulmonary infections and chronic lung disease. Patients usually have hypogonadism, leading to infertility. Although there have been a few reported successful pregnancies in affected females [224]. Patients have a high incidence of diabetes and decreased intelligence [222]. Due to replication malfunctioning, patients experience an increased incidence of malignancies of lower and upper gastrointestinal tract, genitalia, urinary tract and skin.

Before the age of 20, leukemia is the most common malignancy, while after the age of 20, sarcomas and carcinomas are more common [222]. Other syndromes with increased rates of malignancies generally have specific malignancies but the wide variation of malignancies seen is a distinct characteristic of Bloom syndrome [223].

Ophthalmic Manifestations

The ophthalmic manifestations of Bloom Syndrome are varied. Early onset retinal drusen has been reported [225]. The drusen are generally reported to be hard, small and non-confluent [226]. Aslan et al. suggest that the premature drusen is a sign of early aging and that patients with early-onset aging should be screened more prudently for malignancies, though no specific association has been found [225].

Diabetic retinopathy is generally not seen in patients with Bloom syndrome, but there is a strong association with the development of type-II diabetes mellitus. This is thought to occur due to limited life expectancy of Bloom patients, however diabetic retinopathy has been reported [226].

There is also a case report of leukemic retinopathy in a patient with bilateral intraretinal, subretinal and white-centered hemorrhages throughout the posterior pole [226].

Reports have also included café au lait lesions, photosensitive telangiectatic erythema, madarosis and sectoral iris pigmentation [227], bulbar conjuntival telangiectasia [228], conjunctivitis [229], narrow angles [226], unilateral retinoblastoma [230] and bilateral optic nerve hypoplasia [228].

Diagnosis

Bloom syndrome is frequently diagnosed by bromodeoxyuridine chromosomal analysis, when cells are analyzed for increased sister chromatid exchanges and other DNA abnormalities associated with Bloom Syndrome [222].

Immunoblotting and immunohistochemistry can be used to screen for defect BLM protein though genetic testing is needed for confirmation [231].

Genetic testing to identify a mutated BLM gene can be done and diagnosis can be further confirmed with detected of altered mRNA or RecQL3 delicase protein structures.

Treatment

There is no cure for Bloom syndrome with a generally poor prognosis and an expected mortality in the second or third decade of life. Management is generally limited to prevention and treatment of infection along with aggressive detection and treatment of malignancies [222].

Hyper IgE Syndrome

Definition

Hyper Immunoglobulin-E syndrome (HIES) refers to a group of disease of various origins that result in elevated serum IgE levels. Autosomal dominant HIES (AD-HIES) is the most common form and caused by a mutation in the transcription factor Signal Transducer and Activator of Transcription 3 (*STAT3*) [232]. The classic clinical findings include eosinophilia, eczema, and recurrent skin and pulmonary infections. In addition to elevated IgE levels leading to eosinophilia and atopic disease, the genetic disorder results in defective cytokine signaling including IL-6 and IL-22, which leads to Th17 dysfunction. This explains the immunodeficiency seen clinically [233].

History

The constellation of clinical symptoms were first described in 1966 by Davis et al. with a description of 'cold' abscesses associated with severe atopic dermatitis [234]. The abscesses were referred to as 'cold' given the lack of surrounding calor or erythema. The association between the clinical constellation of symptoms and elevated IgE levels was described by Buckley in 1972, leading to eponym Buckley's syndrome [235]. *STAT3* mutation and its association with the most common autosomal dominant form of HIES were described in 2007 [236]. The defect in *DOCK8* is the most common defect found in the autosomal recessive form [237].

Epidemiology

No formal epidemiological studies have been performed. The NIH classifies the disease as 'rare,' which means an estimated prevalence of less than 1 in 200,000. Over 200 cases have been reported in the literature [237]. There is no gender preference [233].

Systemic Manifestations

HIES is characterized by the classic triad of eosinophilia, eczema and recurrent skin and pulmonary infections. The autosomal recessive forms of the syndrome have a varied clinical presentation, with viral infections more common [237]. AD-HIES has a more classic presentation.

Pulmonary infections are primarily of *S. Aureus* etiology and less frequently *Streptococcus Pneumoniae* and Haemophilus species [235]. Chronic lung disease along with its accompanying complications, such as Pseudomonas and aspergillus infections, can occur. Fungal infections have also been reported to cause gastrointestinal infections and meningitis [238].

AD-HIES has abnormal craniofacial features with characteristic facies, craniosynostosis, and retained childhood dentition [239, 240]. Patients also may have hyperextensibility, scoliosis and osteoporosis [241]. Vascular abnormalities such as coronary artery tortuosity, aneurysms and hypertension have been reported [242]. AD-HIES patients are at an increased risk of malignancy, with non-Hodgkin lymphoma the most commonly reported [243].

Ophthalmic Manifestations

The most commonly reported ophthalmic complication associated with HIES is recurrent chalazia [244, 245], with *S. aureus* as the identified organism in one case [246]. Other reported complications include bilateral kerataconus [247] and candida endogenous endophthalmitis [248]. Corneal ulceration with perforation despite appropriate therapy has been reported [249, 250]. One case report of retinal detachment and complicated cataract [251] has been reported in the literature. Arora et al. hypothesize that the mechanism is similar to reported atopic dermatitis related retinal detachments.

Diagnosis

The NIH developed a clinical scoring that includes immunologic/infectious manifestations and skeletal/connective tissue abnormalities. The scoring system includes elevated IgE level, abscesses, bone and facial abnormalities, etc. Serum IgE levels >2000 IU/mL is the generally accept level for hyper IgE [237]. Molecular genetic testing of *STAT3* confirms the diagnosis of AD-HIES, but a negative test does not exclude the disease due to many reported genetic etiologies of the autosomal recessive form [252].

Treatment

Treatment is focused on prevention and management of infections. Many patients are placed on long-term antibiotics due to recurrent infections. In treatment of respiratory infections, it is important to cover for *Staphylococus aureus*, *Stretococcus pnuemoniae* and H*aemophilus influenzae*. Coverage for *Pseudomonas aeruginosa* and aspergillus should also be considered. There are reports of immunoglobulin use with good outcomes, but this is not considered standard of care [253]. Plasmapheresis, cyclosporine administration and interferon administration have all been reported but not with widespread acceptance [233].

22q11.2 Syndrome

Definition

22q11.2 syndrome is a contiguous gene deletion syndrome and encompasses a wide variety of clinical phenotypes including DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly-face syndrome and cases of autosomal dominant Optiz G/BBB and Cayler cardiofacial syndrome [254]. There are many shared clinical features between these clinical syndromes. Due to the common genotype, which consists of a variable size deletion in the short arm of the chromosome 22, all the phenotypes are commonly referred to as 22q11.2 syndrome. As expected, 22q11.2 syndrome has a very wide clinical presentation. The most salient characteristics are due to a defect in migration of neural crest derived tissues commonly affect thymus, parathyroid glands and large cardiac vessels. Patients suffer from immunodeficiency due to a lack of mature T cells because of thymus hypoplasia.

History

DiGeorge first described common phenotypic features of what would be known as DiGeorge syndrome in 1968 with a report association of congenital ear malformation, hypoparathyroidism, and absent thymus [255]. De La Chapelle first described the 22q11.2 genetic deletion in 1981 which would subsequently lead to the unification of the previously mentioned phenotypic syndromes [256].

Epidemiology

Studies report a wide variety of prevalence rates for the genetic deletion. Kobrynski argues that the best data states that the rate is approximately 1:4500 in the U.S. with a rate of 1:6000–1:6500 in the white, black and Asian population. 1:3800 is reported in Hispanic populations [257].

Systemic Manifestations

As previously mentioned, there are a wide variety of clinical presentations seen in 22q11.2 syndrome. The syndrome classically presents with immune deficiency, cardiovascular abnormalities, palatal defects, hypoparathyroidism, and characteristic facies, though there is wide variation from life threatening complications to only mild phenotypes. The immune deficiency is secondary to thymus hypoplasia and a subsequent absence of mature T cells. This manifests with frequent infections.

The most common cardiac complications include tetralogy of Fallot, interrupted aortic arch, ventriculoseptal defect, and truncus arteriosus [257]. There are a large percentage of patients with palatal anomalies ranging from cleft palate and velopharyngeal insufficiency to bifid uvula. Other common manifestations, as reported by Kobrynski include neurologic abnormalities, speech delay, renal anomalies, developmental delays, schizophrenia, and lower limb anomalies. There is also an increased incidence of development of IgA deficiency, another immunodeficiency previously described [257].

Ophthalmic Manifestations

Forbes et al. give a thorough review of ophthalmic manifestations of 22q11.2 deletion syndrome. The two most common manifestations were posterior embryotoxon in 49 % of patients and tortuous retinal vasculature in 34 % of affected patients. In order of decreasing prevalence, Forbes reports the following manifestations: strabismus (exotropia > esotropia), eyelid hooding, amblyopia, ptosis, distichiasia, prominent iris crypts, prominent corneal nerves, and tilted optic nerve [254].

Since that review, case reports describe uveitis [258], absence of nasolacrimal duct [259], and Peters anomaly [260]. Crewther describes muscular abnormalities lead to decreased accommodation, convergence, fusional reserves, and stereopsis thought to be related to generalized hypotonia experienced by patients [261].

Diagnosis

The diagnosis starts with clinical suspicion based on at the constellation of presenting symptoms. The diagnosis can be confirmed with FISH testing chromosomal micro array for the chromosomal deletions. A negative test does not exclude the diagnosis, as another locus for phenotypic DiGeorge and velocardio syndromes have been described.

Treatment

Treatment consists of managing of the variety of complications that can occur. Bacterial infections are treated appropriately with antibiotics. The highest morbidity and mortality is from cardiac defects and should be addressed. Cardiac surgery is commonly needed. Patients must take life-long calcium and Vitamin D due to hypoparathyroidism. Thymus transplantation for completely absent thymus has been reported with good success [262].

Hereditary Angioedema

Definition

Hereditary Angioedema (HAE) is a rare autosomal dominant immune system response. It is characterized by repeated episodes of angioedema in various parts of the body. There are three types. Type I and type II are due to lack of functioning C1 inhibitor (C1-INH) protein, which lead to over-expression of the complement system, and subsequent over-activation of related cytokines and inflammatory response. These types of HAE are due to mutations in the C1 inhibitor gene found on chromosome 13. Type I leads to decreased C1 inhibitor levels and type II leads to a dysfunctional, as opposed to absent, protein. Type III is a distinct entity in that C1 inhibitor levels are measured to be normal. There is thought that this type is due to malfunction of the factor XII gene, though there is not consensus on the subject [263]. Type II occurs predominately in females and seems to be related to estrogen levels.

History

Milton first described angioedema in 1876 and Quicnke used the term angioneurotic edema to describe edema associated with an increased emotional state [264]. The first description of HAE is commonly attributed to Osler in 1888, when he described three generations of one family affected by swelling of arms, buttocks, legs, and throat. Osler also describes GI disturbances associated with the episodes [265]. Donaldson and Evans first described an absence of C1-INH in patients with the disease [266].

Epidemiology

Estimated prevalence of disease is 1:50,000 with reported worldwide prevalence rates ranging from 1:10,000 to 1:150,000 [267].

Systemic Manifestations

HAE classically presents in the early part of the second decade of life, though there have been reports of early onset [268]. HAE presents with repeat episodes of angioedema of arms, legs, lips, eyes, tongue, genitals and abdomen. The intestinal swelling usually presents with abdominal cramping, vomiting, diarrhea and pain. The largest cause of mortality is due to airway blockage if throat edema is substantial, with larynx involvement reported to be involved in approximately 2% of attacks [269]. Patients can also have hoarseness and demonstrate symptoms of distributive shock. There is typically no itching/hives, as the mechanism is bradykinin-related, as opposed to histamine-related.

In a review of pediatric HAE, patients also suffered from atopy, frequent infection, asthma, and migraines [268]. There is a reported association with smell impairment. There are reported associations with HAE and autoimmune diseases, most commonly SLE, though this association is not universally accepted [267].

Ophthalmic Manifestations

Hereditary angioedema can manifest as edema of subcutaneous and submucosal tissues of the skin and other organ systems as described above. Periorbital involvement is nonspecific to HA, but there have been case reports that demonstrate ocular involvement [270]. HA can present with subacute edema of the eyelids [264]. There has been a case report of HA causing unilateral lacrimal gland atrophy and subsequent unilateral dry eye syndrome in one patient [271].

Diagnosis

There is commonly a 10-year delay between onset of symptoms and diagnosis. Deficiency of the C4 complement component and normal concentration of C3 can be used for screening purposes. C1 inhibitor levels and functional levels are needed to confirm diagnosis for type I and II HAE [269].

Treatment

A recent panel review of guidelines for the HAE treatment gave the following recommendations:

Epinephrine, corticosteroids, and antihistamines are not efficacious and are not recommend for HAE. Fresh frozen plasma has been used in acute attacks, though reports of exacerbating the attacks have made this treatment modality controversial. Management of attacks should be based on the region of body swelling with special consideration of laryngeal swelling and its ability to affect airway patency. Five drugs have been shown to be efficacious and safe for treatment of HAE attacks. Three of the drugs involve replacement therapy with C1-INH (Cinryze, Berinert, and Rhucin). The two other drugs antagonize bradykinin generation by inhibiting plasma kallikrein (ecallantide) or antagonizing at the bradykinin B2 receptors (icatibant).

Prophylaxis with fresh frozen plasma (FFP), C1-INH replacement or short anabolic androgen therapy may be indicated in patients for short term when the patient is to undergo

pregnancy, significant dental work, surgical procedures, or invasive medical procedures such as endoscopy. Long-term prophylaxis is not universally recommended [272].

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Ocular Manifestations of Cardiac Disease

4

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Introduction

Pediatric cardiovascular disease is considerably different than that of adults. Most pediatric heart disease is congenital heart disease whereas most adult heart disease is acquired. Symptomatic infants typically have a limited set of symptoms frequently comprised of tachypnea, poor feeding, and sometimes, slow weight gain. Some forms of congenital heart disease are not diagnosed until later in life. Likewise, ocular manifestations of cardiac disease vary greatly in the pediatric versus adult population. Congenital disorders of the anterior segment, optic nerve, and retina predominate. These disorders may be overlooked unless referred to a specialist.

This chapter will focus on associations of pediatric heart disease and ocular manifestations with a focus on congenital heart disease and hypertension. In addition, a table will outline the multitude of syndromes that commonly have both cardiac and ocular abnormalities. There are pediatric heart diseases that cause significant morbidity but that are rarely associated with ocular findings. These conditions, such as arrhythmias and cardiomyopathy, will not be covered in detail.

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Congenital Heart Disease

Definition

Congenital heart disease (CHD) may be divided into cyanotic and acyanotic defects. Cyanosis refers to the bluish discoloration of the skin secondary to the presence of a sufficient quantity of deoxyhemoglobin in the blood, estimated to be between 2 and 5 g/dL. Cyanosis as a result of congenital heart disease occurs as a result of a right to left shunt or because of mixing of systemic and pulmonary venous return. Tetralogy of Fallot (TOF) is the most common cyanotic heart defect. Ventricular septal defect (VSD), an acyanotic defect, comprises 30–40 % of congenital heart disease making it the most common form of congenital heart disease [1].

History

In 1861, Knapp first described the changes in the fundus in patients with cyanotic congenital heart disease. He presented his cases and a watercolor painting of the findings in a lecture before the Heidelberg Society. In 1863, Liebreich described a case of his own with similar findings and coined the term "cyanosis retinae." Posey summarized the above cases as well as his own case in an 18-case series of cyanosis retinae. He reported "enormously dilated and tortuous veins, attaining a size, which is rarely equaled in any other condition." The arteries are similarly distended, but to a lesser degree. Both vessels are also darker than normal, with veins a deep violet color and arteries the color of normal veins. Capillaries are also distended and more obvious. Pulsations are absent. Small hemorrhages can be frequent, located near the disk, though larger hemorrhages may be seen in the macula, affecting vision [2] (see Fig. 4.1).

Carpenter, in 1894, described the "everyday experience" of extracardiac malformations in patients with CHD, including ocular defects, such as corneal opacity, iris coloboma,

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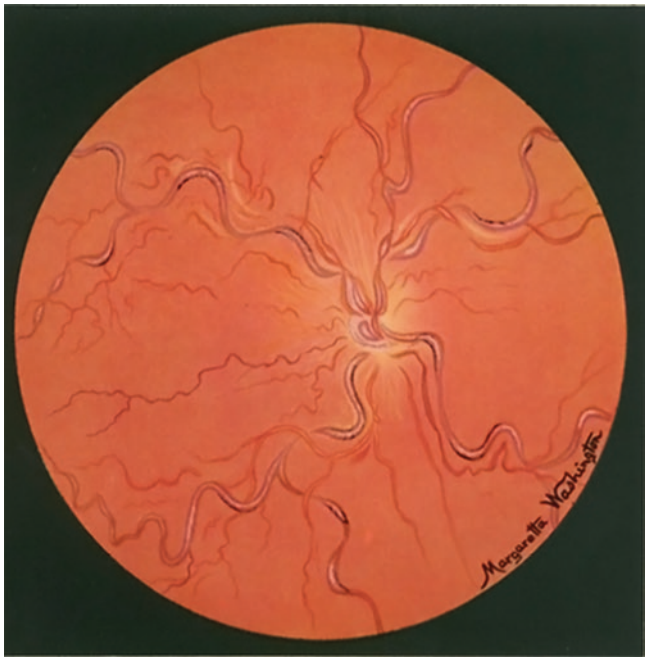

Fig. 4.1 Dilated and tortuous retinal veins and arteries characteristic of cyanosis retinae [2]

orbital defects, and ptosis. He also described cyanosis retinae, emphasizing the dark, cyanotic color of the red reflex, as well as an increased number of vessels of the optic disc. He proposed that the cyanotic fundus in combination with the tortuosity of retinal vessels indicated a complex cyanotic heart defect involving pulmonary stenosis (later known as TOF). He emphasized the importance of the fundus exam in patients with cyanotic CHD [3].

Tyson described his own patient with findings suggestive of TOF. In addition to the characteristic fundus with violet color of cyanosis retinae, there was a bluish tint to the palpebral conjunctiva with dilation of conjunctival vessels encroaching on the cornea. Color fields were markedly contracted. Vision was 20/20 [4].

Epidemiology

The incidence of congenital heart disease (CHD) varies depending on methodologies of research. The incidence of moderate to severe forms of CHD is about 6/1,000 live births. The incidence is as high as 75/1,000 live births if small, trivial lesions are included [1]. While the cause of most CHD is classically thought to be multifactorial in origin, genetic syndromes cause a significant number of cases. The prevalence of extracardiac malformations associated with CHD was reviewed in the Nationwide Inpatient Sample database from 1998 to 2008 by Egbe, et al. Their group found the total prevalence of extracardiac malformations to be 13.6 %. The prevalence for nonsyndromic malformations was 11.4 % and the prevalence for genetic syndromes was 2.2 %. The most common malformations involved the musculoskeletal, central nervous system, and renal-urinary systems. They hypothesized that the epidemiology of patients with congenital anomalies has been altered by changes in prenatal factors, such as termination of pregnancy for fetal anomalies and prenatal vitamin supplementation [5]. Indeed, other studies have found higher rates of extracardiac malformations, ranging from 25 to 44 % [6, 7].

It is not widely known, but many patients with CHD have a much higher incidence of ocular manifestations as well. In a review of 500 patients with CHD aged six days to fifteen years, Alfano noted that 14.4 % of these patients had an abnormality of either the eyes or the ocular adnexa [8]. A large number of recognizable syndromes consist of abnormalities involving multiple systems. The specific association of these abnormalities may be important in delineating the etiology and pathogenesis of the syndrome. The association of cardiac and eye defects is common in many of these multiple malformation syndromes. See Table 4.1 for a complete listing of disorders that contain cardiac and ocular abnormalities.

Systemic Manifestations

Heart disease presents in the newborn and young infant in a variety of ways, including respiratory distress, cyanosis, shock, arrhythmia, and heart murmur. The older infant or child generally presents with feeding difficulties, tachypnea, failure to thrive, and heart murmur. Many children with CHD are asymptomatic. Diagnostic modalities include electrocardiography, echocardiography, cardiac catheterization, and cardiac magnetic resonance imaging. Echocardiography is the primary diagnostic tool used to define cardiac anatomy in children.

Rare complications of CHD include stroke and cerebral abscess. Stroke tends to occur in young children less than two years of age, and the predisposing conditions include endocarditis, a right to left shunt that allows paradoxical emboli to the brain, and increased blood viscosity. Neurologic signs include acute hemiplegia, local or generalized seizures, and ataxia. Cerebral abscess results from a local suppurative infection of brain tissue, and the most important mechanism predisposing to this condition is the right to left shunting of blood. Signs of increased intracranial pressure are predominant in cerebral abscess. Neuro-ophthalmologic signs may be common to both, including papilledema, third and sixth cranial nerve palsies resulting in diplopia, abnormal pupillary findings, and ptosis [9].

Table 4.1 Cardiac defects and associated eye defects

Syndrome	Eye abnormality	Cardiac abnormality
Chromosomal abnormality syndromes		
Trisomy 21 (Down syndrome)	Up-slanted palpebral fissures, epicanthus, Brushfield spots with peripheral hypoplasia of iris, strabismus, high percentage of refractive errors, amblyopia, nystagmus, blepharitis, optic nerve abnormalities, cataract, glaucoma, acute keratoconus with corneal hydrops [41, 42]	Cardiac abnormalities in 40–65 %; most commonly atrioventricular septal defect, ventricular septal defect, also isolated atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, aortic arch abnormalities, aberrant subclavian artery [43]
Trisomy 18 (Edwards syndrome)	Hypertelorism, hypoplastic supraorbital ridge, colobomatous microphthalmia, corneal opacity, cataract, microcornea, retinal depigmentation, congenital glaucoma [44, 45]	Cardiac abnormalities in >90 %; most commonly ventricular septal defect, patent ductus arteriosus, atrial septal defect, also bicuspid aortic and/or pulmonic valve, pulmonic stenosis, coarctation of the aorta, transposition of the great arteries [46]
Trisomy 13 (Patau syndrome)	Colobomatous microphthalmia, cataract, corneal opacity, glaucoma, persistent fetal vasculature, intraocular cartilage, retinal dysplasia [44, 47]	Cardiac abnormalities in >80 %; ventricular septal defect, patent ductus arteriosus, atrial septal defect, dextroposition, in decreasing order of frequency [46]
Deletion 4p syndrome	Strabismus, iris coloboma, ocular hypertelorism, epicanthal folds [44]	Ventricular septal defect, patent ductus arteriosus [46]
Deletion 5p (Cri du Chat syndrome)	Hypertelorism, epicanthus, strabismus [44]	Ventricular and atrial septal defects, patent ductus arteriosus [46]
Deletion 13q syndrome	Epicanthal folds, ptosis, hypertelorism, microphthalmia, iris coloboma, retinoblastoma [44]	Ventricular septal defect, atrial septal defect [46]
Deletion 18q syndrome	Optic disc pallor, nystagmus, pigmentary retinopathy [44]	Cardiac defects of variable type in 25 %[46]
Trisomy 22 (Cat eye syndrome)	Coloboma; microphthalmia, macular hypoplasia, pale discs [44]	Cardiac abnormalities in 33 %; total anomalous pulmonary venous return, persistence of the left superior vena cava [46]
XO (Turner syndrome)	Strabismus in 33 %. Ptosis, hypertelorism, red-green color deficiency, epicanthus, downward-slanting palpebral fissures, blue sclera, nystagmus [44, 48]	Cardiac defects in about 20 %, the majority are coarctation of the aorta, bicuspid aortic valve, aortic stenosis [46]
Syndromes of very small stature, not skeletal dysplasia [46]		
Cornelia de Lange syndrome	Long curly eyelashes, bushy eyebrows, synophrys; strabismus, myopia, ptosis [44]	Cardiac defects in about 30 %, most commonly ventricular septal defect [46]
Rubenstein-Taybi syndrome	Epicanthus, strabismus, refractive error, cataract, coloboma, ptosis, long eyelashes, hypertrichosis [44]	Cardiac abnormalities in 33 %; most commonly ventricular septal defect, patent ductus arteriosus most common [46]
Syndromes of moderate short stature, facial, ± genital defects [46]		
Smith-Lemli-Opitz syndrome	Bilateral ptosis, epicanthus, strabismus [44]	Endocardial cushion defect, coarctation of the aorta, tetralogy of Fallot, ventricular septal defect, pulmonary valve atresia and stenosis [46]
Williams syndrome	Epicanthal folds, ocular hypertelorism, strabismus [46], hyperopia, retinal vascular tortuosity	Cardiac abnormalities in 75 %; most commonly supravalvular aortic stenosis, peripheral pulmonary artery stenosis, pulmonic valve stenosis, ventricular and atrial septal defect, also renal artery stenosis with hypertension, hypoplasia of the aorta [46]
Noonan syndrome	Ptosis of one or both eyelids, exophthalmos, hypertelorism, myopia, keratoconus, strabismus, nystagmus [13, 46, 49]	Cardiac defects in about 67 %. Most common are pulmonary stenosis, ventricular and atrial septal defects, patent ductus arteriosus, branch stenosis of pulmonary arteries [13, 46]
Syndromes with facial features as major feature [46]		
Treacher-Collins syndrome	Lower lid coloboma [46]	Variable congenital heart defects in minority [46]
CHARGE association	Colobomatous malformation sequence in 80 %, ranging from isolated iris coloboma without visual impairment to clinical anophthalmos, most commonly retinal coloboma [46, 49–51]	Cardiac abnormalities in 64 %; most commonly conotruncal defects (tetralogy of Fallot, double outlet right ventricle), aortic arch anomalies [49, 51, 52]
Storage disorders [46]		
Hurler syndrome	Corneal clouding, ptosis, strabismus, thickened eyelids, glaucoma, pigmentary degeneration of retina [44]	Coronary artery disease, aortic and mitral insufficiency [53]
Scheie syndrome	Corneal clouding but central area less severely affected, open angle glaucoma, frequently in fourth to fifth decade [44]	Aortic valve disease [46, 53]

(continued)

Table 4.1 (continued)

Syndrome	Eye abnormality	Cardiac abnormality
Hunter syndrome	Cornea usually clear, pigmentary degeneration of retina often seen [44]	Coronary artery disease, valvular disease [53]
Morquio syndrome (Types A, B)	Corneal clouding by age five to ten years [44]	Aortic valve disease [53]
Maroteaux-Lamy syndrome	Corneal clouding in early life [44]	Aortic valve disease [53]
Connective tissue disorders [46]		
Marfan syndrome	Lens subluxation, increased axial globe length, myopia, retinal detachment [44, 54]	Ascending aorta dilatation, mitral valve prolapse, mitral regurgitation, aortic regurgitation, aortic dissection [46]
Homocystinuria	Dislocated lenses, cataract, secondary glaucoma, peripheral cystic degeneration of retina [44]	Arterial and venous thrombosis, medial degeneration of the aorta and large arteries [46]
Ehlers-Danlos syndrome	Epicanthal folds, blue sclera, keratoconus, lens subluxation, retinal detachment [44]	Mitral valve prolapse ± tricuspid valve prolapse, aortic root and/or sinus of Valsalva dilatation, increased susceptibility to dissecting aneurysm [46]
Hamartoses [46]		
Incontinentia pigmenti	Peripheral retinal nonperfusion [44]	Patent ductus arteriosus, hypertension [46]
Tuberous sclerosis syndrome	Hamartomatous tumors of the disc and retina, intracranial lesions producing papilledema or optic atrophy [55]	Myocardial rhabdomyoma [46]
Neurofibromatosis	Neurofibromas within the soft tissues of the lids and orbits, visual pathway glioma, Lisch nodules [55]	Coarctation of the aorta, renal artery stenosis [46]
Multiple lentigines (LEOPARD) syndrome	Hypertelorism, ptosis [46, 56]	Hypertrophic cardiomyopathy, mostly involving the left ventricle, pulmonic stenosis, ECG conduction abnormalities (prolonged PR interval) [46, 56]
Environmental agents [46]		
Fetal alcohol syndrome	Tortuosity of retinal vessels, optic nerve hypoplasia or atrophy, esotropia on downward gaze, blepharophimosis, hypotelorism, ptosis, epicanthus, thickened eyebrows [44]	Ventricular septal defect, atrial septal defect, tetralogy of Fallot, coarctation of the aorta [46]
Fetal hydantoin syndrome	Epicanthus, mild hypertelorism, ptosis, strabismus [44]	Pulmonary or aortic valvular stenosis, coarctation of the aorta, patent ductus arteriosus, septal defects [46]
Congenital rubella syndrome	Ocular abnormalities in 78 %; most commonly retinopathy, cataract, strabismus, nystagmus, microphthalmia, also glaucoma, coloboma, optic atrophy, corneal opacity, dacryostenosis [57]	Cardiac abnormalities in 58 %; most commonly patent ductus arteriosus, pulmonic stenosis, ventricular septal defect; also tetralogy of Fallot, coarctation of the aorta, mitral stenosis, atrial septal defect [57]
Miscellaneous		
Arteriohepatic dysplasia (Alagille) syndrome	Posterior embryotoxon [46]	Peripheral pulmonic stenosis, atrial and ventricular septal defect, patent ductus arteriosus, coarctation of the aorta [46]
Leber congenital amaurosis syndrome	Poor vision with often normal-appearing fundus, markedly reduced or absent electroretinogram, chorioretinal degeneration later in life [44, 58]	Dilated cardiomyopathy [58]
Kearns-Sayre syndrome	Chronic progressive external ophthalmoplegia with ptosis presenting in childhood, pigmentary degeneration of the retina [59–62]	Atrioventricular block [59, 60, 63]
Kartagener syndrome	Retinal pigmentary degeneration, cataract [44]	Dextrocardia, heart block [46]
Goldenhar (Oculo-Auriculo-Vertebral) syndrome	Epibulbar dermoid involving conjunctiva and cornea, coloboma of upper lid, strabismus, lacrimal drainage system anomalies [44, 64]	Most commonly tetralogy of Fallot, also ventricular septal defect [46, 65]
Axenfeld-Rieger syndrome (FOXC1 mutation)	Anterior segment abnormalities, glaucoma [46, 66]	Valve abnormalities, atrial septal defect [46]
Bardet-Biedl syndrome	Pigmentary retinopathy [46]	Aortic stenosis [46]
Mowat-Wilson syndrome	Microphthalmia, coloboma, Axenfeld anomaly, pupillary atrophy, ptosis, cataract, retinal aplasia, strabismus, nystagmus [46, 67]	Cardiac abnormalities in 45 %; patent ductus arteriosus, atrial septal defect, ventricular septal defect, tetralogy of Fallot, pulmonary atresia, pulmonary stenosis, aortic valve abnormalities [46, 67]
PHACES syndrome	Ocular abnormalities in 33 %; morning glory disc, choroidal hemangiomas, cryptophthalmos, exophthalmos, colobomas, posterior embryotoxon, optic atrophy, microphthalmia, strabismus, cataract, glaucoma, optic nerve hypoplasia [68]	Cardiac abnormalities in 44 %; aortic aneurysm, coarctation of the aorta, arterial anomalies [69]
Graves disease	Ocular abnormalities in 50 %; lid retraction, proptosis, mild corneal exposure, chemosis, fat pad enlargement, restrictive strabismus [70, 71]	Sinus tachycardia, mitral valve prolapse, and mitral regurgitation [72]

Infective endocarditis is defined as a bacterial or fungal infection of the endocardium, heart valves, or related structures. Risk factors for endocarditis include congenital heart disease, intravascular hardware such as central venous catheters, intravenous drug use, immunosuppression, and a previous diagnosis of endocarditis. The American Heart Association recommends antibiotic prophylaxis prior to procedures known to cause bacteremia for people with cyanotic heart disease, a previous diagnosis of endocarditis, within six months of intracardiac surgery, after surgery for congenital heart disease with a residual lesion adjacent to prosthetic material, or after cardiac transplantation with valvulopathy. The most common presenting symptoms include prolonged fever, malaise, and arthralgias. Common exam findings include weight loss, splenomegaly, petechiae, new or changing heart murmur, heart failure, and embolic events. Emboli to the cerebral circulation are not very common [10].

Ophthalmic Manifestations

A prospective study from 1968 attempted to define the types of eye defects in a group of 85 children with various types of both cyanotic and acyanotic heart disease [11]. This study had some notable design flaws: these children were all over the age of six years, had no major congenital malformations, and the study was completed before corrective cardiac surgery was available for many of these heart defects. The eye conditions that were surveyed were amblyopia, strabismus, structural defects, and refractive anomalies.

Patients with cyanotic disease, including tetralogy of Fallot (TOF) and dextrotransposition of the great arteries (TGA), had the highest incidence of ophthalmic abnormalities at 86 %. Patients with acyanotic lesions characterized by obstruction including aortic stenosis and pulmonary stenosis, had a 64 % incidence of eye abnormalities. Acyanotic left to right shunts, such as atrial septal defect, ventricular septal defects, and patent ductus arteriosus had ophthalmic abnormalities in 49 % [11].

All four types of ophthalmic defects were more common in the cyanotic patients. The overall incidence of strabismus was 14 %, but this incidence doubled in the cyanotic patients at 28 %. Structural defects were highest in the cyanotic patients. Amblyopia was present in one or both eyes of 50 % of the cyanotic TOF patients. In contrast, only 15 % of children with other heart lesions had amblyopia. Overall, 12 % were hyperopic and 24 % myopic. In cyanotic TOF patients, 38 % were myopic [11].

This study required strict criteria for eye normality, and many of these eye defects were minor and did not require intervention. The eyes of children with left to right shunts were probably little different from normal populations since many of their defects were of a trivial nature. The results as a whole showed a trend for more ocular lesions in the acyanotic obstructive group, and an even higher incidence in cyanotic patients [11].

Of the total group of 85 children, 23 had eye lesions reducing their visual acuity to 6/18 or less. With thorough ophthalmologic evaluation nine of these patients had severe visual defects not detected previously. The authors concluded that screening exams were certainly warranted in cyanotic patients [11]. In the modern era it is difficult to generalize these data to current practice, however, because medical and surgical therapy for most forms of congenital heart disease is quite different now than it was in 1968.

Several investigators have noted the association of ptosis with CHD [12–14]. Larned reviewed the records of 156 cases of congenital ptosis that presented to the pediatric ophthalmologic clinic at a major eye hospital [12]. Seven cases of documented structural heart defects were detected, with an observed frequency of 4.4 % (five times the incidence of CHD in the general population). Of note was the fact that all the heart defects were acyanotic, which was also noted in the 12 patients described by Sonoda [14]. The conclusion of these investigators is that the association of ptosis with acyanotic heart disease might be specific, but the etiology of this association is unknown [12].

Cyanotic heart disease has been found to be associated with retinopathy, in some cases resulting in vision loss [15, 16]. Petersen examined the retinas of 83 patients with cyanotic heart disease coming in for cardiac catheterization [15]. The majority of these patients had TOF or TGA. They found that 52 had some degree of retinopathy, with dilated and tortuous retinal blood vessels, and 12 had papilledema. The severity of these changes was closely related to the arterial saturation and hematocrit, but not to pCO2, pH, CVP, patient's age, or type of cardiac lesion. Severe retinopathy and papilledema were present only when the arterial saturation was less than 86 %, or the hematocrit was greater than 49 % [15]. The hyperviscosity secondary to elevated hematocrit may rarely lead to central retinal vein occlusion [16].

The effect on the retinal vasculature of the removal of cyanosis has also been studied [17]. Twelve cyanotic patients were examined prior to surgery, and marked dilatation and tortuosity of both retinal arterioles and venules were noted in all. As in the previous study, the abnormalities were most severe in those with the highest hematocrit. Post operatively, it was noted that the fundi became lighter, the abnormal vascularity returned to normal, and the tortuosity and dilatation improved. The greatest changes were noted in the first two weeks postoperatively, with further improvement up until three months postoperatively.

Retinopathy of prematurity (ROP) can be a devastating eye disease of premature infants. Hyperoxia was initially identified as the culprit in this disease, although now it is recognized to be multifactorial. Since hyperoxia continues to

be a major contributing factor, it was theorized that cyanotic premature infants, with low levels of arterial p02, could be immune to this disease [18]. However, studies have noted that ROP certainly does occur in cyanotic premature infants, and they may even be at an increased risk [18, 19]. Thus, the hypoxemia of heart disease does not protect from ROP, and these patients should be appropriately monitored. Furthermore, cyanotic heart disease may cause retinal vascular abnormalities, including arterial dilation and venous tortuosity. These vascular findings are also known as "plus disease." When a premature infant develops plus disease during ROP screening, the ophthalmologist must treat the infant to prevent retinal detachment. Generally after treatment, arterial dilation and venous tortuosity subsides, signifying an adequate response to treatment. However, in cyanotic heart disease such as tetralogy of Fallot, the plus disease may not resolve following treatment. This may create confusion for ROP screening and treatment [20].

Horner syndrome is a well-known disorder consisting of three components: miosis, ptosis, and anhydrosis [21]. The miosis is due to paresis of the sympathetically innervated pupillary dilator, with an unrestricted parasympathetically innervated pupillary constrictor. The ptosis is often slight, the result of paresis of sympathetically innervated smooth muscle in both upper and lower lid. The main elevator of the lid, levator palpebrae, is unaffected given its innervation by the oculomotor nerve. Anhydrosis is present on the affected side, along with deficient vasoconstriction. Horner syndrome can be congenital in origin, but may also be acquired. Cases have been reported secondary to large aortic aneurysms [21, 22]. It is thought that the clinical features of Horner syndrome are caused by traction or pressure on ascending preganglionic sympathetic fibers [21]. In addition, many infants with coarctation of the aorta receive subclavian flap aortoplasty. A rare complication of this operation is traumatic injury to the sympathetic ganglion chain with resultant Horner syndrome [23].

Familial cases of eye defects associated with CHD have been reported [24, 25]. A mother with glaucoma had three daughters, all with congenital glaucoma and tetralogy of Fallot (TOF) [24]. Congenital glaucoma is usually inherited in an autosomal recessive manner, but in these cases an autosomal dominant pattern is evident. An abnormality of neural crest cell development and/or migration is responsible for conotruncal defects such as TOF. These cells also give rise to the iridocorneal angle, so that the conotruncal defects and glaucoma may be related pathogenetically [24]. A family has also been reported in which the father and all three sons had ptosis and complex coarctation of the aorta. Again, autosomal dominant inheritance is apparent [25].

The most common ocular feature of endocarditis is a blot hemorrhage in the intraretinal and preretinal layer, often found near the optic disc [26]. It may have a pale center, which is a cotton wool spot (ischemic area) known as the Roth spot. Roth spots are not specific to bacterial endocarditis. They are uncommon, occurring in only five to seven percent of children with endocarditis. Most young patients with bacterial endocarditis do not have any ocular symptoms [10]. However, rarely vision loss can occur secondary to central retinal artery occlusion attributed to an embolic process [10, 27].

Diagnosis

Many infants and children with congenital heart disease are asymptomatic. Infants with complicated heart disease occasionally present at birth with profound cyanosis or cardiogenic shock. The improved accuracy of fetal diagnosis of heart disease has decreased the frequency of emergent neonatal presentation of congenital heart disease. When symptomatic, common symptoms in the first year of life are poor feeding, tachypnea, and poor weight gain. Older children may manifest exercise intolerance or respiratory insufficiency. Diagnosis is usually made with transthoracic echocardiography. The majority of pediatric cardiac catheterization is interventional. There is growing experience and use of adjunctive imaging modalities including three-dimensional echocardiography and cardiac magnetic resonance imaging [28].

Management

Treatment of congenital heart disease involves medical management, transcatheter interventions, and surgical palliation. Care of the patient with congenital heart disease is a lifelong endeavor. The current population of adults with congenital heart disease in the United States is larger than the population under age 18 with congenital heart disease [29].

The management of the various eye defects associated with CHD is no different from that in similar patients without heart disease. In general, it is preferable to withhold eye surgery until the appropriate cardiac surgical procedure has been performed.

Hypertension

Definition

Hypertension in childhood may be defined as systolic or diastolic blood pressure greater than or equal to 95th percentile for age and height on three or more occasions. Blood pressure measurements between the 90th and 95th percentile for age and height are considered prehypertension [30].

Blood pressure is determined by the product of cardiac output (CO) and systemic vascular resistance (SVR).

Any process which increases one of these factors, while the other factor remains the same, will increase blood pressure. Causes of increased cardiac output include increased sympathetic stimulation secondary to anxiety, and increased blood volume secondary to excess salt intake. Increased peripheral resistance may be caused by alpha-adrenergic receptor stimulation (i.e. increased circulating catecholamines from pheochromocytoma), increased renin-angiotensin activity (i.e. renal arterial obstruction or renal parenchymal disease), or mechanical factors (i.e. coarctation of the aorta).

History

The first reports of eye findings in young adults with hypertension date to the late 1800s and early 1900s. Vision loss was found in young adults with chronic kidney disease and hypertension (Bright's disease). Ophthalmoscopy revealed papilledema, cotton-wool spots, exudates, and hemorrhages. Pathologic examination upon autopsy revealed marked medial hyperplasia and hyalinization with narrowing of the lumen in retinal arterioles. Microscopic evaluation of cotton-wool patches consisted of microinfarcts or cytoid bodies in the nerve fiber layer. The macular star was identified as collections of lipoidal histiocytes in the outer plexiform layer. No evidence of inflammation was found in the retina or choroid [31].

In 1941, Court described 12 cases of malignant hypertension in children, with an average age of 10 years. All children presented with the clinical symptoms of headache and vomiting. Other symptoms included visual disturbance (67 %), seizures (50 %), abdominal pain (17 %), and exertional dyspnea (8 %). The average highest systolic blood pressure recorded in this study was 230 mmHg and the highest diastolic pressure was 160 mmHg. Hemorrhage was found in 58 % of patients, in the form of hematuria, melena, or epistaxis. The average duration of symptoms was two years, ranging from six months to five years. The disease was 100 % fatal, with death caused by cardiac or renal failure or from cerebral disease or infection. A notable distinguishing sign in children compared to adults was hematuria. Notable absences in children were symptoms of nervousness, lack of energy, exertional dyspnea, and nocturnal frequency. Ophthalmoscopy revealed papilledema with retinal hemorrhages and exudates in all cases [32].

Epidemiology

The prevalence of clinical hypertension is much less in children than in adults. Essential hypertension is the predominant cause of hypertension in the adult, and there is sufficient evidence to conclude that the roots of essential hypertension begin in childhood. Although essential hypertension is also the most common cause of hypertension in childhood and adolescence, a specific etiology is more commonly identified in this age group. In general, the younger the patient with significant hypertension, the more likely a specific correctable cause can be found, and the more aggressive the subsequent investigation should be [33].

Systemic Manifestations

The systemic manifestations of pediatric hypertension may differ depending on the cause. Diagnosing sustained hypertension in childhood is best approached from a consideration of the more common causes at specific ages. In newborn infants, the most common causes are renal artery stenosis and thrombosis, coarctation of the aorta, bronchopulmonary dysplasia, and congenital renal malformations. From infancy to six years, coarctation of the aorta, renal artery stenosis, and renal parenchymal diseases predominate. From six to ten years, renal artery stenosis, renal parenchymal diseases, and primary hypertension predominate. In adolescence, primary hypertension and renal parenchymal diseases are the common causes [30].

Coarctation of the aorta represents an important treatable cause of pediatric hypertension. This condition is secondary to a constriction of the thoracic aorta, usually just distal to the origin of the left subclavian artery. This produces the distinctive clinical feature of normal upper extremity arterial pulsations with upper body hypertension (including the ophthalmic artery), and weakened or absent femoral artery pulses. Strafford studied a group of 65 consecutive patients over the age of one year who were referred and subsequently diagnosed as having uncomplicated coarctation of the aorta. Despite the fact that 89 % of the patients had elevated upper extremity systolic blood pressures and all had differential blood pressure readings between the arms and legs, the diagnosis of coarctation was made prior to referral in only 14 % of the cases [34].

As in adults, it is uncommon for signs or symptoms to be present in children with chronic hypertension. However, with severely elevated blood pressure, one may find signs or symptoms related to the neurologic, visual, cardiac, or renal systems. Neurologic findings include focal or generalized seizures, localizing signs, isolated facial nerve palsy, and headaches [33]. Headaches are a very common finding in children and very non-specific for hypertension, but a severe occipital headache which occurs on awakening may be due to a markedly elevated blood pressure [30]. Common visual disturbances include blurred vision, papilledema, retinal hemorrhages or exudates, and constriction of retinal arteries. Cardiac findings include left ventricular hypertrophy and pulmonary edema. Renal findings are severe back or abdominal pain, renal masses or bruits, and decreased renal function [33].

Ophthalmic Manifestations

In adult hypertensive patients, common retinal changes include sclerosis of retinal arterial walls, retinal arterial tortuosity, and retinal venous compressions at arteriovenous crossings [26]. These findings have been found in pediatric patients as well [35]. The prevalence of retinal vascular abnormalities was studied in a group of 97 children and adolescents, ages six to twenty-three years, being followed in a children's hospital hypertension clinic. The average age of the patients was 14.7 ± 3.5 years, and the average reported duration of hypertension was 30.3 ± 31.1 months. All of these patients had systolic or diastolic blood pressures greater than the 90th percentile for age and sex. Secondary causes of hypertension had been ruled out in all cases. Fundus photography revealed a prevalence of 41 % for arteriolar narrowing, 14 % for tortuosity, and 8 % for arteriovenous nicking. 51 % of the patients had at least one abnormality. Interestingly, there were no statistically significant differences in prevalence of retinal abnormalities between race and sex groups, and no relation between level of systolic or diastolic blood pressure and presence of retinopathy. Patients with retinal vascular changes were significantly younger than those without such changes (13.9 compared to 15.6 years). The conclusion of this report was that the prevalence of retinal vascular abnormalities in this group of hypertensive pediatric patients is similar to the reported prevalence in adult hypertensive patients [35].

Pediatric patients with severely elevated blood pressures have different retinal and/or choroidal manifestations. A shiny, boggy appearance of the retina is probably the most common fundoscopic feature recognized [26]. This is probably due to the leakage of plasma components through the walls of retinal arterioles and/or capillaries, which results in the accumulation of edema and exudates in the retina. More specific signs of severe pediatric hypertension include retinal arterial constriction with luminal attenuation and retinal arterial straightening, but these signs are not commonly observed. Flame hemorrhages, superficial striate intraretinal accumulations of blood, can be demonstrated frequently in severely hypertensive adults but are only occasionally seen in their pediatric counterparts. In some severely hypertensive pediatric patients, diffuse, usually bilateral, shallow to bullous retinal detachments develop. Hypertensive encephalopathy can manifest with papilledema that can occur in the absence of other fundoscopic features of malignant hypertension [26].

Hypertensive retinopathy has even been reported in neonates [36]. In a prospective study of 1941 neonates admitted to a neonatal intensive care unit over a two-year period, Skalina identified 23 neonates (1.2 % of all admissions) with hypertension, defined as a mean arterial pressure greater than 70 mmHg on at least three separate days. Two of these patients died. The remaining 21 infants had a mean birth weight of 2566 g and a mean gestational age of 35.6 weeks. Eleven of twenty-one neonates had a spectrum of retinal abnormalities. All eleven had an increased ratio of venous to arterial calibers. Of these eleven, six had arterial spasm, three had venous dilation, and two had both. Abnormal tortuosity and nicking of the retinal vessels was present in three patients, while four had flame hemorrhages and two had retinal exudates. Of the seven patients with long follow-up, five had complete clearing one to six months after the initial exam (blood pressure had normalized). Retinopathy of prematurity was thought not to be the cause of these retinal changes, since eight of eleven patients were breathing room air for at least 72 h prior to ophthalmoscopy, and the characteristic peripheral retinal vascular changes of ROP were not present in nine of the eleven patients [36].

Coarctation of the aorta is associated with a characteristic corkscrew-shaped tortuosity of the retinal arterioles [37]. Granstrom examined 40 patients with coarctation of the aorta, ranging in age from eight to forty-two years. He found striking tortuosity of the arterioles in 24 (60 %) out of 40 patients. In contrast to tortuosity of retinal vessels that can be found in normal patients, the retinal venules were generally unaffected. In addition to the tortuosity of retinal arterioles, Granstrom noted, and Walker later emphasized a characteristic swinging pulsation of the arterial branches [38]. This "serpentine" pulsation was described as a side-to-side shift of the artery with each heartbeat. These findings were noted more frequently with advancing age, and persisted even after surgery for coarctation of the aorta [39]. In contrast to hypertensive retinopathy, there were very little arteriovenous nicking, hemorrhages, or cotton-wool spots. Fluorescein angiography has revealed tortuosity of the retinal arterioles and an increased density of retinal and choroidal capillaries in the capillary filling phase [40]. The stimuli leading to proliferation of the capillary meshwork in the choroid and retina is the high intra-arterial pressure existing since fetal life.

Diagnosis

The identification of high blood pressure in children is fraught with more difficulties than in adults, and the proper methodology for obtaining the blood pressure is more important. In infants, Doppler techniques are considered superior to cuff pressures, which are difficult to obtain. Dynamap oscillometric unit is probably the most accurate in infancy. In children, proper cuff size is essential. The appropriate sized cuff should be long enough to completely encircle the circumference of the arm, and wide enough to cover approximately 75 % of the upper arm. In general, the cuff blood pressure should be obtained on the right arm, in the sitting position, with the arm on a supportive surface at heart level [30]. It is important to also measure blood pressure in a leg when considering the diagnosis of coarctation of the aorta

with attention paid to a differential between the leg and the right arm in a patient with a left aortic arch. The blood pressure in normal individuals is slightly higher in the leg than the arm. In coarctation of the aorta, the leg pressure will be lower. Published normal values of blood pressure usually always refer to the right arm pressure even when not explicitly stated. When accurate measurements with proper technique have shown consistent elevations in blood pressure, a systematic investigation should be performed. The urgency of the investigation depends upon the severity of the hypertensive process. A thorough history, including a family history to elicit the presence of cardiovascular events such as stroke, myocardial infarction, and sudden death, is indicated. A directed physical examination should be performed, with special emphasis on the following: (1) blood pressure recordings in the arms and legs, and palpation of the femoral pulses to rule out coarctation; (2) palpation of the abdomen for masses; (3) auscultation of the epigastrium and renal angles for bruits; and (4) careful cardiac auscultation to detect cardiac lesions known to be associated with widened pulse pressures and elevated systolic blood pressures (i.e. aortic insufficiency, patent ductus arteriosus) [33].

Some screening laboratory tests are in order, including urinalysis, urine culture, serum electrolytes, BUN, and creatinine. A renal ultrasound with Doppler interrogation of the renal arteries is indicated to assess for renal artery stenosis. These tests should help identify the majority of secondary causes of hypertension, with more specialized tests generally needed to determine treatment and/or prognosis. With definite abnormalities of the physical examination or laboratory studies, one should keep in mind the most common causes for secondary hypertension in each particular age group, as outlined above [33].

Management

Nonpharmacologic therapy should be the initial therapy, including weight reduction as appropriate, regular physical conditioning, avoidance of smoking, and dietary modification to avoid foods high in saturated fats. These measures should be continued even if drug therapy is required. Indications for drug therapy include significant diastolic hypertension, evidence of target organ injury, or signs or symptoms related to increased blood pressure [30].

If drug therapy is deemed essential, a stepped care approach is suggested. First-line therapy usually includes a thiazide-type diuretic or adrenergic inhibitor (i.e. beta-blocker). In adolescents with hyperkinetic-type hypertension, a beta-blocker is often considered first-line therapy. Second- and third-line drugs include smooth muscle vasodilators (i.e. hydralazine) and angiotensin-converting enzyme inhibitors (i.e. captopril) [30].

Management of the ophthalmic disease requires controlling the hypertension, either by medical or surgical means. One can predict improvement in the findings of even severe hypertension. There should be normalization of retinal and choroidal blood vessels; resolution of intraretinal accumulations of blood, edema, and exudates; absorption of subretinal fluid; and even resolution of bullous retinal detachments within several days [26].

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Ocular Manifestations of Child Abuse

5

Naomie Warner, Kathryn M. McCans, and Alex V. Levin

Introduction

Child abuse is categorized into physical abuse, neglect and noncompliance, sexual abuse, and emotional abuse. Each can have ophthalmic manifestations. In the United States, child protection agencies investigated 3.2 million child abuse cases in 2012 [1]. Of all victims, 78.3 % were victims of neglect, 18.3 % physical abuse, 9.3 % sexual abuse, and 78.5 % emotional abuse [2]. Approximately 5 % of all child abuse involves the eye at presentation [3, 4]. By law, all physicians are mandatory reporters and have an obligation to report any suspected abuse to the appropriate child protective authorities.

Physical Abuse

Abusive Head Trauma/Shaken Baby Syndrome

Definition

The American Academy of Pediatrics has identified abusive head trauma to include all forms of abusive injury to the head [5]. The definition includes the subset of injuries due to violent acceleration-deceleration forces with or without blunt head impact, also known as shaken baby syndrome (SBS) which is recognized specifically as a "serious and clearly definable form of child abuse". The degree of forces which result in SBS are so severe that the act would easily be recognized as dangerous. Some estimate that this shaking can be as short as 2–4 s or up to 5–10 s with 10–30 shakes [6, 7]. Starling evaluated 81 cases of perpetrator confessions. Thirty-two perpetrators admitted to shaking only, of which four were assumed to be inaccurate due to the presence of skull fractures or scalp swelling. Of the 32 victims of those perpetrators who admitted to shaking 29 victims had subdural hemorrhage and 27 had retinal hemorrhages [8]. The characteristic constellation of injuries so commonly seen in SBS, as compared to single impact accidental injury is likely due to the effect of repetitive acceleration-deceleration which results in a stacking of forces over time [9].

History

Guthkelch first described injury that that he attributed to shaking, stating that "direct violence is not an essential part" of causing a subdural hemorrhage [3]. Caffey further supported this theory with reference to an admission by an infant nurse who killed three children by confessed shaking [10]. He later described violent shaking as the "whiplash shaken infant syndrome" [11]. Ludwig and Warman first published the term "shaken baby syndrome" in 1984 after reviewing 20 case reports [6]. In 1986, Greenwald published the landmark paper recognizing the entity of traumatic retinoschisis. In 1987 Duhaime and coworkers, suggested that impact was required to produce these injuries, but other work thereafter, including her own, has informed us that shaking alone, without impact, can be fatal [12–14]. A study using lambs has shown that shaking alone, without blunt trauma, can cause brain injury, retina hemorrhage and death [15].

Epidemiology

Abusive head trauma is the most common type of child abuse that results in death [2]. It represents 2.9–4.9 % of all cases reported to child abuse teams [16]. From 2003 to 2008, approximately 0.76 out of 100,000 children between the ages of 0–4 died from abusive head trauma and 8.6 out of

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100,000 were hospitalized for abusive head trauma [17]. Between the years of 2005 and 2009, 30 % of all deaths reported to the U.S. National Child Death Review Case Reporting System were victims of abusive head trauma [18]. Victims of SBS are usually under 1 years old, and almost exclusively under 4 years old, but even adult cases have been reported [3]. Crying has been identified as the highest risk factor for becoming a victim of shaking [18]. The age-specific incidence of children being hospitalized for SBS is similar to the normal age-related crying curve. A normal crying curve demonstrates that an infant will increase the amount of time they cry in the first 23 weeks of life where it peaks and gradually tapers off over the next year. SBS hospitalizations follow this curve with a delay of approximately 4–6 weeks later [19, 20].

Approximately one third of SBS victims die due to their injuries [7, 21–23] and of survivors, 30–65 % sustain permanent neurologic, visual, or learning/behavioral sequelae [3, 24–26]. Vegetative states or severe neurologic disability are seen in 39 % of victims whereas 52 % have mild to moderate disability [21, 27]. Long term follow-up suggests that almost half of all surviving children have below average intelligence and the other half are normal children [27, 28]. Shaking is used as a form of punishment throughout the world [29]. A parental discipline survey conducted in Brazil, Chile, Egypt, India, Philippines, and United States found that greater than 20 % of parents admitted to shaking their children as punishment [30]. In a survey completed by UNICEF rates of shaking were 18 % in Eastern Europe, up to 36 % in West Africa and Central Asia and up to 42 % in urban India slums [29].

Traumatic brain injury due to abuse has a strong correlation with the severity of the injury, socioeconomic status, pre-injury adaptive abilities and age [26]. Individuals at higher risk may include premature children, or children with disabilities. Twins and multiple births are also at higher risk [31]. Lower socioeconomic classes also have higher mortality rates [32]. Males are more often the perpetrators [31]. Other risk factors for perpetrators include drug addiction, feelings of inadequacy, single parents and previous exposure to domestic violence, but there are no epidemiologic factors which exclude anyone from being a possible perpetrator: all groups are represented [31]. Perpetrators are most often the mother's husband or paramour but may also be mothers, babysitters and other caretakers [31, 33–35]. A recent study examining the disability-adjusted life year (DALY) burden of head trauma in children determined that depending on the severity of head trauma (mild, moderate, or severe) there was a correlation with years lost to premature deaths anywhere from 4.7 to 24.1 years [36].

Systemic Manifestations

Victims of SBS most often present with no history to explain the child's condition and no external findings of trauma. The most common history that is offered by caretakers, although inadequate to explain the injuries, is a short fall [3].

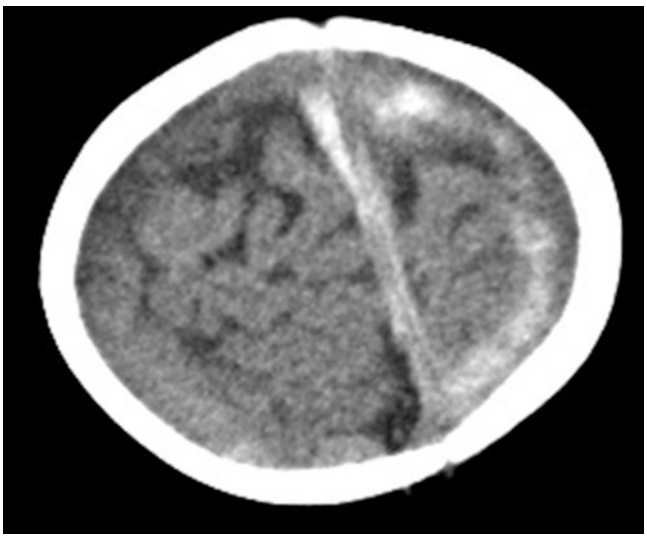

Fig. 5.1 CT of brain. Note subdural hemorrhage extending into the interhemispheric fissure

The characteristic findings of SBS involve primarily brain, skeletal and eye injuries. The most common manifestations of the brain injury are seizures, altered mental status or apnea [7, 31]. Subdural hemorrhage has been reported in up to 93.6–100 % of victims and subarachnoid hemorrhages in up to 22 % [37–39]. Subdural hemorrhage is typically bilateral over the cerebral convexities, small volume and/or in the posterior interhemispheric fissure (Fig. 5.1). Maxeiner proposed that rapid and severe cerebral edema due to parenchymal injury leads to a tamponade of torn bridging vessels resulting in no detectable subdural hemorrhage in some children by neuroimaging [40]. Initial CT scans may be read as "normal" in some cases, although MRI may reveal undetected findings. Cerebral parenchymal damage can manifest as edema, ischemia, or contusion and over time be seen as atrophy [3]. One important form of brain injury is diffuse axonal injury, which can be attributed to the movement that occurs between the brain and skull during the inciting incident and the ensuing shearing forces experienced by brain parenchyma as well as vascular and hypoxic factors [41]. It is specifically related to more angular, rather than translational, acceleration/deceleration [42, 43]. Early detection of diffuse axonal injury can be difficult, but may be aided by the use of serum and cerebrospinal fluid biomarkers and radiologic information [44]. Neuroimaging findings of axonal injury, seen in 10 % of patients, usually those with more serious neurologic compromise, include hemorrhagic punctate lesions in the corpus callosum, grey-white matter junction, and pontine-mesenphalic junction [42]. It can also be identified on autopsy with beta-APP immunostaining showing neuronal disruption and is recommended for forensic evaluation of infants with fatal craniocerebral trauma [45–47].

Although not obligatory, neck injury , including injury to the soft tissues as well as the cervical chord, may also be seen [48]. Although reported by some as "rare"—as low as 4 % in one inpatient study and on autopsy seen less than half of the time-increasing attention to postmortem full neck dissection and examination of the cervical chord and nerve roots is showing that these injuries are more common than previously reported [49–51]. The head and the neck of an infant are distinctly unique in their mechanical properties, therefore the nature of the injury will be different than observed in an older population [52]. Vertebral subluxation and spinal cord injury, including axonal injury, subdural hematomas, subarachnoid hemorrhage, spinal cord nerve root avulsion and hemorrhage, and damage to the neck musculature have been reported [53, 54]. Cervical brainstem injury can lead to apnea, hypoxia, cerebral edema, increased intracranial pressure, and further respiratory depression [55–57]. Additional neck injuries including bruising and abrasions have been reported [58]. One study even suggested that infant victims may also sustain hearing loss [59]. Subdural hemorrhage is secondary to the shearing of bridging veins in the potential subdural space as a result of the repeated acceleration-deceleration forces which allows the brain to move independently within the cranial vault while the bridging veins remain fixed to the venous sinuses [31]. The relatively large head, immature brain and weak cervical neck muscles of infants renders them particularly susceptible [60]. Blunt impact to the head may cause dramatic amplification of the forces experienced by the brain [61, 62]. The blunt trauma may manifest as skull fracture (in up to 25 %) or scalp contusion [39]. Although skull fractures may be simple linear fractures, concerns about abuse are raised when the fractures are complex, depressed, stellate, or bilateral [63]. Impact directly to the vertex or occiput can cause bilateral fractures.

Although there are usually minimal if any external signs of trauma, cutaneous ecchymosis may be observed on the face, chest and/or back. Impressions are occasionally left by the perpetrators hands grasping the child during the event either on a limb or around the chest.

Up to 29 % of SBS victims can exhibit rib fractures from the perpetrator grabbing the child's chest during shaking [64] fractures are usually posterior or posterior-lateral [39, 65, 66]. Multiple fractures may be seen, sometimes in different states of healing thus suggesting more than one abusive event. It had been suggested that rib fractures have perhaps the highest correlation with abuse [65]. In SBS, rib fractures may also occur due to the compression of the rib cage by the perpetrator's hands [54, 67, 68]. These fractures are seen posteriorly or posterolaterally (Fig. 5.2) [69, 70]. But rib fractures are often rare, occurring 6.7 % in one study [71]. They are not required for the diagnosis of SBS [72].

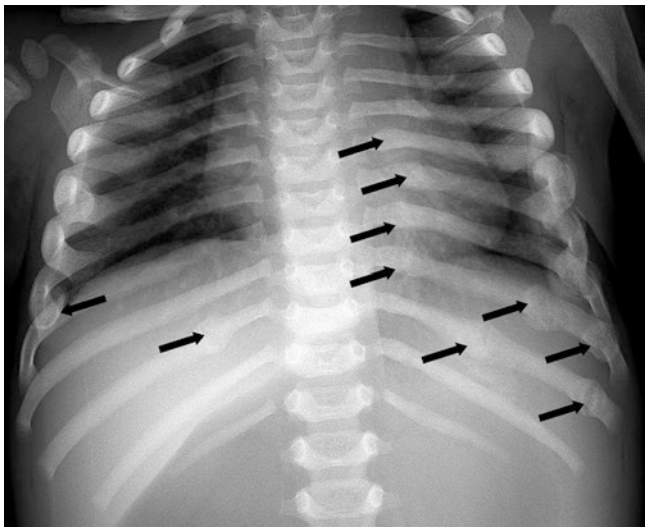

Fig. 5.2 Multiple rib fractures (*arrows*)

Ophthalmic Manifestations

Retinal hemorrhages are the most common manifestation of shaken baby syndrome, being seen in approximately 85 % of cases [73, 74]. Though retinal hemorrhages often occur throughout all layers of the retina, the most frequent finding is flame shaped hemorrhages in the nerve fiber layer [75, 76]. There are many specific causes of white centered hemorrhages yet virtually any retinal hemorrhage in any setting can have a white center, sometimes just from the reflex of the illuminating light [77, 78]. Morad and coworkers found that almost two thirds of victims with retinal hemorrhages will show too numerous to count multilayered hemorrhages including nerve fiber layer and deeper intraretinal hemorrhages as well as pre- and subretinal hemorrhages [79]. It has also been reported to be bilateral in 62.5–100 % and unilateral in 2 %[75]. Although hemorrhages are more frequent in the posterior pole, involvement to the ora serrata has particular diagnostic significance [80]. There is also a correlation between the severity of retinal hemorrhages and the severity of brain injury [81]. Although diffuse retinal hemorrhages are usually seen in the presence of subdural hemorrhage [82], rarely, retinal hemorrhage can be seen in the absence of intracranial bleeding or brain injury [83, 84].

As the vitreous is particularly firmly attached to the macula in infants and young children [85], repetitive acceleration-deceleration forces can cause the retina to be split, with accumulation of blood within the ensuing cavity [86]. These retinoschisis cavities are seen in 8 % of victims of which up to 20 % may be unilateral [74]. The most common form of traumatic retinoschisis is sub-internal limiting membrane blood. Circumlinear perimacular folds, hypopigmentation (from disruption of the retinal pigmented epithelium) or hemorrhage may or may not be seen at the edge of a retinoschisis cavity.

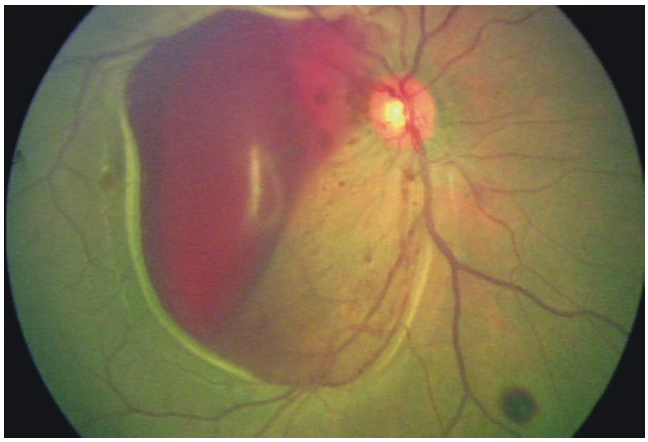

Fig. 5.3 *Right* eye of infant victim of shaken baby syndrome. Note large area of retinoschisis with blood under the internal limitingmembrane. *Bottom left* shows a preretinal hemorrhage, at the edges of the retinoschisis there is a whiteperimacular fold. (Reprinted from Levin AV. Child abuse. In: Levin AV, Wilson T, eds: The Hospital for Sick Children's Atlas of Pediatric Ophthalmology; 2007, p. 136 [259] with permission from Wolters Kluwer.)

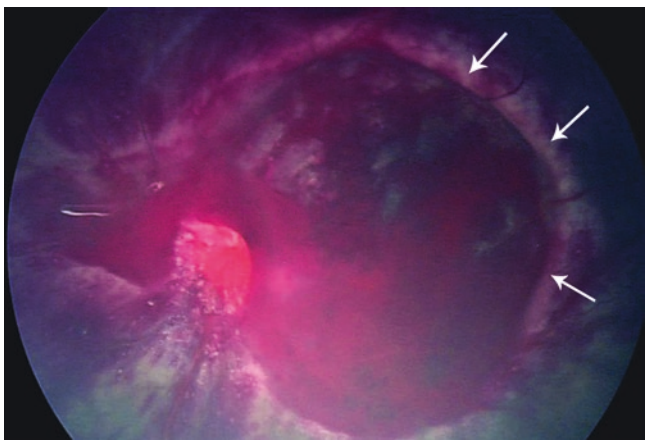

Fig. 5.4 Perimacular fold (*arrows*) in an infant victim of shaken baby syndrome. The internal limiting membrane has flattened to form a "crater" within the folds, now filled with vitreous hemorrhage. (Reprinted from Levin AV. Child abuse. In: Levin AV, Wilson T, eds: The Hospital for Sick Children's Atlas of Pediatric Ophthalmology; 2007, p. 137 [259] with permission from Wolters Kluwer.)

Perimacular folds can be seen in 2–14% of SBS (Figs. 5.3 and 5.4) [74, 87]. When the schisis cavity settles within the surrounding folds, a "crater-like" appearance is created. Folds persist indefinitely and may be a later sign that abuse had previously occurred.

Multiple lines of research indicate that the mechanism of retinal hemorrhage formation in SBS is vitreoretinal traction during repeated acceleration and deceleration movements [88]. The vitreous attaches to the retina in very specific locations including the optic nerve, macula, peripheral retina, and superficial retinal vessels [89–91]. The predilection of hemorrhages to occur in the peripheral retina and the formation of macular retinoschisis are consistent with this anatomy. Likewise, sparing of the mid-periphery, an area with relatively less vitreous adhesion, supports this theory [88, 92]. Many researchers have developed finite element models to analyze retinal stress levels during repeated acceleration-deceleration motion [9, 14, 93–95]. A finite element model is developed using software to more accurately assess the forces obtained in an eye from shaking and impact motions [96]. Cirovic and coworkers demonstrated that the eye is most likely held in place more by the surrounding orbital fat rather than the extra ocular muscles or optic nerve [95]. Both Rangarajan and he have suggested that the repeated acceleration-deceleration causes a cumulative increase in the forces experienced at the vitreoretinal interface [9, 14, 93–95]. This accumulated force causes stress maximums at the posterior pole and the peripheral retina, where most hemorrhages are seen in SBS [9, 14, 93–96]. Porcine eyes also demonstrated this anatomic relationship [43]. When young piglets are subjected to even a single, rapid, head rotation, the location of intraocular hemorrhage was at the vitreous base [43]. These forces have been suggested to be strong enough to cause capillary disruption and peripheral ischemia, leading to later neovascularization of the peripheral retina [97–99]. Peripheral retinal nonperfusion is more common when preretinal or vitreous hemorrhage is seen [97]. The vitreous traction is strong enough to cause macular hole, retinal tears and/or perimacular folds [100–102]. Optical coherence tomography has been used to show the vitreoretinal traction causing ILM separation and folds [103].

Other theories or mechanism of injury have been suggested as causes of retinal hemorrhages. An increase in intrathoracic pressure has been hypothesized to result in restricted venous outflow from the eye in the face of unimpeded arterial inflow, thus resulting in ruptured retinal vessels. Yet multiple studies examining children who might likely have such circumstances, including cardiopulmonary resuscitation with chest compressions [104–108], seizures [106, 108–113], coughing [113, 114], and vomiting [114–116] have found little or no retinal hemorrhages. Geddes and coworkers wrote that hypoxia was the cause of retinal hemorrhages despite no experimental or clinical data, a theory she later retracted under oath in court [117]. Although increased intracranial pressure (ICP) can cause peripapillary hemorrhages in the setting of papilledema, it is not responsible for widespread multilayer hemorrhaging except in cases of hyperacute pressure elevation such as aneurysm, fatal head crush injury or fatal motor vehicle accidents, unlike the subacute pressure rises in abusive head trauma [118–121]. Papilledema is uncommon in SBS [81, 122]. The presence of any intracranial hemorrhage in association with any intraocular hemorrhage is known as Terson syndrome [123–125]. Although the mechanism is unknown, one theory invokes the passage of

blood from the brain directly into the optic nerve sheath due to increased intracranial pressure. Postmortem studies of SBS victims have found optic nerve sheath hemorrhage is often discontinuous which also argues against a Terson mechanism [126–128]. Terson syndrome is rare in children [129].

The overall sensitivity of intraocular hemorrhage for abusive head trauma is 75 % and specificity is 94 %[74]. Starling estimated that retinal hemorrhages occur in 70 % of victims where there is impact alone, 84 % with shaking alone, and 94 % when both shaking and impact occur [8]. There is a positive correlation between retinal hemorrhages and being abused and increasing severity of retinal hemorrhages could correlate with an increase in likelihood of abuse [130]. Binenbaum and coworkers reported that the presence of retinal hemorrhage was highly associated with definite or probable abuse versus definite or probable accident (age-adjusted odds ratio 5.4 [95 % CI, 2.1–13.6]). The odds ratio in children younger than 6 months (n = 81) was 11.7 (95 % CI, 2.9–66.8) [130]. Similarly, Maguire and coworkers reported that the odds of abuse when a child has retinal hemorrhages is 14.7 with an estimated probability of 91 % [131]. Many others have also shown a statistically higher incidence of retinal hemorrhage in abusive head trauma as compared to accidents [80, 132]. The location of the hemorrhages also differs with pre-retinal, peripheral and vitreous hemorrhage all being much higher in SBS [80]. Although retinal hemorrhages can be seen in critically ill children from other causes, the bleeding is not as extensive with regard to location or layer of retinal involvement or distribution to the ora. More extensive bleeding was seen in the presence of severe coagulopathy, leukemia, traffic accidents and witnessed fatal falls down stairs, all of which are readily distinguishable via history and testing [133].

The timing for resolution of retinal hemorrhages is different depending on the type of hemorrhage seen, and not a reliable indicator of the timing of the trauma. Much is known about the time for resolution of birth hemorrhages but those time frames are not applicable for abusive head injury , where the retinal hemorrhages are caused by a different mechanism. Knowing the time of resolution of birth hemorrhages does assist the clinician in determining if the observed hemorrhages could be due to birth. Birth induced flame hemorrhages usually resolve within 72 h but may rarely persist up to 1 week [134–137]. Dot/blot hemorrhages usually resolve in 10–15 days [134, 137, 138]. Rarely, a single larger blot hemorrhage may persist as long as 4–6 weeks and intrafoveal hemorrhage may last even longer. Birth induced preretinal hemorrhage and vitreous hemorrhages can last weeks or even months. Retinoschisis has not been reported due to birth. Binenbaum and coworkers showed that in victims of SBS flame hemorrhages resolve prior to dot/blot hemorrhages [139, 140]. The presence of preretinal hemorrhage alone in a baby otherwise diagnosed as a victim of abuse is an indicator of an earlier onset [139, 141–143]. Numerous flame hemorrhages in victims of SBS can resolve in less than 24 h or hemorrhaging can get worse during the first days of admission. Some children can present with asymmetric retinal hemorrhages between eyes and then progress to a more symmetrical appearance with in the first 24 h [144]. This may be due to ongoing bleeding from injured vessels in the face of complex medical issues following the injury during hospitalization. Ophthalmology consultation should be obtained as soon as possible after presentation, preferably within 24 h [145].

At autopsy, significant findings may include areas of retinoschisis with vitreous gel still attached to the internal limiting membrane [76, 146]. Autopsy may also reveal small areas of sub-internal limiting blood that are difficult to detect clinically [82]. A better view of the far peripheral retina may also be obtained showing the extent of the retinal hemorrhages. Intrascleral hemorrhage at the junction of the optic nerve and globe has only been seen in postmortem specimens from children who are victims of SBS [126, 146, 147]. The presumed mechanism is shearing of posterior ciliary vessels as the eye translates in the orbit during acceleration-deceleration creating a fulcrum at the optic nerve-globe junction [148]. In a study of 18 victims of shaken baby syndrome compared to 18 victims of fatal accidental head trauma, optic nerve sheath as well as optic nerve intradural hemorrhage was seen more commonly in shaken baby syndrome ($P < 0.0001$) [126]. Hemorrhage in the orbital structures may involve the fat, extraocular muscles, and cranial nerves [126, 149]. Those children who die from traumatic causes other than abuse, who were found to have orbital hemorrhage, albeit in lesser amounts, either had direct orbital crush injury or mechanisms of injury that involved large or repetitive acceleration-deceleration.

Almost half of all survivors of SBS have vision issues including cortical visual impairment [28, 73, 150, 151], visual field cuts [28, 73], strabismus [28, 73, 152], ectopia lentis [150, 152], macular scarring [73, 150–153], and optic atrophy [28, 73, 108, 150, 152–158]. All survivors are at risk for amblyopia [73, 150]. Other, long term injuries, include microcephaly, macrocephaly, cranial nerve palsy, and seventh cranial nerve palsy [28, 159].

Other less commonly reported intraocular findings include retinal detachment , which is thought to be a result of the vitreoretinal traction from the acceleration-deceleration forces of shaking [102, 160, 161]. In one case this was also a proposed mechanism for a retinal pigment epithelial tear [100]. Other findings that have been reported in non-accidental trauma include corneal abnormalities, hyphema, macular hole [162], retinal avulsion at the optic nerve, subconjunctival hemorrhage, ptosis, and cataract [16, 135, 163–166].

Diagnosis

Diagnosis of abuse in children requires a multispecialty team approach often involving child abuse pediatrics, social work, nursing, psychiatry, neurosurgery, orthopedics, radiology

and others. The diagnosis should never be based solely on the ocular findings although some findings, such as multilayered too numerous to count retinal hemorrhages extending to the ora with retinoschisis in the absence of a reported obvious etiology such as fatal head crush injury, is highly specific and sensitive for a diagnosis of abuse. History (or lack of explanatory history), and systemic findings must be considered. Appropriate imaging and laboratory studies, are essential. In all cases, a thorough differential diagnosis should be considered including the elimination of concern, where appropriate, of possible coagulopathy, infection, or metabolic disorders.

Management

A trained ophthalmologist should see the child in the first 24 h, if possible, as retinal findings may not persist or can change over the course of time [144]. Photos can be obtained if able [167, 168]. Documentation of the retinal findings should include number, location, and types of hemorrhages as well as the presence of retinoschisis, asymmetry between the eyes and any particular patterns of the hemorrhage distribution. A detailed drawing of the retinal findings may also be useful to accompany the description. In writing the consultation, ophthalmologists should consider a differential diagnosis only as appropriate to the findings. If the eye findings are highly suggestive of abuse, without a recognizable alternative, then the consult may state so. If the child dies, an autopsy can be very helpful in identifying other injuries that were not previously detected on clinical examination. Gilliland and coworkers have written a protocol for preparation of ocular tissues [76, 169]. The orbit should be removed *en bloc* to help with the determination of abuse [170]. Consent is usually not needed for this procedure given the forensic nature of the investigation [169–171]. Autopsy evaluation of children with known trauma should include orbital contents, multiple retinal sections, gross photography, and careful documentation [169].

Battered Child Syndrome

Definition

Battered child syndrome refers to the child who sustains all other injuries of abuse usually including bruising and/or fractures. The outcome may include permanent damage or death [172].

History

Although physical child abuse has been known for centuries, the French physician, Ambroise Tardieu, is often credited as the first to describe many manifestations of child maltreatment in the medical literature [173]. His original paper described not only physical injuries but also the toll that child labor can take on the physical and mental health of victims. His work was unrecognized, criticized, and disbelieved as many assumed that children would fabricate these stories [174]. The first publicly recognized case of child abuse in the US was in New York City in 1874. A 10 year old girl, Mary Ellen McCormack, was repeatedly assaulted by her adoptive mother. The severely battered child drew the attention of neighbors who complained. Due to the lack of infrastructure and child protection laws at the time, the case was brought before the American Society for the Prevention of Cruelty to Animals (ASPCA). As a result of this case, the first child protective agency in the world was developed, the New York Society for the Prevention of Cruelty to Children [175]. It would not be until 1962 that the American medical community first acknowledged this as the Battered Child syndrome with the landmark publication by Kempe and coworkers [172]

Epidemiology

A 10 year autopsy study suggested that approximately 55 % of battered children are less than 1 year old, and 79 % less than 2 years old, with an average age of 14.3 months [176]. Triggers for all types of physical abuse include crying in 20 % followed by disobedience (6 %), domestic disputes (5 %), toilet training (4 %), and feeding problems (3 %) [18]. It has also been reported that children who are fatally maltreated are typically from houses that are financially unstable compared to children who survive the abusive situations they suffer through [177]. Eighty percent of perpetrators are the child's parents [2]. Child abuse cases present more commonly in winter and on weekdays [65]. There is a well-documented disproportionate rate of investigating and reporting visible minorities from lower socioeconomic strata as compared to higher socioeconomic class Caucasians [178, 179].

The cost of battered children is also very expensive. Children who have been identified as maltreated or at risk for maltreatment account for approximately 9 % of all Medicaid expenditure. Their costs are on average >$2600 higher per year compared to children who are not identified as battered [180].

Systemic Manifestations

Injuries can affect every part of the body. Child abuse should be considered in virtually any child who presents with any injury but in particular when the injuries are multiple, recurrent, inconsistent with the history provided, inconsistent with the developmental level of the child or affecting unusual body parts [181, 182]. For example, fractures in a child who is not yet ambulatory, bruising in older children that is seen on the chest or buttocks or old and new injuries presenting at the same visit should raise concern about abuse. Multiple fractures (often of different stages of healing), traumatic abdominal injuries (including rupture or contusion of viscera), and soft tissue injury are often findings in battered children [183].

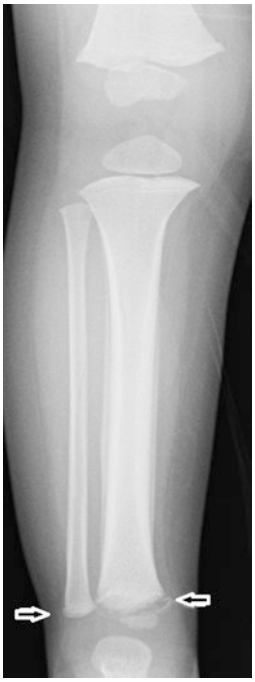

Fig. 5.5 Metaphyseal lesion (*arrow*) due to child abuse

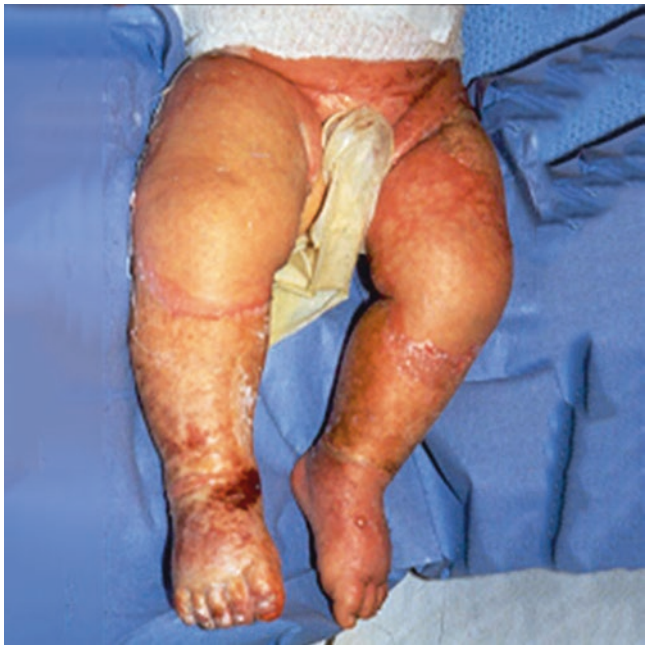

Fig. 5.6 Immersion burn. Note total involvement of lower limbs. (Courtesy of Brian Holmgren)

Fractures of long bones needing orthopedic management occur in up to 28 % of cases [65, 184], but a far greater percentage have fractures that do not require treatment and may be asymptomatic, including rib and long bone epiphyseal fractures (Fig. 5.5). Battered children are at risk for obtaining multiple injuries separated over time, therefore one fracture may have time to heal before another fracture is obtained [185]. Spiral fractures may be more concerning for child abuse due to the twisting, oblique squeezing, or dragging mechanism that the fracture suggests [10]. Rib and clavicle fractures may also be due to squeezing but have rarely been reported due to birth [31, 186]. Although femur fractures were long thought to be highly indicative of abuse [187], they may also occur due to accidental injury [188]. A discriminating factor is attainment of ambulation. Femur fractures are often accidental, no matter the form of the fracture, once a child is able to ambulate [179].

Abdominal injuries, including liver or bowel laceration or contusion may occur. Abdominal trauma may be suspected on the basis of elevated hepatic transaminase, elevated amylase or abdominal ecchymosis [187]. Current recommendations include obtaining an abdominal CT scan in children with suspected abuse who have greater than 80 IU/L of either aspartate aminotransferase or alanine aminotransferase [189].

Bruising patterns can also indicate abuse. Any child who is less than 6 months old that has bruising has a very high likelihood of obtaining these injuries from abuse and a very low chance of having a coagulopathy [190, 191]. Testing for bleeding disorders should be considered for a child who presents with two or more unexplained bruises. If there is a concern for a coagulopathy, at a minimum prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), should be ordered, but often these are negative and no coagulopathy is found [187]. In ambulatory children, bruising over bony prominences is more likely to be accidental [191]. Bruising in patterns that are away from bony prominences (i.e. face, back, buttocks, abdomen, ears or hands) and ecchymosis in clusters or of similar shape, are more indicative of abuse [192]. Concerning shapes of bruises can be in the form of straight edges from belts, switches, chords or bite marks. Burn patterns may also help to distinguish abuse from accidents [190, 193]. Inflicted hot water burns are often found on the lower extremities or buttocks from sitting a child in hot water or holding their limbs under the tap (Fig. 5.6) [193]. A full thickness burn can happen as quickly as 30 s in water that is 149 °F [194]. Cigarette burns can also cause full thickness injuries if they are held in place for greater than 1 s [195]. They usually have heaped edges around a central crater.

Ophthalmic Manifestations

Virtually any eye injury can be sustained as a result of abuse. It has been estimated that 4–6 % of abusive eye injuries first present to the ophthalmologist [4]. Eyelid or facial trauma can result in lacerations, burns, or ecchymosis anywhere from the forehead to either eye or both eyes [183]. A study on postmortem eyes from known or suspected child abuse found conjunctival hemorrhage in 8.5 % [76]. Conjunctival hemorrhages can also result from blunt trauma and increased thoracic pressure, for example during suffocation [76]. Birth

related conjunctiva hemorrhages can occur and are associated with multiparity, longer labor, increased birth weight, head circumference, and gestational age [196]. They always last longer than retinal hemorrhages from birth [196]. They have been described as semilunar occurring just outside of the limbus and wedge shaped with a base towards the limbus [197]. Hyphema, leukocoria, ectopia lentis, cataracts, sixth nerve palsy, orbital hemorrhage, and globe rupture have also been reported [31, 135, 163–166, 183, 198–203].

Diagnosis

A multidisciplinary team approach, usually led by a child abuse pediatrician, is critical for the evaluation of these children. Child abuse should be suspected when the history does not match the injury, there is a history of inflicted injury, or the history is continuously variable. Although there may be child-parent interactions that seems bothersome, this in of itself does not allow for a diagnosis of abuse.

Management

The management of eye injuries due to child abuse is no different than when these injuries are sustained in non-abusive manners except for the ophthalmologist, or the team's, duty to report to child protective services if non-accidental trauma is suspected. The ophthalmologist should carefully document all injuries. Appropriate imaging, including photographic documentation, is recommended. The ophthalmologist should coordinate with other professionals to help provide long-term treatment and follow-up for these victims [204]. Reporting a child abuse incident is not considered a breach of doctor-patient confidentiality by law and is not protected under HIPAA. Even with this protection, some health practitioners still do not obey the mandatory reporting laws [205]. After reporting an incident, the ophthalmologist is rarely asked to testify in court. Any testimony should be treated as a scholarly endeavor to educate the courtroom rather than testimony to win a case on behalf of the prosecution or defense. Ophthalmologists should be encouraged to consult with peers and the literature to ensure that they to give the most accurate scientific responses in court [206].

Medical Child Abuse

Definition

Medical Child Abuse, previously referred to as Munchausen Syndrome by proxy, caregiver-fabricated illness in a child, factitious disorder by proxy or pediatric factitious disorder, "occurs when a child receives unnecessary and harmful or potentially harmful medical care at the instigation of a caretaker" [207, 208]. Often times the caregiver creates the appearance of an illness in a child either by the falsification of history, alteration of laboratory specimens (e.g. contaminating a culture swab), or the creation of physical signs [208–210]. This type of abuse can lead to potentially harmful medical investigations and/or treatment [208].

Epidemiology

Medical child abuse is relatively uncommon with an estimated incidence of 0.5–2.0 per 100,000 children under age 16 years. Based on a 2 year prospective study conducted in the UK and Ireland, most affected children were less than 5 years of age, which is not surprising as younger children are less likely to understand or reveal what their caretaker is doing [211]. The median age was 20 months [211]. Although most victims are infants and toddlers, up to 25 % can occur in children over the age of 6 years [212–214]. As children get older they may even participate in the falsification of symptoms or history. The mother is the perpetrator in over 95 % of cases [215]. In the age of social media, mothers are now blogging about their child's medical illness and often grossly distorting the facts that were given by the medical provider [216]. Reasons why caregivers exhibit this type of behavior is beyond the scope of this chapter, but it seems that secondary gains and perhaps narcissistic psychopathology may play a role. Males and females are victimized equally [211, 212] and sibling siblings may also be victimized, sometimes serially [211]. Abuse will often continue if a patient is hospitalized and not fully supervised, thus allowing acts to be committed undetected. Up to 75 % of the morbidity experienced by children happens while admitted [208]. Mortality rates in these children can be up to 6–9 % and another 6–9 % can suffer long term disability or permanent injury, therefore early diagnosis is often life-saving [208, 212].

Systemic Findings

There is no single presentation for this type of abuse due to the wide spectrum of manifestations which are related to the nature of the falsified symptoms as well as the potential unnecessary medical investigation or treatment that well-meaning physicians enact to address those symptoms and signs. Although apnea and failure to thrive are the most common manifestations reported, others include induced bleeding, seizures, central nervous system depression, diarrhea, vomiting, fever, traumatic retropharyngeal abscess, induced infection, chronic intestinal pseudo-obstruction, polymicrobial infections and rash [207, 208, 212, 217, 218]. Up to a quarter of these children can also be afflicted by urinary tract issues [219]. Manifestations often involve multiple organ systems and result in consultations with multiple subspecialists [208]. Perpetrators may also change physicians to avoid detection.

Ophthalmic Findings

Ophthalmic findings can occur alone or in conjunction with other organ systems. In theory, a caregiver could provide history to raise concerns for ocular disorders of any kind that would result in unnecessary and potentially harmful medical testing or care. Recurrent conjunctivitis was reported by Baskin et al. [220]. Other ophthalmic manifestations include swelling, periorbital and orbital cellulitis from repeated injections, recurrent hemorrhagic conjunctivitis, ulcerations of the eyelids, corneal epithelial defects and keratitis, anisocoria from covert instillation of mydriatics, and periorbital cellulitis [208, 220]. Figure 5.7 demonstrates a corneal injury due to medical child abuse. The patient went on to require multiple corneal transplants. Note the characteristic affectation of the inferior cornea as a result of forced instillation while the child's eyes move upward in the Bell's phenomena. Children may also present with nystagmus and other eye movement disorders as well as pupillary abnormalities due to the central nervous system effect of covert poisoning or suffocation induced cerebral hypoxia.

Diagnosis

The diagnosis of medical child abuse should be considered when there is any recurrent or persistent illness that cannot be explained or is not getting better with the appropriate treatment. Unfortunately, it may take upwards of 14 months to 2.7 years before the diagnosis is made [212, 214]. The diagnosis should also be considered when a patient has been subjected to multiple treatment plans or medical procedures or present with a discrepancy in history, exam, and overall health [208].

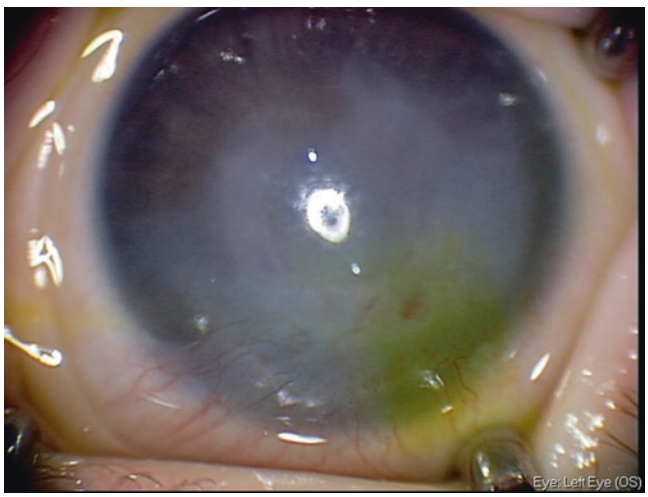

Fig. 5.7 Corneal injury from medical child abuse. Instilled agent was not clearly identified. Note that the inferior cornea is more affected and vascularized. Patient required corneal transplant

Perpetrators may seem unexpectedly without distress over the induced illness, or demonstrate remarkable concern and willingness to contribute to the child's care, often taking over the duties of nurses, which in turns allows the perpetrator the opportunity to cause harm.

Making the diagnosis of medical child abuse first requires this diagnosis be considered. Secondly it may require careful review of medical records and previously performed evaluations including imaging or laboratory studies to identify discrepancies in provided history from observable medical findings. A multidisciplinary evaluation which involves all medical providers is necessary [207].

Flaherty suggests asking the following three questions when evaluating patients who could potentially be victims of caregiver fabricated illness. Are the history, signs, and symptoms of disease credible? Is the child receiving unnecessary and harmful or potentially harmful medical care? If so, who is instigating the evaluations and treatment? [208] If a child victim of medical abuse is suspected and they are able to speak, they should be interviewed separately from the caregiver [208]. It is important to remember that up to 30 % of children with fabricated illnesses do have an underlying medical illness [221]. Although it is relatively rare, physicians should have a low threshold for questioning if medical abuse is happening and report it immediately to the child protective services agency [222].

Because some of the abuse happens while a child is in the hospital, the use of covert video surveillance (CVS) has now been suggested to ensure safety of the child while admitted [208, 223, 224]. This may be controversial as it can be seen as an infringement on patient privacy and/or as falsely accusing caregivers of abuse. Covert video surveillance has been found to be helpful in one series up to 50 % of the time and identified real medical problems in 10 % of cases [208, 223]. Prior to implementing a CVS system, the hospital should take precautions and develop a plan for its use as well as a response plan for intervention if the child is in fact seen to be abused [208].

Management

Management will require referral to child protective services and implementation of a safety plan to prevent on-going abuse. The safety plan will likely need to engage medical professionals who have been involved in the care of the patient, and non-involved caregivers. It may be necessary to remove a child from the possibly abusive environment to document the falsification of symptoms which would resolve as a consequence of the removal or in order to prevent on-going harm.

Before reporting, it is essential to ensure that the diagnosis, or at least the suspicion of the diagnosis, is well founded. This may require a careful review of old medical records, covert video surveillance in hospital, or admission to hospital

to see if the induced disease resolves when the child is out of contact with the family. Many states do not list "medical child abuse" on their child abuse reporting forms, therefore it is important to focus on the specific ways in which the child is suffering from abuse and report all areas of abuse sustained from this fabricated illness including physical and emotional abuse [208].

Neglect and Medical Noncompliance

Definition

Neglect includes lack of care for a child, or failure to prevent an adverse event and protect from harm [18, 225, 226]. Intentional neglect is rare. Failure to provide medical care may be due to a lack of understanding or education from the parental standpoint, or an inability to comply, due to financial or other socioeconomic or family factors [70]. But when harm occurs despite appropriate attention and intervention, then abuse is reportable and should be considered.

Epidemiology

Neglect is the most common form of child maltreatment in the United States [18, 70, 227]. Seventy-eight percent of all reported child maltreatment cases in 2012 were due to neglect [1]. One study found that neglect accounted for 51 % of deaths and these children were primarily less than 5 years old [228]. Most children who suffered from fatal neglect have had no prior report with child welfare before their death. Risks for neglect include higher number of children in the home, along with previous family involvement with child welfare [228]. Some cases of neglect have been mistaken for sudden infant death syndrome (SIDS) [229]. There is evidence that neglect can have permanent effects on the process of brain development [230].

Systemic

Neglected children often have failure to thrive and severe neglect can lead to a failure to thrive amongst infants and children [231, 232]. Psychosocial dwarfism is a medical manifestation of severe neglect. Rarely, neglect can be so severe as to lead to death by starvation. Failure to thrive is usually multifactorial, stemming from inadequate nutrition as well as a disturbed social environment [233]. Neglect may also present systemically as inadequately or untreated illness or injury, or progressive injury/disease as a result of delayed care. Physical trauma accompanying failure to thrive, including burns, bruises, and fractures, may be seen. Injury can also occur from neglectful supervision or failure to prevent harm.

Ophthalmic

Neglect may also include noncompliance with recommended medical treatment, such as compliance with eye drops or patching. Failure to provide treatment may result in permanent vision loss [215]. Often these families fail to keep their scheduled appointments [234]. Ophthalmic manifestations seen in children with failure to thrive include lagophthalmos due to listlessness and unwillingness to move in a debilitated state, leading to corneal exposure and epithelial breakdown [234].

Diagnosis

Initial diagnosis should include an assessment of the child's needs, family resources, their efforts to provide for the child, psychosocial challenges and options for ensuring optimal health for the child [235]. It is sometimes difficult to define when neglect has occurred. Certainly if there is harm, such as untreated amblyopia or uncontrolled glaucoma, which appear to be a result of neglectful caretaking, then a diagnosis of abusive neglect may be considered. A careful history can identify whether it would have been reasonable for the caretaker to appreciate a need for prompt care. For example, if a child was struck in the eye accidentally by a stick, and was left with a red, painful eye for 3 days without care, this would fall outside what a reasonable caretaker would do *if* they had the means (e.g. insurance coverage) to obtain such care. A parent who is not attending appointments or providing care due to alcoholism, is also an example of neglect. Failure to attend or deliver care due to religious objection may not be neglect unless the child is suffering in a fashion which can be alleviated through medical care. A parent may not make a decision that causes harm to their child, including religious or cultural objections. Ultimately, the diagnosis is based on a combination of damages to the child and reasons for failure of care delivery.

Management

Resolution of barriers to care such as cost of transportation or patches, through the assistance of a social worker or other support personnel, may obviate the need for child protective service intervention. Altering care regimens to better fit the parental capabilities, if it is safe to do so, may also be useful. For example if a parent is working all day, selecting a twice daily regimen may be easier than a four times daily regimen. Management of neglect should include having a low threshold for contacting the appropriate people when lack of care or neglect is suspected [236]. Reporting is warranted when there is direct physical or social evidence of neglect or when the physician is unable to eliminate the possibility that the

maltreatment contributed to the child's illness or injury [237]. It should also be reported when an evaluation of failure to thrive is suspicious for neglect as opposed to an identified organic cause [233]. Social workers or other health care ancillary staff are often helpful in coordinating care for these children as well as communicating with the proper authorities to ensure they are aware of the concern for child neglect. Detailed communication related to the physician's concerns, resultant harm and what interventions were attempted by medical staff to alleviate the concern of neglect is important as it assists child protection authorities to understand the medical basis and provide appropriate safety planning or supports to the family.

In situations where there is a developing pattern of noncompliance and neglect, such as missed appointments or failure to obtain patches for amblyopia therapy, consideration can be given to the use of contracts. This has been suggested in the literature regarding dental caries. These documents are signed by the primary caregiver, physician, and a witness [234, 238]. After all barriers to care have been alleviated, the ophthalmologist can write a short statement in the medical record, indicating that continued failure to attend or institute care will result in a report to child protective services. This statement is signed by the physician, a witness, and the parent/guardian. If the family then continues to demonstrate neglect and noncompliance, reporting can then ensue and will likely be more effective. Given the limited and competing resources of child protective agencies, neglect may sometimes take a lower priority when the agency is also faced with simultaneous cases of abusive head trauma or other abuse that may cause imminent harm especially that which may be life threatening. Having the evidence of a signed contract such as this may help promote intervention from protective services.

Sexual Abuse

Definition

Sexual abuse may manifest as a range of behaviors including inappropriate sexual touching, exposure of a child to inappropriate for age sexual content or scenarios, or any sexual acts. Perpetrators and victims may be of any combination of genders. Children may be too young to know that a sexual act is inappropriate or they may be threatened not to reveal its occurrence. Sexual abuse is often chronic, covert, and perpetrated by someone known to the child who occupies of position of relative power and influence over the child. Violent acts, such as rape, are rare. Sexual acts with an adult may be considered as potentially abusive or coercive even if the teen pleas that it was consensual. Age of consent varies between states. Many states have statutory rape laws that define age of consent and with whom an adolescent can consent to sex.

Epidemiology

Sexual abuse has been reported in 3–38 % of all abuse cases [57, 239, 240]. Unlike other areas of abuse where the incidence between males and females is approximately equal, sexual abuse victims are more often female [239]. A study anonymously surveying mothers from North and South Carolina found that sexual abuse may have an incidence that is 15 times more common than what is actually documented in official child abuse reports [241]. It has been suggested to be particularly underreported in males [242]. It is estimated that 6–62 % of women and 2–15 % of men have experienced child sexual abuse and that one to two thirds have occurred with a family member as the perpetrator [242]. Peak ages of vulnerability are between 9 and 12 years old [242]. Even infants may be victims. Sexual abuse may also involve the use of children in pornography.

Systemic

Sexual abuse rarely results in physical injury but uncommonly one can see evidence of trauma such as palatal bruising from fellatio, vaginal injuries, or anal injuries. Sexually transmitted disease may also occur. One must distinguish between transmission of these infections through the birth canal at the time of birth. Latency periods may vary. For example, some have estimated that the latency for chlamydia after perinatal transmission may be in excess of 2 years. The presence of gonorrhea, chlamydia, or syphilis in the vagina, anus, throat or urethra always indicate sexual contact beyond these periods [243, 244]. HIV infection in the absence of another known risk factor such as blood transfusion or perinatal acquisition, also indicates sexual contact. These infections cannot be spread to these sites via fomites. Although pubic lice, herpes simplex, papilloma virus, Trichomonas vaginalis and molluscum can be spread non sexually, their presence in these sites is also concerning [245].

Ophthalmic

Sexual abuse may result in conjunctivitis or other ocular manifestations due to sexually transmitted diseases [246]. In the perinatal period, conjunctivitis caused from sexually transmitted diseases such as gonorrhea or chlamydia are not necessarily related to abuse, however between the latency period after birth and puberty, the likelihood that these specific organisms are a result of sexual abuse is high [247]. Rarely, cases have been reported where gonococcal infections have been found in children where an extensive history has not lead to the suspicion of sexual abuse, although an adult family member was identified to also be infected [248]. These victims were preverbal thus making detailed

interviewing impossible. Although organisms may have been transmitted via ejaculation, facial contact with infected genitalia, or oral sex, since the conjunctiva is an externalized mucous membrane it may also be able to be infected through non sexual means, although this has never been demonstrated experimentally [247]. Though uncommon, other findings of ophthalmic sexual abuse includes pubic lice (*Phthirus pubis*) on the lashes [246]. Children can present with recurrent periorbital redness and lice seen on the eye lashes [249]. Ocular manifestations of syphilis should always be considered in a child with uveitis or retinitis. One must also be sensitive to the commonality of nonsexual etiologies for ocular herpes and molluscum.

Sexual abuse has also been reported to manifest as retinal hemorrhages when the abuse is in conjunction with physical abuse [250]. Two such cases were described in the literature with a Purtcher retinopathy thought to be caused by sexual abuse along with shaking [250].

Diagnosis

Diagnosis of ocular manifestations of sexual abuse includes appropriate concern of the possibility leading to culturing of conjunctivitis or lesions around the eye. Alternatively, the diagnosis may be made unexpectedly as a result of culture or testing, for example, in the work-up of uveitis or retinitis.

Management

If a sexually transmitted disease is discovered, the primary care physician of the child should be notified or a direct referral to a child abuse pediatric team can be made. This will lead to appropriate interviews of the child, examination and culturing of other orifices and cultures of family members or caretakers. All affected individuals should be treated with appropriate antibiotics or medical therapy. Direct reporting to child protective services by the ophthalmologist may not be appropriate considering the possibility of nonsexual transmission of some infections. This should not however preclude notification of the pediatrician to initiate further evaluation.

Emotional Abuse

Definition

Emotional abuse may be difficult to define. Certainly, all forms of abuse have an emotional impact on the child, some of which may be a lifelong burden leading to increased rates of addiction, criminal behavior, maladaptation, and even becoming a perpetrator of abuse. A child can be maltreated to a degree that seriously interferes with their cognitive, psychological or social development. Forms of such emotional maltreatment include ignoring, rejecting, isolating, exploiting, verbally assaulting, or terrorizing a child [230].

Epidemiology

Isolated emotional abuse has been reported in 1.3–33 of abuse cases [57, 240, 251, 252]. It contributed to 1.6 % of all child abuse related deaths in 2013, according to the U.S. National Child Death Review Case Reporting System [18].

Systemic

In more severe cases of emotional abuse, alterations in the brain can be seen including an up-regulation of the stress response including a dysregulation of the hypothalamic-pituitary-adrenal axis, along with parasympathetic and catecholamine responses [230]. Increasing chronicity in an environment may also contribute to altering the development of the brain [230]. Additionally it has been shown that there is a strong relationship between the breadth of exposure to emotional abuse or dysfunctional homes during childhood and risk factors causing death in adults. as a result of alcoholism, drug abuse, depression, and suicide [253].

Ophthalmic

One ocular manifestation of emotional abuse is the presentation of functional vision loss or other non-organic ocular signs (e.g. blinking) [254]. Functional vision loss occurs most commonly in female teenagers and may be unilateral or bilateral [255]. It can involve visual acuity and/or visual field abnormalities [255]. In approximately half of patients, a normal VA was obtained at initial consultation [255]. A study examining functional vision loss in 23 children determined that three children were actually victims of sexual abuse and one a victim of physical abuse. Their chief complaint was blurred vision associated with headaches [256]. Occasionally early hereditary optic neuropathies and macular dystrophies have been misdiagnosed as functional vision loss [255]. Stressors which induce functional vision loss or other signs are readily detectable in 50 % of patients and may include such things being a victim of bullying, parental divorce, or the death of a family member or pet [254]. If the signs do not resolve within 3 months of seeing the eye doctor or the signs are replaced by others, then further investigation by the primary care physician should be considered and done so with the consideration of possible covert abuse.

Another form of emotional abuse which relates to the visual system, occurs when children see things they should not see: violence, sexual activity, drug abuse, crime. The impact of these exposures is unknown. For example a study in Chicago of middle/high school kids revealed that 35 % had witnessed a stabbing, 39 % had witnessed a shooting, and 24 % witnessed murder. In children aged 2–8 years old an alarming 30 % had witnessed a stabbing and 26 % had witnessed a shooting [257].

Diagnosis

Physicians should be concerned about emotional abuse when any other form of abuse is recognized or when children demonstrate behaviors that seem outside the range normally observed. Children who are not thriving in school also raise concern. More often, the ophthalmologist is faced with functional vision loss, the diagnosis of which includes various exam techniques to "trick" the patient into seeing better. The reader is referred elsewhere in this regard [258].

Management

Early intervention in emotional abuse is crucial to avoid long term adverse outcomes but methods of intervention, other than appropriate reporting to child protection, are usually well beyond the sphere of the ophthalmologist [230]. A multidisciplinary approach is advised including the use of child abuse pediatricians, psychologists/psychiatrists, social workers, and nurses.

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Oculofacial Manifestations of Chromosomal Aberrations

6

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Introduction

A chromosome is a complex structure made up of DNA, and containing genes, regulatory elements and noncoding regions. Normally, human cells have two sets of chromosomes. Diploid cells contain 46 chromosomes formed from the union of one haploid ovum and one haploid sperm. These 46 chromosomes are in fact 23 pairs, each pair including one chromosome from each parent. Chromosomes 1 through 22 are termed autosomes, and the 23rd pair are sex chromosomes. Females have two X-chromosomes, while males have one X- and one Y-chromosome. The chromosome structure comprises a centromere, a short arm (p), and a long arm (q).

A chromosomal aberration is an abnormality in chromosome number or structure, which can cause a disease either by a quantitative imbalance of genetic information (e.g.,: gains or losses), or by a rearrangement of the DNA sequence, which affects the functionality of one or more genes and/or their regulatory elements. Numerical chromosomal abnormalities can affect the whole genome, or individual chromosomes. Structural chromosomal abnormalities involve the disruption of the genomic sequence. In this chapter we will discuss chromosomal change, which is largely detectable by karytotype indicating that the rearrangement almost always will involve more than one gene. Monogenic Mendelian disorders are usually caused by sequence changes within a single gene and therefore not covered herein.

Chromosomal aberrations are detected by conventional karyotyping (Fig. 6.1), fluorescence in situ hybridization (FISH) (Fig. 6.2), or chromosomal microarray (Fig. 6.3). Karyotype and FISH are performed with a microscope, and detect chromosome changes that almost always involving more than one gene. About 8 % of congenital ocular anomalies are associated with abnormal karyotypes [1]. Different tissues may be obtained for cytogenetic analysis (e.g.,: skin, blood, chorionic villi, amniotic fluid). To get cell synchronization, colchicine is added to arrest cells in metaphase. Then, chromosomes are dispersed with hypotonic solutions that swell the cells. The cells are placed over microscope slides, which results in a metaphase chromosome spreading. Those chromosomes can be stained, resulting in different light or dark areas. The most common method of staining is giemsa or G-banding. In FISH, instead of banding, fluorescence-labeled DNA probes are used to tag segments of DNA. This technique is important in small deletion/duplication syndromes. DNA sequences can be recognized if the probe has at least a size of 2000 base pairs (2 Kb), although commercial probes used in clinical laboratories are ~1 Mb.

Chromosomal microarray (CMA) technology now allows for more sensitive detection of copy number variation (CNV) throughout the genome, which may or may not be pathogenic. This level of analysis provides for another dimension of genetic diagnosis [2]. CMA is now used for genetic testing of patients with unexplained developmental delays or disabilities, or multiple congenital anomalies. CMA offers a 20 % higher diagnostic yield over karyotyping. Balanced translocations cannot be detected as array does not evaluate chromosome structure but rather, dosage. The reported submicroscopic copy number variations are to numerous to count and well beyond the scope of this chapter. Clinicians are encouraged to consult on-line databases (e.g., http://genome.ucsc.edu/) to unravel the clinical significance of these microscopi CNVs.

Trisomy 13 and 21 are the most common chromosomal aberrations associated with congenital ocular malformations identified in newborns [1]. In addition, some systemic malformations associated to ocular congenital malformation seem to predict a chromosomal abnormality (e.g.,: talipes-equinovarus, microcephaly, hydrocephalus, facial dysmorphism,

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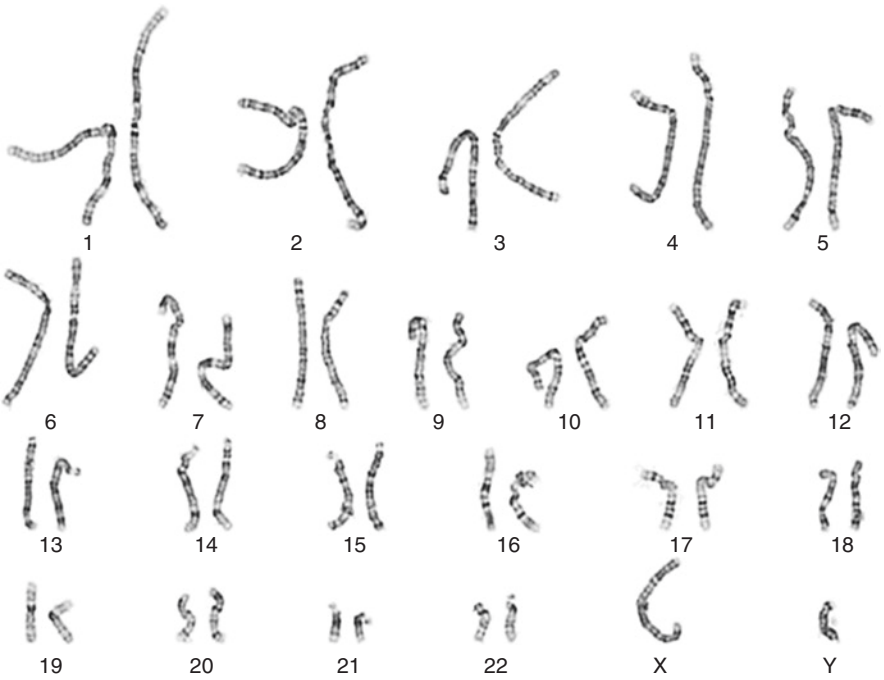

Fig. 6.1 Normal Male Karyotype: 46, XY (courtesy of Genomic Pathology Program at Thomas Jefferson University Hospital)

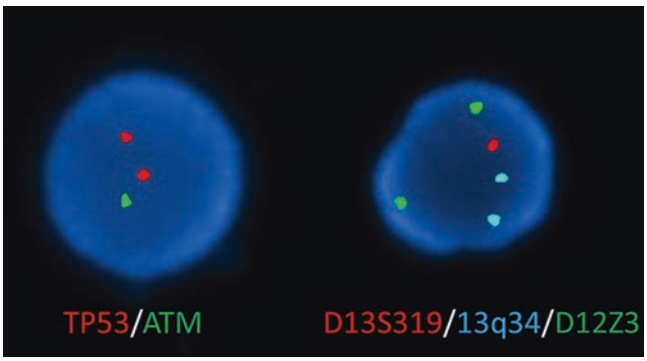

Fig. 6.2 FISH panel for chronic lymphocytic leukemia (CLL): Results from a peripheral blood sample hybridized with the Abbott Molecular CLL panel. Left panel shows a deletion of ATM (11q22) (*single green*) and a normal signal pattern for TP53 probe at 17p13. Right panel shows a deletion of 13q14 (*single red signal* and two aqua signals for the locus on 13q34), and a normal signal pattern for chromosome 12 centromere (courtesy of Genomic Pathology Program at Thomas Jefferson University Hospital)

and hypertelorism) [1]. Consideration of a chromosomal aberration should occur when there are other organ systems involved in addition to the eye, a recognized pattern of malformations, a pedigree that shows multiple prenatal losses or malformations, or a clinical scenario that is not likely explained by a single gene abnormality.

This chapter covers only non-complex chromosomal abnormalities. If a deletion of 13q is associated with duplication in 21p, it is hard to associate the phenotype to the 13q deletion and/or the 21p duplication. Only phenotypes associated with single chromosome deletions or duplications will be discussed.

Abnormalities of Chromosome Number

Polyploidy. The presence of one or more entire extra set of chromosomes is referred to as polyploidy. Polyploidy is usually not compatible with long-term viability. Triploidy (3 sets = 69 chromosomes) results mainly from dispermia (fertilization of a single haploid egg by two haploid sperms) while tetraploidy (4 sets = 92 chromosomes) is mainly generated by an abnormality in the first mitotic division after fertilization.

Aneuploidy. An additional chromosome, also known as trisomy, occurs when a meiotic non-disjunction result in two copies of the same chromosome in one germ cell. Trisomies 13, 18, 21 and those involving the sex chromosomes are the most common trisomies compatible with life. Monosomy is the presence of only one chromosome instead of a pair. The loss of an entire chromosome in human development usually results in spontaneous abortion. One common monosomy compatible with life is 45,XO, which causes Turner syndrome. Mechanisms for creating partial aneuploidy (partial trisomy or monosomy) include rearrangement, duplication, unbalanced segregation, or deletion within a chromosome.

Alterations of Chromosomal Structure

Translocations. A chromosome **translocation** is caused by rearrangement of parts between nonhomologous chromosomes. Translocations may be balanced, that is, an exchange without loss or gain of genetic information, and therefore functional, or unbalanced, where the exchange is unequal,

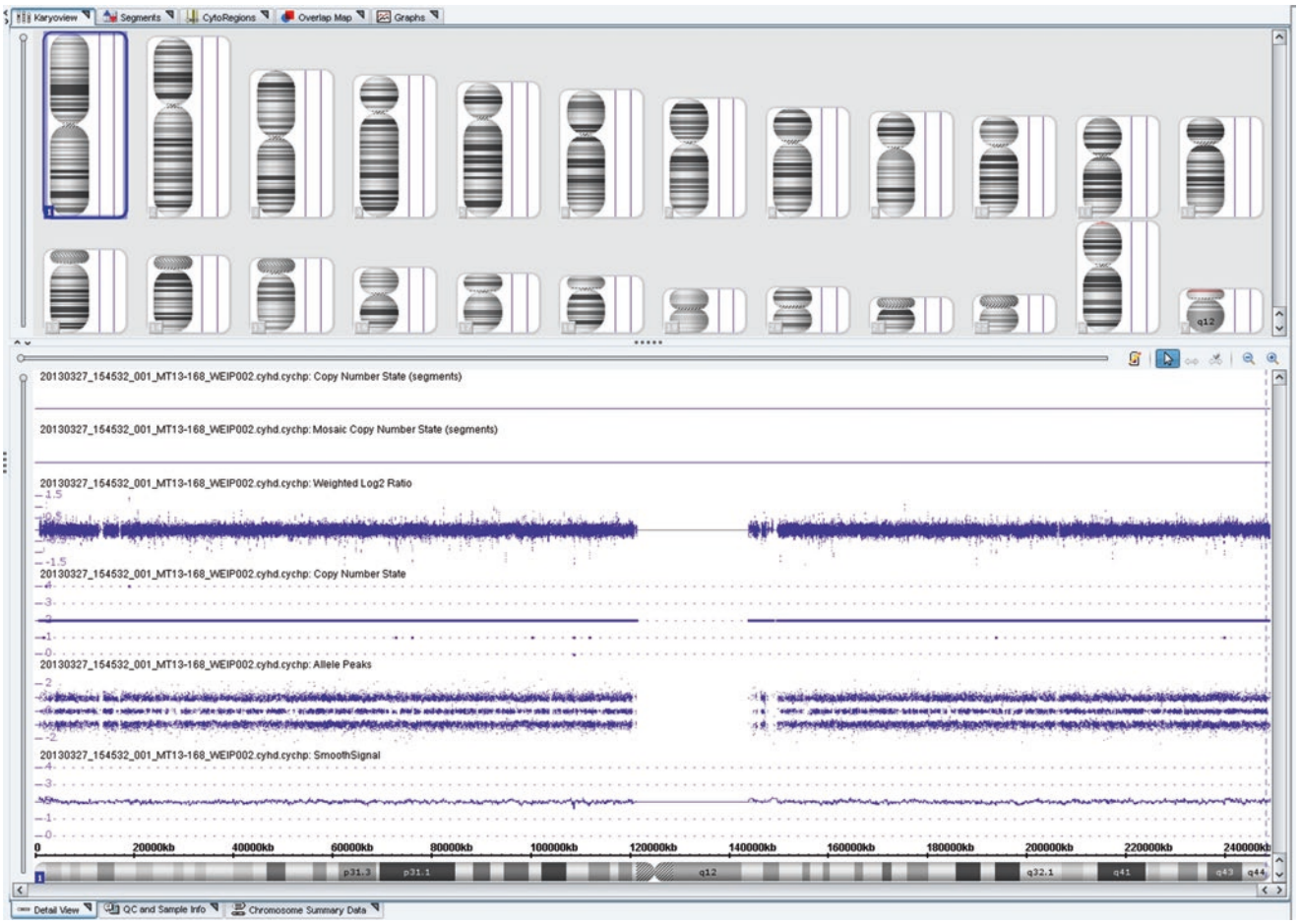

Fig. 6.3 Normal Male Virtual Karyotype by SNP Microarray: Top panel shows Karyoview without gain or loss of any regions in the genome; Bottom panel shows detailed view of chromosome 1: log2Ratio of sample/normal, SNP allele tracks (AA, AB & BB) and copy number of the chromosome 1 (courtesy of Genomic Pathology Program at Thomas Jefferson University Hospital)

and resulting in loss of functionality. Most translocations include two chromosomes (**reciprocal translocations**). Frequently, these are balanced although there are exceptions, as when the break in a reading frame or a regulatory region, or if the translocation is unbalanced at the molecular level. The six different products from meiosis when chromosomes have a balanced translocation are the normal copy of each chromosome, the balanced translocated chromosomes, and four with unbalanced segregation products. Balanced translocations are diagnosed by karyotype analysis. It has to be suspected in recurrent fetal loss or in children with malformations due to unbalanced translocation.

Other translocations are **Robertsonian translocation** and **insertional translocation**. In the former, translocations involve acrocentric chromosomes [13–15, 21, 22], which have a small short arm. Translocations involving these chromosomes occur in 1 of 900 newborns. The most common involves chromosome 21, resulting in Down syndrome, causing ~3 % to 5 % of Down syndrome. In insertional translocations, a chromosomal segment may be deleted from within a donor chromosome. Its removal may disrupt one or more genes at one or both breakpoints on the donor chromosome. When the donor chromosome fragment inserts into another recipient chromosome, it can disrupt a gene or insert between two genes. If no genes are disrupted, deleted, or duplicated on either the donor or recipient chromosome, the result is a balanced translocation.

Deletions and duplications. The organization of the human genome is highly complex. Throughout the human genome, there are repeated DNA sequences, some of which occur in tandem. Where these "tandem repeats" exist, there is a risk of slippage during meiosis. During recombination, segments of DNA within the chromosome can then delete or duplicate by unequal crossing-over.

If an interstitial **deletion** occurs, it may result loss of several genes located close together., resulting in a **contiguous gene deletion syndrome** (also known as a microdeletion syndrome). If there is a deletion, the person is then monosomic for the deleted segment, which is called partial monosomy.

Interstitial and terminal deletions can occur by other mechanisms such as missing segments after chromosomal breaks, or unbalanced transmission of a reciprocal translocation.

Similarly, interstitial **duplication (microduplication syndrome)** may occur, but the phenotypic effects tend to be less apparent.

Inversions. **Inversions** occur when two breaks within one chromosome invert and reinsert. "Tandem repeats" called segmental duplications predispose to these structural rearrangements. If the segment includes the centromere, the inversion is denoted as pericentric. If the inversion occurs within an arm and without involving the centromere it is denoted as paracentric. Pericentromeric inversion of chromosome 9 is frequent in general population and is considered as normal variant (heteromorphism). Only a small percentage of people carrying an inversion have a phenotype or related disease, usually due to disruption of a gene or a regulatory element. However, there is a risk of genetic imbalance for the offspring.

Ring chromosome. This abnormality can occur in two situations. First, when the two telomeric ends of a chromosome fuse, which usually result in no loss of chromosomal material. The other alternative is that a chromosome loses the tip of both short and long arms, with fusing of broken ends, which results in a partial monosomy.

Other structural abnormalities. There are other complex rearrangements. These are infrequent and beyond the scope of this chapter.

Other Abnormalities

Somatic and germinal mosaicism. A **mosaic patient** has cell lines that were derived from a single zygote, but that differs in genotype. Genetic mutations or chromosomal aberrations can arise in a single cell in either the prenatal or postnatal period, producing clones of cells that are genetically different from the original zygote. Thus, the effect of mosaicism is dependent on the stage at which the abnormality developed. If the aberration occurred early after conception (**somatic mosaicism**), one or more organs will be involved, mainly depending on the embryonic stage at which the aberration happened: the later in development, the more confined the abnormality (e.g., hypomelanosis of Ito). Molecular study or a karyotype of the affected tissue is helpful in diagnosing mosaicism. Genetic analysis from a blood sample may be normal, but an aberration will be detected on skin biopsy. Somatic chromosomal aberrations that occur postnatally cause many types of cancer.

Chromosomal aberrations have many opportunities to occur during germ cell development because of several mitotic divisions, and the result is referred to as **germline mosaicism**. Germline mosaicism does not necessarily produce any somatic abnormalities. Recurrence risk counselling for parents of a child with a chromosomal aberration but normal parental chromosomes must include a discussion of possible germline mosaicism. If the affected child is the product of an abnormal sperm or egg from a mosaic population of germ cells, then the risk of recurrence is increased as subsequent pregnancies can occur from additional abnormal eggs or sperm. The risk is estimated to be less than 1 %.

Genomic Imprinting anomalies. During embryonic development, a limited number of genes are unique in expressing only one of the two alleles, either the paternal copy or the maternal copy. The allele that should not be expressed is silenced by an epigenetic mechanism called **genomic imprinting**, which occurs by default in eggs and sperms. For example, the 15q11-q13 region is a complex chromosomal segment with genes affected by maternal imprinting and others with paternal imprinting. In this region, the paternal copy of the *UBE3A* gene is silenced in all sperms (paternal imprinting), while the *SNRPN* gene and other surrounding genes are silenced in all eggs (maternal imprinting). Consequently, any alteration that prevents the maternal allele expression of *UBE3A* gene cause Angelman syndrome, while any anomaly in the paternal expression of *SNRPN* and other genes causes Prader-Willi syndrome.

Uniparental disomy (UPD) happens when a patient inherits both copies of all or part of a chromosome from only one parent with no contribution for that chromosome from the other parent. When a single chromatid from a parent is present in duplicate, the term isodisomy is used. Heterodisomy refers to situations in which both homologs are present.

Prader-Willi syndrome can result from paternal deletion or maternal UPD of 15q11-q13, due to lack of allele inherited from the father. Conversely, Angelman syndrome can occur from maternal deletion or paternal UPD of 15q11-q13, due to lack of allele inherited from the mother. Mutations of maternally inherited UBE3A also cause Angelman syndrome. UPD should be considered in an autosomal recessive disorder with one identifiable carrier parent (assuming correct paternity); a known syndrome, but with uncommon features to the disorder; if the parent and patient have an autosomal recessive condition in the absence of consanguinity, founder effect, or incorrect paternity; and, male to male transmission of an X-linked recessive disorder. Disorders of imprinting are beyond the scope of this chapter as they are not detectable by karyotype, FISH or microarray

Chromosome 1

Balanced translocation rate is 1.39 per 1000 children [3] and chromosome 1 is involved in 43 % of these. In contrast, the rarity of deletions and trisomies in live children could be related to severity of their consequences.

Deletions of 1p

Definition and Epidemiology

Reported breakpoints of 1p result from interstitial deletions, malsegregation of balanced translocations, and *de novo* translocations [4, 5]. The majority of terminal deletions include 1p34 [4]. Interstitial proximal deletions cluster in the 1p22-p31 region [4, 5]. 1p36.3 is considered as a hot spot for breaks [6]. The estimated incidence for del(1)(p36) varies between 1:5000 to 1:10,000.

Systemic Manifestations

The reported phenotypes are variable and have not been clearly associated to particular break points [4]. Mental retardation, developmental delay, or psychiatric/behavioral symptoms have been found in all reported cases [4, 6, 7]. Reported survival ranges from 5 months to 30 years [8, 9]. Malformations include low set and or posteriorly rotated anomalous ears [8–10], short neck, bulbous nose, clinodactyly of the fifth finger as well as other less frequent anomalies, including absent thumb [8–12] and congenital heart disease [4, 5]. Mild ataxia or dysarthria as well as generalized hypotonia [7, 8] or seizures [6] may also occur. Other anomalies reported in some cases include high arched or cleft palate [8, 10], microcephaly [9, 10], hypertrichosis [9, 10], cryptorchidism [7, 10], dental anomalies [9], micrognathia [9, 11], preauricular tags [4], and deafness [6]. One child with del(1)(p21-p22.3) had a particularly severe phenotype in comparison to other similar deletions [5]. The patient presented with severe congenital heart disease, absent thumb, vertebral anomalies, and bilateral cleft lip and palate. Other patient with del(1)(p32.1-p32.3) had cherubic appearance, umbilical hernia and foot abnormalities [13].

1p36 deletion usually has moderate mental retardation, speech impairment and hypotonia [14]. Feeding problems and poor weight gain are more common findings [14]. The del(1)(p36) phenotype also includes large anterior Fontanelle, pointed chin, seizures, flat nasal bridge, clinodactyly and short fifth finger, low set ears, hearing deficits, and abusive behaviour [15]. Brain atrophy has been also reported in 1p36.3-pter deletion [16]. Congenital heart disease and cleft lip/palate are infrequent [15, 16]. One child with del(1)(p36.22) had hydrocephalus, small face with midline hypoplasia, frontal bossing, microstomia, polydactyly [17]. Other patient presented with gastroesophageal reflux, brachycephaly and telangiectatic and hypopigmented skin lesions [17].

Ophthalmic Manifestations

The most frequent oculofacial feature reported is small or narrow palpebral fissures (30 %) [4]. Other findings reported include almond shaped eyes [7], fissure upslanting [8], epicanthal folds [7, 10], hypertelorism and hyperopia [10]. Two patients with del(1)(p22.1-p22.2) had bilateral coloboma [4, 9]. One patient with bilateral microphthalmia had iris and choroidal coloboma [9]. One child was reported with cataracts [12]. Exotropia, hyperopia and long lashes were reported in a child with del(1)(p32.1p32.3) [13]. One patient with del(1)(p36.22) had bilateral iris coloboma and hypertelorism [17]. A patient with del(1)(p36.31-p36.33) had optic atrophy with impaired vision [6]. Case series of patients with del(1)(p36) revealed ophthalmological findings in up to 75 %, including strabismus, cranial nerve VI palsy, amblyopia, refractive errors, anomalous optic discs and lacrimal defects [14]. Other ocular problems observed in del(1)(p36) include nystagmus, visual inattention, unilateral cataract, fundus hypopigmentation and unilateral optic nerve coloboma [18–20]. Terminal deletions may be associated with deep set eyes [6]. Both long eyelashes and synophyrs have been reported [4, 9].

Deletions of 1q

Definition and Epidemiology

Most frequent 1q deletions are del(1)(q21q25), del(1)(q25q32) and del(1)(q42qter) [21]. Del(1)(q42qter) is the most common 1q deletion and usually includes 1q42 and/or 1q43 [22]. Although approximately 30 % of patients with del(1)(q) die in the first 2 years of life, two reported survivors are a severely retarded 12 year old, and a 35 year old woman [22].

Systemic Manifestations

Findings of interstitial del(1)(q21q25) include developmental delay, hypotonia, microbrachycephaly, cleft palate, posteriorly rotated ears, club foot, transverse plamar crease and malformations of the heart, external genitalia and kidneys abnormalities [21]. One patient had myelomeningocele with hydrocephalus and anal atresia [21]. Autism and schizophrenia have been described in del(1)(q21.1) [23, 24]. Prune belly syndrome and Potter sequence were described in patients with del(1)(q25q32). Pancreatic anomalies have been reported in del(1)(q31.2q44) [25].

Terminal deletion of 1q present with profound mental retardation, growth deficiency, and microcephaly. Some individuals show genital and heart abnormalities [22, 26, 27]. Hypothyroidism and growth hormone deficiency have also been described [26]. Patients may also exhibit abnormal behavior or spontaneous laughter [22, 26]. Minor malformations may include a round facies with downturned mouth, flat philtrum with thin lips, low-set ears, micrognathia, short broad nose, short or thick neck, and clinodactyly [22, 26, 27].

Del(1)(q41q42) has been recently described with characteristic features, including developmental delay, dismorphic features and seizures, suggesting an association with *FBXO* [28]. One case with del(1)(q42) syndrome was reported with congenital cardiac disease, genital anomalies, neural tube defects and abnormalities of hands and feet [29]. Del(1)(q44) has been associated with hemiconvulsion, hemiplegia

and epilepsy [30]. Six additional cases were reviewed from a literature search. Del(1)(qter) has been associated to short stature, developmental delay and mental retardation, microcephaly, seizures, abnormal corpus callosum, and abnormal ear shape [31]. A 6-year-old girl and de novo interstitial del(1)(q24.3-q31.1) had multiple pituitary hormone deficiency, severe cognitive impairment, bilateral cleft lip and palate, midline facial capillary malformation, erythema of hands and feet and dysplastic cranial vessels, low antithrombin III activity, hemifacial overgrowth due to progressive infiltrating lipomatosis with bone overgrowth [32].

A case with interstitial deletion of 1q having delayed psychomotor development, mid face hypoplasia, low set ears and tapering fingers was reported [33]. MRI showed hypoplasia of the corpus callosum.

Ophthalmic Manifestations

Epicanthal folds are a frequent feature of the distal 1q deletions. Upward-slanting palpebral fissures [22], strabismus [22], "protruberant eyes" [27], and "upper eye fullness" have also been described [32].

A case with interstitial deletion of 1q had ptosis and Duane syndrome. Microphthalmia, strabismus, Duane syndrome and bilateral congenital cataracts were described in patients with del(1)(q21.1) [34].

One patient with an unbalanced translocation with a partial trisomy of 4q and a terminal deletion of 1q was reported with sparse eyebrows and lashes, and bilateral retinal and optic nerve colobomas [35]. In addition, a patient with del(1)(q) and bilateral iris coloboma has been reported, although that the patient's sibling had the same 1q deletion, but did not have coloboma [36]. Recent reports of del(1)(q41q42) and del(1)(q44) also include hypertelorism [28, 30].

Duplications of 1p

Definition and Epidemiology

Is a rare condition, with few cases reported in the literature.

Systemic Manifestations

Congenital heart disease, hand anomalies, growth retardation, microcephaly, flat nasal bridge, cleft lip/cleft palate, ear anomalies, micrognathia, and cryptorchidism have been reported [37]. An 8 year old male patient with dup(1)(p13.1p22.1) was reported with clinical findings of Nikawa-Kuroki syndrome, including mental retardation, microcephaly, syndactyly, persistant fetal finger pads, flat nose with short columella [38].

Ophthalmic Manifestations

Ocular manifestations consistent with Nikawa-Kuroki syndrome, including flare of lateral eyebrows, euryblepharon, long lashes, epicanthal folds, bilateral ptosis and blue sclera were observed in the patient with dup(1)(p13.1-p22.1) [38].

Duplications of 1q

Definition and Epidemiology

Complete trisomy of chromosome 1 usually results in embryonic death [39], although there is a patient that lived at least to 4 years of age [27]. Few cases have been reported with duplication 1q.

Systemic Manifestations

Reported findings include severe mental retardation, congenital heart disease, micrognathia cleft lip and palate, hirsutism, cryptorchidism, renal dysplasia and hypoplasia, low set ears, high arched palate, nasal skin hemangioma, hearing defects, and absence of the gall bladder [27, 39–42]. The brain may have microgyria, absent olfactory nerves, cerebral dysgenesis or hydrocephalus [41, 42]. It may also predispose to neoplasia formation [43].

Ophthalmic Manifestations

Reported oculofacial findings include "small and wide-set" eyes [27, 39] and downslanting of the palpebral fissures [41]. One case with dup(1)(q31q32) had infantile glaucoma associated with iris stromal dysgenesis and vascularized iris processes in an otherwise open angle [44]. *GLC1* gene was identified in the duplicated region. One neonate with trisomy (1)(q32qter) was reported with goniodysgenisis, persistent tunica vasculosa lentis, hyaloid vessels, hypopigmentation of the posterior iris pigment epithelium, ectopia of ciliary processes, abnormal insertion of ciliary muscle and cataract [45]. One child had congenital glaucoma and dup(1)(q41qter), but this was attributed to an associated del(9)(p23pter) because of an earlier report [46].

Optic disc hypoplasia have been reported with dup(1)(q32.1q44) [47]. Other ocular manifestations of partial trisomy (1)(q42qter) include hypertelorism, shallow orbits with exophthalmic appearance, arched eyebrows, narrow palpeberal fissure, bilateral iris coloboma, punctate cataract and optic nerve coloboma [48].

Ring Chromosome 1

Definition and Epidemiology

This is a rare condition. One patient had ring 1 in all cells but mosaic for an absence of either chromosome 1 or 3 [49]. Another patient was also mosaic, with some cells having a normal karyotype and others having one or more ring 1 chromosomes [50]. Survival was described at least to 9 years old [51].

Systemic Manifestations

Ring 1 exhibit microcephaly, mental retardation, and short stature [12, 49, 51]. "Elfin" facies with upturned mouth, left palate, abnormal ears, congenital hip dislocation, preauricular sinuses, clinodactyly [51], and ascites have been described [49–51].

Ophthalmic Manifestations

One publication did not report any ocular abnormalities [49]. One patient had small palpebral fissures, epicanthal folds, and down-slanting palpebral fissures [50]. Slight up-slanting of the fissures have also been reported.

Chromosome 2

Deletion 2p

Definition and Epidemiology

Deletion 2p is a rare condition, with few cases reported in the literature.

Systemic Manifestations

Lobar holoprosencephaly, microcephaly, short neck, large ears, clinodactyly, protuberant abdomen, cognitive impairments and cardiac defects have been reported with del(2)(p21p22.2) [52, 53]. One 5 year old male with 2p11.2 deletion showed mental retardation and bilateral clubfoot [54]. Two siblings with del(2)(p21) showed severe hypotonia, feeding problems, micrognathia, increased serum lactate, mild intellectual disability, hypospadias and cleft palate [55]. Urogenital abnormalities, psychomotor retardation and vitiligo were reported in del(2)(p11.2p13) [56]. A patient with del(2)(p16.3) presented with diaphragmatic hernia, developmental delay and short stature [57]. Nine patients have been reported with del(2)(p15p16.1), including severe developmental delay, intellectual disability, microcephaly, complex craniosynostosis and facial dysmorphism [58].

Ophthalmic Manifestations

Epicanthal folds, long palperal fissures, wide spaced eyebrows and synophthalmia/cyclopia have been reported with del(2)(p21p22) [52, 53]. Arched eyebrows, telecanthus and ptosis were reported with del(2)(p11.2p13) [56] as well as blepharophimosis [59]. A patient with del(2)(p21) had ptosis and epicanthal folds [55]. A 9 year old female patient with del(2)(p16.3) presented with bilateral ptosis, downslanting palpebral fissures and long eyelashes [57]. Patients with delayed psychomotor development and del(2)(p16.1) had ptosis, telecantus and epicanthal fold [60, 61]. In patients with del(2)(p15p16.1), optic nerve hypoplasia, strabismus, ptosis and telecanthus have been described [58].

Deletion 2q

Definition and Epidemiology

Different 2q deletions with varying phenotypic features have been reported in several cases [60–63]. Over 100 patients with interstitial deletion of 2q have been reported. Frequently, these deletions are proximal to or include 2q33. Del(2)(q36) is rare [64]. Approximately 50 % of the reported deletions involve a chromosome region between 2q24.3-31.1 [63] or are terminal 2q37.3 deletions [65].

Systemic Manifestations

Deletion of 2q is associated with developmental delay, mental retardation, gonadal cysts, digital anomalies, hyperactivity with autistic traits and dysmorphic features including Pierre Robin sequence and temporal bone abnormalities. Hypoplastic lungs have been described [66]. Del(2)(q32) syndrome has been reported with growth retardation, microcephaly, facial dysmorphism, cleft palate, campodactyly, severe intellectual disability and ectodermal anomalies [67]. Del(2)(q33.3-q34) has been associated with Seckel syndrome, which includes intrauterine and postnatal growth retardation, developmental delay, microcephaly, receding forehead, large beaked nose, micrognathia, radial head dislocation, clinodactyly, and absent ear lobes. Hypotonia and hypospadius may also be present. Myelomeningocele, mild congenital heart disease, developmental delay, and minor dysmorphic features, including long philtrum, hypoplastic nasal bridge, prominent anteverted nasal tip, and mild abnormalities of the fingers have been reported with del(2)(q36). One patient with del(2)(q37.3) had speech delay, hyperactivity, mental retardation, autism, and brachydactyly [68].

Interstitial del(2)(q14.1q22.1) is rare. To the date, nine patients have been reported with deletions either within the region 2q13 or 2q14 to 2q22.1, having a combination of cognitive disability, growth retardation, hypotonia, craniofacial and limb abnormalities, and cardiac, renal and/or brain malformations, suggesting that there may be a recognizable phenotype. In this specific region there are 14 known disease-associated genes [69].

A recent publication reports the first familial case of interstitial del(2)(q37.3) affecting two genes, *HDAC4* and *TWIST2*. Patients presented with brachydactyly and short stature without intellectual disability, which is usually described in brachydactyly-mental retardation syndrome, also known as Albright hereditary osteodystrophy [70]. Mutations in *TWIST2* are usually associated with Settleis bitemporal forceps mark syndrome.

Ophthalmic Manifestations

Frequent findings of del(2)(q21q24) include microphthalmia, ptosis and cataract [71, 72]. Bilateral iris coloboma have been reported in individuals with del(2)(q21-q23.2)

[73] or del(2)(q23.3-q24.2) [74] suggesting two separate critical areas. One child with del(2)(q24q32) had bilateral down-slanting palpaberal fissures, blepharophimosis, bilateral microphthalmia, iris coloboma, corneal opacities, and large chorioretinal coloboma involving the macula [75]. Thick eyebrows, synophrys, and hypertelorism are reported with del(2)(q31.2) and del(2)(q32.3) and optic nerve hypoplasia with del(2)(q31q33) [76]. Prominent supraorbital ridges, thick eyebrows, synophrys and proptosis were seen in a patient with del(2)(q31.2-q32.3) [77]. One patient with del(2)(q36) was described with hypertelorism, and in addition, "narrowness" of the palpebral fissures, although this is not evident in the associated photographs [64].

Epicanthal folds, Brushfield spots, and short palpaberal fissures have been described in terminal del(2)(q37.1). Coloboma has been described with del(2)(q37.3) [78] Seckel phenotype can present with down-slanting palpebral fissures. "Small eyes" have been described in a case of del(2)(q37.1qter), although there was concomitant duplication of part of the 1q [40]. Progressive keratoconus have been reported in a patient with del(2)(q37.3) [68]. Narrow palpebral fissures, deep set eyes and upslanting palpebral fissures have also been reported [79].

Duplication 2p

Definition and Epidemiology

There is no typical hotspot region in 2p duplication. Few cases with ophthalmic findings have been reported in the literature.

Systemic Manifestations

One patient with an inverted duplication of 2p and terminal 2p deletion presented with developmental delay, cardiac anomalies, pulmonary stenosis, micrognathia, low set ears, prominent forehead and depressed nasal bridge [80]. Two boys with microduplications 2p16 and 2p22 were reported with severe growth retardation, macrocephaly and broad forehead [81].

Ophthalmic Manifestations

The individual with inverted duplication of 2p and terminal 2p deletion showed hypertelorism, short palpebral fissures and nasolacrimal duct obstruction [80]. The two male patients with microduplications 2p16 and 2p22 had sparse eyebrows and hypertelorism [81].

Duplication 2q

Definition and Epidemiology

Most duplications of 2q result from unbalanced translocations resulting in trisomy for the entire q arm [82]. Different interstitial duplications of distal 2q have been reported including two siblings with dup(2)(q24.3q32.1)[71]. Their father had a balanced translocation and was clinically normal. There are five reports of patients with 2q duplication and ophthalmic findings.

Systemic Manifestations

There is evidence that the extent of the trisomic region correlates with phenotypic severity. Features common to virtually all distal trisomies of 2q include developmental delay, prominent forehead, depressed nasal bridge, anteverted nares, and long philtrum with thin upper lip. Ear anomalies include ear lobe creases [82]. Other reported findings include inguinal hernia, brahcycephaly, clinodactyly and pectus excavatum [82]. A patient with dup(2)(q32.1-q33.3) showed epilepsy, developmental delay and autistic behavior [83].

Ophthalmic Manifestations

Hypertelorism has been reported in all cases of distal dup2q. Some patients also had upslanting palpebral fissures and epicanthal folds [82]. One of the sibling pair had esotropia. A patient with dup(2)(q32.1q33.3) had hypertelorism, but not coloboma or epicantal folds reported in other dup2q patients [83]. Hypertrichosis, shallow orbits with prominent eyes, and blue sclera have been also reported in patients with dup(2)(q32q37) [84]. Nystagmus has also been reported.

Trisomy 2

Definition and Epidemiology

Complete trisomy of chromsome 2 has been reported in live born patients only as mosaicism . Less than 50 cases have been described in the literature.

Systemic Manifestations

One individual was reported with multiple non hepatic malformations including growth failure, congenital heart disease, hydronephrosis, gastrointestinal dysfunction, brain dysgenesis, hypotonia, microcephaly and developmental delay [85]. The child had cholestasis and hepatic fibrosis. The trisomy was only detected on liver biopsy, but was not found in intestinal mucosa, skin, ascitic fluid, or blood. Caudal dysgenesis and Hirschsprung disease have also been described.

Ophthalmic Manifestations

Lower canthal folds [85] and anophthalmia have been described in a patients with trisomy 2 mosaicism. Hypertelorism and nasolacrimal duct obstruction have been reported with dup(2)(p23pter) [86].

Chromosome 3

Deletion 3p

Definition and Epidemiology

Distal deletion of 3p is infrequent, with less than 50 patients reported.

Systemic Manifestations

Patients with distal 3p deletion show developmental delay, low birth weight, growth retardation, feeding problems, cardiac septal defects, seizures, hypothyroidism, micro- and brachycephaly, broad and flat nose, long philtrum, micrognathia, low set ears and syndactyly [87–89]. Individuals with del(3)(p21-p31) are characterized by developmental delay, dysmorphisms, elevated serum creatine kinase levels and white matter involvement [90].

Ophthalmic Manifestations

Patients with del(3)(p14) have several oculofacial findings, including up-slanting fissures, deep set eyes, almond shaped eyes, eyebrows with medial flare, and epicanthal folds. Nasolacrimal duct stenosis have been also reported with del(3)(p14) [91]. One case with del(3)(p12p21.2) and a CHARGE phenotype was reported with iris coloboma, heart defect, choanal atresia, growth retardation and development delay, genital hypoplasia and ear anomalies with hypertelorism and bilateral microphthalmia [92]. Hypotelorism has also been reported [89]. Oculofacial findings associated with del(3)(p25-pter) are down-slanting palpaberal fissures, bushy eyebrows with synophrys, blepharophimosis, hypertelorism, epicanthal folds, ptosis and periorbital fullness [87, 88, 93–95]. Patients with del(3)(p21p31) have arched eyebrows, hypertelorism and upslanting palpebral fissure [90].

Deletion 3q

Definition and Epidemiology

Mutations in the *FOXL2* gene (located in 3q23 region) are responsible for the blepharophimosis-ptosis-epicanthus inversus syndrome (BPES), a condition that mainly affects development of the eyelids. Approximately 20 % of these patients exhibit BPES as part of a contiguous gene deletion syndrome [96]. 3p25 and q23 are two locations on chromosome 3 which may give rise to BPES [97]. This syndrome is typically inherited in an autosomal dominant pattern. The prevalence of BPES is unknown. In females, the eyelid malformation may be associated (type I BPES) with premature ovarian failure. Type I BPES is associated with female infertility and transmitted only by males, whereas males and females transmit type II. Bilaterally shortened horizontal palpaberal fissures, epicanthus inversus, and congenital ptosis with poor levator function characterize BPES.

Systemic Manifestations

An individual with BPES associated with diaphragmatic hernia was reported with del(3)(q21-q23) [98] and with microcephaly and developmental retardation in del(3)(q22.2-q23) [99] One neonate was reported with blepharophimosis, iris coloboma, hearing loss, post axial polydactyly, aplasia of corpus callosum, hydroureter and developmental delay [100]. Del(3)(q29) includes intellectual disability, schizophrenia, autism, bipolar disorder, depression and facial dysmorphism [101]. An 18 month old female with del(3)(q21.3-q22.1) presented features of Aicardi Syndrome [102]. A female newborn with del(3)(q26) had anal atresia, nasal skin tag, low set and protruding ears and growth delay [103].

Ophthalmologic Manifestations

A patient with del(3)(q26) encompassing *SOX2* had bilateral microphthalmia, iris coloboma and cataract [103]. Del(3)(q29) microdeletion has been associated with slight pale optic disc, although no further investigation is provided [101]. A peripapillary chorioretinal lacunae was reported in a 18 month old female with del(3)(q21.3-q22.1) [102].

Duplication 3p

Definition and Epidemiology

Duplication 3p is a rare chromosomal aberration with few cases reported.

Systemic Manifestations

Developmental delay, dolicocephaly, low set and abnormal ears, cavernous hemangioma over the lumber spine, sacral dimple, clinodactyly and hypotonia were reported in an individual with dup(3)(p11.1-p14.2).

Ophthalmic Manifestations

The patient described above had ptosis and hypertelorism [104].

Duplication 3q

Definition

Dup(3)(q21qter) has been reported in patients with a phenotype that looks like Cornelia de Lange syndrome (CdLS) [105].

Systemic Manifestations

Patients having the CdLS phenotype associated with 3q duplications have hirsuitism, anteverted nares, carp shaped mouth with downturned corners, ear deformities, cardiac

defects, mental retardation, and growth abnormalities. Limb reduction malformations are less frequent, whereas craniosynostosis, urinary malformations, and cleft palate more common in dup(3)(q) [105]. Two patients with dup(3)(q25q26) were reported with this phenotype [105]. Dup(3q)(13.2q13.31) has been associated with microretrognathia, cleft palate, septal defect, pulmonary hypertension, severe gastrointestinal reflux and mild hearing impairment [106].

Ophthalmic Manifestations

The dup(3)(q) CdLS-like phenotype has been associated with hypertelorism, synophyrs, epicanthal folds thick and long lashes, down-slanting palpebral fissures, nasolacrimal duct obstruction, and strabismus [107, 108]. In proximal interstitial duplication, high arched eyebrows and upslanting palpebral fissures have been reported [105]. Other ocular abnormalities seen in patients with CdLS, are frequently absent in dup(3)(q), although glaucoma, iris coloboma, cataract and anophthalmia, all uncommon or absent in CdLS, have been described [108]. Microphthalmia and corneal opacity were described in an individual with dup3q21-27 in the context of anomalous cerebellar development and Dandy-Walker malformation [109]. Dup(3)(q13.2-q13.31) has shown hypertelorism [106].

Pericentric Inversion of Chromosome 3

Definition and Epidemiology

This is a rare chromosomal abnormality, with two breaks on either side of the centromere.

Systemic Manifestations

One newborn with pericentric inversion of chromosome 3 showed atrial septal defect, polycystic kidney, clubbed feet, umbilical hernia, mental retardation, long and narrow hands and subluxation of the elbows [110].

Ophthalmic Manifestations

This patient with pericentric inversion of chromosome 3 presented several ophthalmological findings, including epicanthal folds, exotropia, microcornea, miotic pupil, iris neovascularization, cataract, glaucoma, hazy vitreous, subretinal hard exudates, exudative detachment, posterior hyaloid detachment with elevated neovascularization of the disc, and aneurysmal dilation of the peripheral retinal vessels, resembling Coats disease [110]. Some of these ocular findings may have been secondary to the primary retinal vascular malformation. Other patients reported with pericentric inversion of chrosome 3 had bilateral coloboma of the iris [111], upward slanting palpebral fissures, and hypertelorism.

Chromosome 4

Deletion 4p

Definition and Epidemiology

The most characteristic phenotypes for del4p are Wolf-Hirschorn syndrome (WHS) and Pitt-Rogers-Danks syndrome (PRDS), now recognized as part of the same spectrum due to a deletion of 4p16.3 region [112]. The critical region for WHS, referred to as WHSCR-2, falls within a 300–600 kb interval in 4p16.3 [112] and contains the candidate gene *NELFA*. Small deletions could result in milder phenotypes. About 50 % of patients with WHS have a *de novo* pure deletion of 4p16 and nearly 40 % have an unbalanced translocation.

One author described patients who lacked the characteristic facial features, but showed non-specific manifestations of WHS [113]. The patients had deletions distal to WHSCR. Others developed a numerical scoring system for phenotypic features which may be helpful in identifying patients with normal karyotypes, on whom further molecular analysis might be indicated [114].

The critical region lies distal to the Huntington disease (HD) locus [115, 116]. No patient with both syndromes has been reported, maybe because of death before the typical adult onset for HD. WHS is caused by haploinsuficiency and Huntington disease results from an expanded CAG repeat leading to a pathologic gain of function.

Growth retardation and developmental delay have not been attributed to a specific gene, suggesting that more than one loci may be contributing [117]. It is apparent that WHS represents a contiguous gene deletion syndrome.

Interstitial deletion of the p14-16 region of chromosome 4 may present a distinct phenotype which is different from that of Wolf-Hirschhorn syndrome, with multiple minor anomalies and mental retardation [118].

The incidence of WHS is 1:50,000 live births [119]. About 90 % of cases are *de novo*, while 10–15 % arise from balanced translocations. *De novo* deletions are usually on the paternal chromosome [119, 120].

Systemic Manifestations

The distinctive WHS phenotype is defined by the presence of typical facial appearance consisting of ‘Greek warrior helmet appearance’ of the nose (the broad bridge of the nose continuing to the forehead) microcephaly, high forehead with prominent glabella, ocular hypertelorism, epicanthus, highly arched eyebrows, short philtrum, downturned mouth, micrognathia, and poorly formed ears with pits/tags. Patients have mental retardation, growth delay, congenital hypotonia and seizures.

Major manifestations are developmental delay growth retardation, cleft lip and/or palate, micrognathism, genital abnormalities, congenital heart disease, and seizures [114–116, 119, 121–123]. When the deletions involve the

LETM1 gene, seizures are more likely to be observed [113]. Other less frequent features include low-set posteriorly rotated ears, preauricular tags, hearing loss, short philtrum, bowed or carp-shaped mouth, scalp defects, hypotonia, decreased tendon reflexes and abnormalities of the corpus callosum [114–116, 119, 121]. Skeletal anomalies include tapered fingers, scoliosis, concave or hyperconvex nails and clinodactyly [114, 115, 119]. Other associations are congenital heart disease, fused teeth, and hypospadias [124, 125]. In addition, extensive Mongolian spots have been reported in del(4)(p16.3) [126]. Most individuals with WHS die in the first 2 years of life. In those who survive longer, severe retardation may be present [125]. Common causes of death are respiratory and cardiac [125]. Interstitial deletions proximal to the WHS region are usually found within 4p12-p16 and have a somewhat different phenotype [118].

One author demonstrated that there was a deletion in 4p16 region that overlapped and extended beyond the WHS critical region in each direction, considering likely that PRSD and WHS result from deletion in the same region [127]. Others had the same conclusion at a molecular level. Currently, WHS and PRDS represent clinical variation of a single disorder and the prognosis will be determined by the range and severity of symptoms present in the individual cases.

Developmental delay, hypotonia, high arched palate, thick lower lip, micrognathia, and prominent nose are seen in deletions that involve 4p14-p16 region, proximal to the WHS region. They vary from WHS individuals mostly because of their tall thin habitus, myopathic facies, and nipple abnormalities [118].

Ophthalmic Manifestations

Minor oculofacial manifestations include hypertelorism [128, 129], arched eyebrows, epicanthus, and upslanting or downslanting of the palpebral fissures. Less frequent findings are periorbital swelling, proptosis, shallow orbits, or blue sclera [114, 115, 117, 119, 121, 122, 124, 125]. Centrally distributed Brushfield-like spots on the iris [120] and iris heterochromia are could be seen [114], with a different distribution than those seen in Down syndrome. Cataracts may also occur [114, 125]. Possibly the most frequent ocular malformation of WHS is coloboma (30%) or corectopia with or without microphthalmia [125]. Microcornea, disc abnormalities and foveal hypoplasia have been described in del(4)(p14p16.3) [130]. Microphthalmia, Peters anomaly and congenital cataract have also been reported with del4p. One patient with WHS was reported with early onset glaucoma involving a 165-kb segment within 4p16.3 region [131]. Coloboma can be unilateral [120, 122, 125] or bilateral. There have been reports of nasolacrimal duct obstruction, esotropia [115], exotropia [120, 125], and nystagmus in WHS [114, 117, 119]. Strabismus is seen in approximately one to two-thirds of patients [117, 119, 125]. Some traits, such as strabismus and epicanthus, may also show variable penetrance [117]. Ptosis has also been described (20–25%) [117, 119, 125]. On a report of 10 patients severe ocular manifestations occurred in association with large 4p deletions, with the most frequent finding of exotropia (90%) [132]. In one publication that included 22 patients with WHS, strabismus and nasolacrimal obstruction were found in patients with small or intermediate deletion, whereas ocular anomalies were found in patients with intermediate and large deletions [128]. Deletions that extend more proximally to 4p16 are associated with strabismus, hypertelorism, epicanthal folds. Abnormalities of the eyebrows occur as well. Less proximal involvement may still result in ptosis [117]. Abnormal slanting of the palpebral fissures appears to map to a 150 kb region between *D4F26* and *D4S9050*.

Nystagmus has been associated to isolated terminal deletions and interstitial deletions proximal to the WHS region [117, 118]. The WHS critical region also includes the phosphodiesterase beta subunit gene. Biallelic mutations in this gene may be associated with retinal dystrophy. However, to our knowledge, retinal dystrophy has not been seen with WHS.

Deletion 4q

Definition and Epidemiology

Distal interstitial deletions are more often than proximal deletions. Most of proximal interstitial deletions are *de novo* [133]. Estimated incidence is 1 in 100.000.

Systemic Manifestations

Clinical presentation of 4q deletion is variable. Major deformities are infrequent but include renal malformations, congenital heart disease, or seizures. Dysmorphic features are a high forehead, flat nasal bridge, and receding chin [133]. Minor anomalies of the digits and nipples can be seen. Deafness and cleft palate are unusual associations. Del(4)(q12q13.1) results in mild mental retardation and dental anomalies, as well as hypotonia [133]. Piebaldism may be seen due to hemizygosity of the *c-kit* gene (4q12 region) [133]. Del(4)(q21q22) is associated with growth retardation, short stature, dolicocephaly and deafness [134]. One patient with del(4)(q21.22q23) was reported having micrognathia, clinodactyly genital malformation, cardiac anomalies, mental retardation, seizures, and a liver tumor [135]. Three patients with Axenfeld-Rieger syndrome and del(4)(q25) had mild learning difficulties, which is not typically seen in patients with this syndrome [136]. Del(4)(q27q31) is associated with mild mental retardation, micrognathia and dental malocclusion but no other systemic findings [137]. Cardiac malformations, Pierre Robin sequence, microcephaly, genito-urinary anomalies, short stature, and learning disability characterizes a deletion syndrome involving 4q31qter

region . One author reported the "tail of a nail" sign in the fifth finger which is stiff with a hypoplastic distal phalanx and hooked or volar nail in del(4)(q34) [138]. Recent cases with del(4)(q21) have been associated with severe intellectual disability, lack of speech, hypotonia, facial dysmorphisms and significant growth retardation [139, 140].

Ophthalmic Manifestations

Eyebrow hypopigmentation and iris color abnormalities can be seen in individuals with del(4)(q12) and piebaldism [133]. In a patient with del(4)(q12q13.1), esotropia, refractive error, and epicanthus were reported [133]. Dystopia canthorum have also been reported. Other ocular abnormalities associated with proximal interstitial deletions include colobomatous microphthalmia, pigmentary retinopathy, and exotropia. Hypertelorism has been described in del(4)(q21.3q23) [141]. One case of bilateral Type II Duane syndrome with ptosis has been reported in a patient with del(4)(q27q31) [137]. One case of Axenfeld-Rieger syndrome and glaucoma was reported in a series of 20 patients with 4q deletions [142]. Four patients with overlapping microdeletions including *PITX2* at 4q25 region were reported having Axenfeld-Rieger syndrome [136]. One author reported bilateral optic disc swelling in tail of the nail syndrome with del(4)(q34) [143]. Narrow palpebral fissure has been described in del(4)(q21) [139, 140].

Duplication 4p

Definition and Epidemiology

4p duplication syndrome is a rare condition, with few cases reported in the literature.

Systemic Manifestations

Trisomy 4p is also associated with microcephaly, mental and growth retardation, abnormal ears, bulbous nose, congenital heart defects, flexion contractures, microphthalmia, and seizures [144, 145].

Ophthalmic Manifestations

Microtia, ocular coloboma and nasolacrimal duct obstruction have been associated with dup(4)(p16) [144].

Duplication 4q

Definition and Epidemiology

Partial trisomy 4q is a rare genetic abnormality.

Systemic Manifestations

One author reported cardiac and renal defects, craniofacial malformation and mental retardation [146]. Mild intellectual disability, cranial malformation, facial dysmorphism and digital anomaly has been also reported with dup(4)(q32.2q34.3).

Ophthalmic Manifestations

One author reported morning glory disc anomaly [146]. Microphthalmia has been also associated to trisomy 4q [147]. Epicanthic folds have been reported in patients with dup(4)(q31.1q32.3) [148] and hypertelorism in an individual with dup(4)(q32.2q34.3) [149].

Chromosome 4 Inversion

Definition and Epidemiology

Chromosome 4 inversion is a rare condition with few cases reported.

Systemic Manifestations

One patient with inv(4)(q12q13.3) showed cleft lip and palate, cardiac abnormalities, meningocele, ear malformations, normal stature, normal cognitive development and otitis media [150].

Ophthalmic Manifestations

This patient had microphthalmia, cataract, retinal dysplasia, and Peters anomaly [150].

Chromosome 5

Deletion 5p

Definition and Epidemiology

The Cri du chat (CdCS) phenotype is due to partial terminal or interstitial deletion of 5p15.2. The incidence of cri du chat syndrome is estimated as 1 in 20,000–50,000 [151]. About 85 % of the patients show a *de novo* deletion. Up to 15 % present a familial cause, with a parental translocation in more than 90 %, or a para/pericentric inversion of chromosome 5 in 5 %.

The telomerase reverse transcriptase (hTERT) gene is located in the critical 5p15.33 region for the CdCS phenotype. hTERT is a limiting component for telomerase activity that is essential for telomeric length maintenance and sustained cell proliferation [152].

Systemic Manifestations

Infants with CdCS characteristically show a distinct cat-like high pitched cry, psychomotor retardation, microcephaly, growth rate failure, microcepahly, round face, and broad nasal bridge [151]. When they become older, the face lengthens and becomes coarse with prominent supraorbital ridges, deep set eyes, hypoplastic nasal bridge, severe dental anomalies and comparatively large mouth will a full lower lip (Fig. 6.4). Hemizygosity of delta-catenin (*CTNND2*) is associated with severe intellectual disability in some patients with CdCS. Although lack of speech was considered a characteristic of the syndrome, it is not yet know whether

Fig. 6.4 Patient with Cri du chat syndrome with del(5)(p15.2) and mild dysmorphic findings (courtesy of Mariana Aracena MD)

language comprehension is impaired to the same extent as language production [153]. MRI of these patients shows atrophy of the brain stem, mainly at the pontine level associated with atrophic middle cerebellar peduncles and cerebellar white matter [154].

Ophthalmic Manifestations

Exotropia, myopia, upward slanting palpebral fissures, hypertelorism, and epicanthic folds have been reported in CdCS [151].

Telecanthus, epicanthal folds, antimongoloid palpebral fissures, optic atrophy, and tortuosity of the retinal vasculature have also been associated to CdCS.

Deletion 5q

Definition and Epidemiology

Few cases with 5q deletion and eye findings have been reported.

Systemic Manifestations

Del(5)(q14.3) has recently been recognized as a clinical entity presenting with severe intellectual disability, epilepsy and brain malformations [155]. One patient with del(5)(q22.1q31.1) was reported with mental retardation, craniofacial abnormalities and typical features of Gardner syndrome, including several adenomatous polyps of colon, osteomas of facial and long bones, and soft tissue tumors [156]. Three previously reported 5q deletion patients had also adenomatous polyposis coli [156] The adenomatous polyposis coli gene (*APC*) is located at 5q21-q22 region. Schizophrenia mental retardation and dysmorphic features were seen in a patient with del(5)(q21q23.1) [157]. One case had dysmorphic features and mewing cry associated with a *de novo* del(5)(q31.1q31.2) [158]. Marked hypotonia, apnea and developmental delay have also been reported in 5q31.3 microdeletion [159]. Neonatal lymphedema, short neck hypotonia, delayed development, and congenital heart defects have been reported with del(5)(q35.1q35.2) [160].

Recently, definition of 5q11.2 microdeletion syndrome based in 6 patients revealed an overlap with CHARGE syndrome and 22q11 deletion syndrome phenotypes, including choanal atresia, developmental delay, heart defects, external ear abnormalities, and short stature [161].

Ophthalmic Manifestations

Del(5)(q14.3) has been associated with hypertelorism [155], and iris coloboma in interstitial del(5)(q14.3q21) [162] Upslanting palpebral fissures with ptosis, exophthalmos and hypertelorism occur consistently with del(5)(q22.1q31.1) [156–158]. Sparse eyebrows, hypertelorism and ptosis have been reported in del(5)(q31.3) [159, 163]. Bushy eyebrows, synophyrs, and irregular lashes have been reported with del(5)(q35.1) and del(5)(35.3) [164].

Duplication 5p

Definition and Epidemiology

There are only few reports on patients with duplications of the short arm of chromosome 5 [165–168].

Systemic Manifestations

Dup(5)(p11p13.2) shows a severe phenotype that includes macrodolicocephaly, craniofacial anomalies, hypotonia, mental retardation, and malformations of the heart, kidneys, intestine and brain. When the duplication is distal to 5p13.3 region, only minor features have been reported, including developmental delay and learning difficulties [166].

Ophthalmic Manifestations

One patient with partial trisomy 5p had atypical Peters anomaly along with down-slanting eye fissures and epicanthal folds [167]. Microphthalmia, coloboma and strabismus have been associated with dup(5)(p13pter) [168].

Paracentric Inversion of Chromosome 5

Definition and Epidemiology

This is a rare condition, with few cases reported. Haplo insufficiency of NR2F1 has been proposed as the cause of deafness and other associated anomalies based on a similarity with the Nr2f1 null mouse [169].

Systemic Manifestations

A 4-year-old girl presented with profound deafness, feeding difficulties, facial dysmorphism, developmental delay, and a *de novo* paracentric chromosome 5 inversion, inv(5)(q15q33.2) [169].

Ophthalmic Manifestations

Upslanted palpebral fissures and strabismus were reported in the previously described patient [169].

Partial Tetrasomy with Triplication of 5p

Definition and Epidemiology

This is an extremely rare aberration with few cases reported in the literature.

Systemic Manifestations

Microcephaly, hypertonia seizures, dysplastic kidneys, cardiac abnormalities and clinodactyly have been reported in a patient with partial tetrasomy with triplication of 5p affecting the 5p14p15.33 region [170].

Ophthalmic Manifestations

The patient had hypoplastic supraorbital ridges, prominent eyes, chorioretinal coloboma and dysplastic retinal tissue at the optic nerve head [170].

Supernumerary Ring Chromosome 5

Definition and Epidemiology

This condition is an extremely rare chromosomal abnormality.

Systemic Manifestations

Convulsions, laryngomalacia, preauricular tags and high arched palate have been reported [171].

Ophthalmic Manifestations

The only reported oculofacial abnormality is telecanthus [171].

Chromosome 6

Deletion 6p

Definition and Epidemiology

Most deletions of 6p are terminal deletions. The 6p23 breakpoint is more common than 6p24. Other significant breakpoint is 6p25, where the forkhead transcription factor *FOXC1* is located. This gene is associated with Axenfeld-Rieger syndrome (ARS), characterized by specific ocular anomalies with or without systemic abnormalities. More than 40 6p deletion cases have been reported.

Systemic Manifestations

6p23 deletion is characterized in most of patients by craniosynostosis, with or without microcephaly, small pinched nose with flat bridge and anteverted nostrils [172]. Majority of these patients have congenital heart disease [172]. Associated hepatosplenomegaly and thrombocytopenia could be related to heart failure. Other authors have described hydrocephalus, hypotonia, malar hypoplasia, high/cleft palate, minor ear abnormalities with or without hearing loss, micrognathia, downturned mouth, and webbed/redundant loose neck skin, hypoplastic nails, minor extremity malformations, and genitourinary abnormalities [172, 173]. Nipple abnormalities have also been reported [172, 173]. Del(6)(p21.3) has been recently reported with severe speech impairment, seizures and behavioral abnormalities [174]. In addition, white matter abnormalities and periventricular heterotopia have been reported on MRI from patients with del(6)(p25) [175]. The 6p25 deletion syndrome is characterized by Dandy-Walker malformation, congenital heart defects, developmental delay, and dysmorphic facial features. When 6p25 is involved (*FOXC1*) Axenfeld-Rieger syndrome features can be seen, including craniofacial dysmorphism with maxillary hypoplasia, hypodontia, and umbilical anomalies; hearing loss, heart abnormalities, and developmental delay.

Ophthalmic Manifestations

Eye abnormalities are seen in up to 70 % of individuals with 6p23 deletions. Reported findings include microphthalmia, iris coloboma, Peters anomaly/corneal opacification, optic atrophy, bilateral optic disc coloboma, nystagmus, and epicanthal folds [172]. Up- or down-slanting palpebral fissures, mild synophyrs, and hypertelorism have been reported [172, 173]. One child had a hemangioma involving the brow [172]. Blepharophimosis, esotropia, high hyperopia and Brushfield spots have also been reported [172, 173]. One patient with del(6)(p21.3) was reported with strabismus, downslated palpebral fissures and mildly dysplastic papillae [174].

Anterior segment disorders such as Axenfeld-Reiger spectrum and/or iris hypoplasia associated with glaucoma are associated to del(6)(p25) [176, 177]. Other ocular findings include posterior embryotoxon, corectopia/polycoria and irido-corneal adhesions. One patient with del(6)(p24pter) [24] had bilateral posterior embryotoxon and, in one eye, progressive corectopia and ectropion uveae. The patient did not present glaucoma but there was bilateral optic nerve hypoplasia. Electroretinogram was normal. Grey-blue sclera can be associated with del(6)(p24p25). Telecanthus, divergent squint, hyperopia, Peters anomaly and mild pigmentary retinopathy were also reported with del(6)(p25) [178].

Deletion 6q

Definition and Epidemiology

Deletions of the long arm of chromosome 6 are rare and are characterized by clinical heterogeneity according to the deletion breakpoint. Interstitial deletions are rare. Approximately 80 cases have been reported.

Systemic Manifestations

Proximal deletions 6cen-q15 region have been associated with umbilical hernia and developmental delay. These children also show palmar creases, hyperextensible skin, joint laxity, microcephaly, and short stature. Individuals with del(6)(q13q15) present ectopic kidney and short necks, and also can have congenital heart disease [179]. Other less common features include genitourinary anomalies, joint contractures, syndactyly, club foot, micrognathia, and large/low-set ears. One author reported absent pulmonary valve in a patient with del(6)(q15q21). One patient with del(6)(q16.1q21) involving *SIM1* had Prader-Willi Syndrome-like features, including obesity, short stature, hypotonia and hypopituarism [180]. One case with a small interstitial del(6)(q24q26) presented with developmental delay, low birth weight, hypotonia, heart murmurs, respiratory distress, craniofacial malformations and genital anomalies [181]. In del(6)(q25.3qter), mental retardation, seizures, microcephaly and cortical dysplasia have been reported [182].

Ophthalmic Manifestations

One child presented with del(6)(q13q15) and hypotelorism, nystagmus, and blue sclera [179]. Other series of children with proximal deletions, reported down-slanting fissures, epicanthal folds, small palpebral fissures and less commonly strabismus, but none of these features were localized to a particular locus. Other ophthalmological findings reported with terminal deletions are macular abnormalities, epicanthal folds, and strabismus [173]. One individual with del(6)(q13q15) was reported with "ocular albinism" [183]. His initial examination at 7 weeks showed iris transillumination but no transillumination was found by 34 weeks. Posteriorly, he developed nystagmus and exotropia. Fundus examination was hypopigmented, and also had macular hypoplasia. Electroretinogram was reported with normal rod but delayed cone response to 30 Hz flicker testing. One patient with del(6)(q16.1q21) with Prader-Willi syndrome-like features, just had downslanting and small palpebral fissures but no other ophthalmological findings were reported [180].

Deletion of 6q24q26 region is associated with epicanthic folds, downslanting palpebral fissures, hypertelorism, and retinal as well as macular abnormalities. A patient with del(6)(q25qter) presented with a crescent shaped hypopigmented area traversing the macula [184]. Strabismus, nasolacrimal duct obstruction, cataract and microphthalmia were associated to 6q deletion [181, 185–188]. In del(6)(q25.3qter) deletion, strabismus, congenital nystagmus and high myopia have been reported [182]. An individual with del(6)(q26qter) was reported a bilateral small oval area of macular degeneration. The absence of retinal changes in a case of interstitial del(6)(q23q25) suggests that the critical area for retinal degeneration could be 6q26. This is a known locus for both rod-cone and cone-rod dystrophy [187].

Duplication 6p

Definition and Epidemiology

Less than 60 cases of partial duplication of 6p have been reported.

Systemic Manifestations

Partial trisomy of 6p is characterized by failure to thrive, low birth weight, craniosynostosis, feeding problems, recurrent respiratory tract infections, and psychomotor retardation [189]. One 11 year old female patient with interstitial tandem 6p duplication presented with mild dysmorphic features, moderate intellectual disability with behavioral disturbances, immunodeficiency and epilepsy [190].

Ophthalmic Manifestations

One patient with dup(6)(p12p21.3) had long lashes, downslanting palpaberal fissures, blepharophimosis and corneal clouding [191]. The patient with 6p trisomy from interstitial tandem duplication had abnormal palpebral fissures [190]. One female infant with *de novo* partial 6p trisomy (dup(6)(p12.3p21.1)) presented with palpebral fissures abnormalities, long eyelashes, epicanthus, ptosis and blepharophimosis, although there is one case of dup(6)(p12p21.3) that was reported with cataract and corneal clouding [189, 191].

Duplication 6q

Definition and Epidemiology

6q duplication is a rare condition. Dup(6)(q26) could be a critical breakpoint for the 6q phenotype [192]. Most cases result from malsegregation of a reciprocal translocation that leads to a terminal 6q duplication and partial monosomy of another chromosome. Less than 15 cases of *de novo* pure duplication have been reported.

Systemic Manifestations

The dup(6)(q) syndrome is characterized by developmental delay, feeding difficulties, microcephaly, prominent forehead, midfacial hypoplasia, micrognathia with carp-shaped mouth, short webbed neck, and club foot. Abnormal palmar creases is less commonly seen. One individual with dup(6)

(q23.3q25.3) was reported with microcephaly, delayed Fontanelle closure, dolicocephaly, congenital cardiac malformations, flexion contractures, abnormal palmar creases, midfacial hypoplasia, and a carp-shaped mouth [192]. Arthrogryposis has been described in a patient with *de novo* dup(6)(q24.2q25.3).

Ophthalmic Manifestations

Oculofacial features of del(6)(q) syndrome include down-slanting palpebral fissures and epicanthal folds. The patient reported with proximal dup(6)(q23.3q25.3) had infraorbital creases, hypertelorism, epicanthal folds, and almond shaped palpebral fissures without down-slanting [192]. This patient also had blue tinted sclera. Brushfield-like spots have been also reported with dup(6)(q21q23.3) [193]. One patient with *de novo* dup(6)(q26q27) presented with up-slanting palpebral fissures and congenital glaucoma [194].

Ring 6

Definition and Epidemiology

Ring chromosome 6 is a rare aberration that generally occurs *de novo*. The associated phenotype is variable, ranging from an almost normal phenotype to severe malformations and mental retardation. The severity seems to be related to the size of the deletion. About 25 cases have been reported.

Systemic Manifestations

Ring 6 manifestations include flat nasal bridge, well formed ears, short neck, microcephaly, micrognathia, bilateral simian crease, seizures, and mental and growth retardation [195].

Ophthalmic Manifestations

Eye findings associated with Ring 6 apparently are related to concomitant deletion of 6p, specially 6p25 region. Reported malformations include anterior segment defects (aniridia, coloboma, ectropion uveae), glaucoma, optic atrophy, and retinal abnormalities [173]. Hypertelorism and epicanthal folds were also reported [195].

Pericentric inversion of Chromosome 6

Definition and Epidemiology

Pericentric inversion of chromosome 6 is a rare condition with few reports in the literature.

Systemic Manifestations

This condition was reported in different generations of a family with several phenotypic findings including hearing loss, dental anomalies, ear anomalies, and mild mental retardation [172].

Ophthalmic Manifestations

Strabismus, coloboma and congenital cataract were reported [172]. Rieger's syndrome has also been described.

Chromosome 7

Deletion 7p

Definition and Epidemiology

7p deletion is a rare condition, with less than 50 cases reported.

Systemic Manifestations

Psychomotor retardation, craniosynostosis, skull abnormalities, broad flat nasal bridge, digital anomalies, cardiac defects, urogenital anomalies and immunodeficiency have been reported in patients with del(7)(p15p22) [196].

Ophthalmic Manifestations

Ptosis and microphthalmia have been associated with del(7)(p15p22) [196]. Hypertelorism was reported in the context of craniosynostosis in a patient with del(7)(p21.1) [197].

Deletion 7q

Definition and Epidemiology

The most frequent deletions of 7q can be classified into 7q11q21, 7q21q32, 7q32q34 and 7q32qter.

Systemic Manifestations

Terminal and interstitial deletions of the long arm of chromosome 7 have been associated with developmental delay, growth retardation, hypotonia, seizures, microcephaly, prominent forehead, nasal dysmorphism, micrognathia, chest anomalies, abnormal hand creases and male genital malformation [198].

Williams-Beuren syndrome is a continuous gene deletion syndrome caused by a del(7)(q11q23). It is characterized by a characteristic facies, supravalvular aortic stenosis, connective tissue abnormalities, clinodactyly, mental retardation and precocious puberty. Patients with Williams-Beuren syndrome and del(7)(q11.23) show disorganized pre-elastic and mature elastic fibers. Skin biopsies may be used to find extracellular matrix anomalies. When associated with infantile spasms, it has been attributed to *MAGI2* gene hemizygosity. One patient with del(7)(q11.21q11-23) and without disruption of *MAGI2* has been reported with infantile spasm [199].

A recent report of del(7)(q36.2q36.3) included short stature, craniofacial dysmorphism in the absence of intellectual disability [200]. Low birth weight, cleft lip and palate, cryptorchidism and complex heart disease have been reported in

del(7)(q34qter) [201]. Patients with terminal deletion of 7q have presented with anencephaly and holoprosencephaly due to hemizygosity for the *SHH* gene at 7q3A r [202].

It has been estimated that approximately 20 % of 7q deletion have either cleft lip and/or palate or congenital heart defect [201].

Ophthalmic Manifestations

Ophthalmologic features in patients with Williams-Beuren síndrome include strabismus (50 %), a typical stellate iris pattern of the anterior stroma, retinal vascular tortuosity (20 %) and hyperopia. One patient with del(7)(q11.21q11.23) has been reported with oculofacial findings, including periorbital fullness and downslanting palpebral fissures [199]. Hypertelorism and epicanthus have also been described in proximal 7q deletion [203]. A patient with del(7)(q22.1q32.2) deletion was reported with optic nerve coloboma [204]. Hypertelorism has been reported in del(7)(q34qter) [201]. A recent report of del(7)(q36.2q36.3) deletion included pale optic disc, coloboma, chorioretinal lesions and retinal pigmentary epithelium changes [200].

A patient with del(7)(q36) presented with nystagmus in the context of holoprosencephaly; *SHH*, *HOX1* and *HTR5A* were deleted [205]. Other reports of 7q deletion includes enophthalmos, exophthalmos, strabismus, optic nerve atrophy and glaucoma [198].

One 13 year old boy with 7q terminal deletion syndrome showed holoprosencephaly with microcephaly, facial dysmorphism, severe intellectual disability, behavior problems, seizures, short stature, penoscrotal transposition, and ulnar ray deficiency. These findings were attributed to dosage expression of the *SHH* gene, although the region includes more than 40 genes [206].

Duplication 7p

Definition and Epidemiology

Isolated duplication 7p is a rare condition, with few cases reported in the literature.

Systemic Manifestations

Dup(7)(p13p22.1) has been described with hypotonia [207]. Dup(7)(p22.1) was associated with macrocephaly, low-set ears and speech delay. The *ACTB* gene is a strong candidate gene for the alteration of craniofacial development [208, 209].

Ophthalmic Manifestations

Patients with dup(7)(p22.1) can present with ocular hypertelorism. Ptosis has been also reported with dup7(p21.1p14.2) [210].

Duplication 7q

Definition and Epidemiology

Few reports describe the ophthalmological findings in 7q duplication.

Systemic Manifestations

Developmental delay, altered dermatoglyphics, low set ears, micrognathia, high arched palate, joint hyper flexibility, and small penis have been reported [211]. Dup(7)(q11.23), involving the Williams-Beuren syndrome deletion region, is an emerging phenotype characterized by dysmorphic facies, hypotonia, developmental delay with variable speech delay and autistic features. One series of eight pediatric patients and one adult all had aortic dilation, being the opposite vascular phenotype of the typical aortic stenosis found in Williams-Beuren syndrome [212].

Ophthalmic Manifestations

Hypertelorism, epicanthus, strabismus, palpebral fissure abnormalities, retinal pigment epithelium alteration, optic nerve anomalies, myopia, anophthalmos, abnormal extraocular muscles, iris coloboma, long eyelashes, microcornea and limbal dermoid have been described in 7q duplication [211, 213–223].

Ring 7

Definition and Epidemiology

Less than 29 cases have been reported in the literature.

Systemic Manifestations

Most common manifestations are growth retardation, microcephaly and dermatological abnormalities. Holoprosencephaly has been reported [224].

Ophthalmic Manifestations

Hypertelorism, epicanthal folds and palpebral fissures abnormalities are the most frequent findings, although proptosis, ptosis, microcornea, cataracts and strabismus have been reported [224, 225].

Chromosome 8

Deletion 8p

Definition and Epidemiology

Most of 8p deletions include 8p23.1 region [226]. Less than 50 cases have been described in the literature.

Systemic Manifestations

Most of individuals with a deletion of the short arm of chromosome 8 are characterized by significant developmental delay, low birth weight, and short stature [226, 227]. The degree of mental retardation may be associated to deletion size [226]. Less frequently, severe behavioral problems may be seen [226]. The most frequent systemic abnormality is congenital heart disease, particularly atrioventricular canal defects [226, 227], although there are patients without heart defects [228]. Dolichocephaly and microcephaly associated to a high forehead may be present [226, 227]. In patients with del(8)(p22) or del(8)(p21) microcephaly is more common [226]. Other common facial features are low-set and/or malformed ears, micrognathia, arched palate, flat nasal bridge, short neck, and short nose [226] Microstomia is seen in less than half of cases [226]. Individuals can also present with abnormal genitalia, cryptorchidism, puffy hands and feet and a broad chest with widely set nipples [226, 227]. Gastrointestinal malrotation has also been observed in patients with terminal 8p deletion [226]. If the deletion extends centromeric to 8p23.1, comprising 8p21 region, other findings may be seen, including trigoncephaly, dysplastic ears, short neck, hypotonia, elbow dimples and narrow thorax [226].

Ophthalmic Manifestations

Ophthalmic findings are relatively frequent in patients with deletion 8p [227–229] A common oculofacial abnormality is epicanthal folds, present in up to 90 % of patients [227]. Hypertelorism is less frequent [227]. One male patient with del(8)(p11.2p21) was reported with "visual impairment", nystagmus, pale optic discs, moderate macular atrophy and a patchy retinal pigment epithelium disturbance. Visual evoked potential was significantly reduced but full field electroretinogram was normal [230]. Strabismus and nystagmus has been described with del(8)(p11.1p21.1) [231] and also microcornea, iris and choroid coloboma, and bilateral retinal dysplasia in a boy with del(8)(p11.2p21.1) [232]. One patient with del(8)(p21.1p23.1) had long, thin sparse eyebrows and deep set eyes. Other authors reported hypertrichosis and synophyrs in a child with del(8)(p23.1pter) [226]. One patient with terminal deletion of 8p was reported to have aniridia and nystagmus, but no further description is provided [228].

Deletion 8q

Definition and Epidemiology

Few cases have been reported in the literature. An important breakpoint is 8q22.

Systemic Manifestations

Del(8)(q22.1) has been associated with Nablus Mask-Like Facial syndrome: tight and glistening facial skin, abnormal ear architecture, upswept frontal hairline and sometimes microcephaly, cryptorchidism, cleft palate and neurological spectrum findings [233]. It has been suggested that del(8)(q22) is not sufficient by itself to cause the Nablus Mask-Like Facial phenotype [234].

Five patients with interstitial del(8)(q22.2q22.3) had intellectual disability, seizures, and dysmorphic features [235]. One patient had a *de novo* deletion in 8q22.3, presenting with seizures, intellectual disability and autistic behavior. In addition, she had mild dysmorphic features, including telecanthus and thick vermilion border of the lips. Array comparative genomic hybridization detected a 1.36 Mb deletion in 8q22.3, including *RRM2B* and *NCALD* [236].

Types I and II of the autosomal dominant tricho-rhino-phalangeal syndrome (TRPS) have been associated to del(8)(q24.1) [227]. Type 1 is characterized by early baldness, large nose, and cone-shaped epiphyses of the middle phalanges whereas Type II (Langer-Giedion syndrome) also have mental retardation, microcephaly, and multiple exostoses. A deletion, disruption or point mutation of *TRPS1* causes TRPS Type I, while simultaneous deletion of *EXT1* cause Type II. The latter therefore represents a contiguous gene syndrome.

Ophthalmic Manifestations

One author reported hypertelorism, deep set eyes with upslanting palpebral fissures associated to del(8)(q21) [237]. One individual with TRPS phenotype and del(8)(q24.1) had bushy eyebrows without synorphyrys [227]. Nablus Mask-Like Facial syndrome associated with del(8)(q22.1) has been reported with blepharophimosis, hypertelorism and sparse eyebrows.

Duplication 8p

Definition and Epidemiology

Duplication of the short arm of chromosome 8 can present as a complete trisomy or mosaicism (Warkany syndrome), or tetrasomy. Phenotype usually does not have a good correlation with degree of mosaicism. 8p23.1 duplication syndrome has an estimated population prevalence of 1 in 58,000.

Systemic Manifestations

Trisomy 8p is characterized by short wide neck, as well as deep hand and foot creases [238]. One individual with an inverted terminal dup(8)(p21.2p23.2) had triangular facies, growth and developmental delay, large ears, and a café au lait spot [239]. Supernumary isochromosome 8p present with agenesis of the corpus callosum, developmental delay, rib anomalies, congenital heart disease, high/cleft palate, enlarged cerebral ventricles with or without gyral anomalies and vertebral anomalies with or without scoliosis [238, 240–243]. Development delay has been reported, although motor delays due to hypotonia seem to be more frequent [240–244].

The most frequent cause of death during the neonatal period is heart disease [238].

Although dysmorphism may be absent [243], the appearance may be characterized by a high forehead/frontal bossing, sparse temporal hair, and mild ear abnormalities [240–242]. A shy behavioural phenotype with obesity has been described [244]. As seen in trisomy 8, abnormal nails [240], clinodactyly [242], or gastrointestinal problems such as duodenitis, hamartomata (intestinal, liver, adrenal), and malrotation may rarely occur [241]. Nevus flammeus may be seen [241]. Although rare, children with virtually none of the clinically detectable malformations above have also been reported [244]. One female patient with dup(8)(q23q24) presented with dysmorphic features, retrognathia, hirsutism and developmental delay [245]. Mild or moderate developmental delay, mild dysmorphism and congenital heart disease are frequent in dup(8)(p23.1) [246] Other reported findings are behavioral problems, cleft lip and/or palate, macrocephaly, seizures, attention deficit hyperactivity disorder, balance problems, hypotonia, and hidrocele [246].

Ophthalmic Manifestations

Glaucoma, epicanthal folds [240, 242] and pseudoesotropia [240] has been reported. The eyebrows and eyelashes may be sparse [241]. Dup(8)(p21.2p23.2) has been associated with hypertelorism [239].

Duplication 8q

Definition and Epidemiology

Duplication 8q is a rare condition with few cases reported in the literature.

Systemic Manifestations

Dup(8)(q22q24) present mental retardation, short stature, broad short neck, cardiac malformations, cryptorchidism, hemangiomas, kyphoscoliosis, EEG abnormalities and muscular hypotonia [247].

Ophthalmic Manifestations

Dup(8)(q22q24) has been associated to hypertelorism, epicanthal folds, strabismus and lid hemangioma [247]. One patient with dup(8)(q23q24) presented with hypertelorism, hypoplastic eyebrows and significant hyperopic astigmatism [245].

Trisomy 8

Definition and Epidemiology

Warkany syndrome is usually mosaic or the result of a translocation. The average peripheral blood and fibroblast mosaicism is nearly 60 % and 70 %, respectively [248]. Degree of mosaicism and severity are not correlated. It seems that dup8q2 is the critical region for the trisomy 8 phenotype [248].

More than 100 cases have been reported in literature. Complete trisomy 8 is usually an early lethal condition. Of spontaneous abortions, 0.7 % are caused by trisomy 8 [249]. It has an estimated frequency of approximately 1:25,000–50,000 births.

Systemic Manifestations

Trisomy 8 is characterized by variable mental retardation, prominent anteverted nasal tip, prominent lower jaw (Fig. 6.5a), absent or dysplastic patella, joint contractures, vertebral defects, urinary abnormalities, a distinctive toe

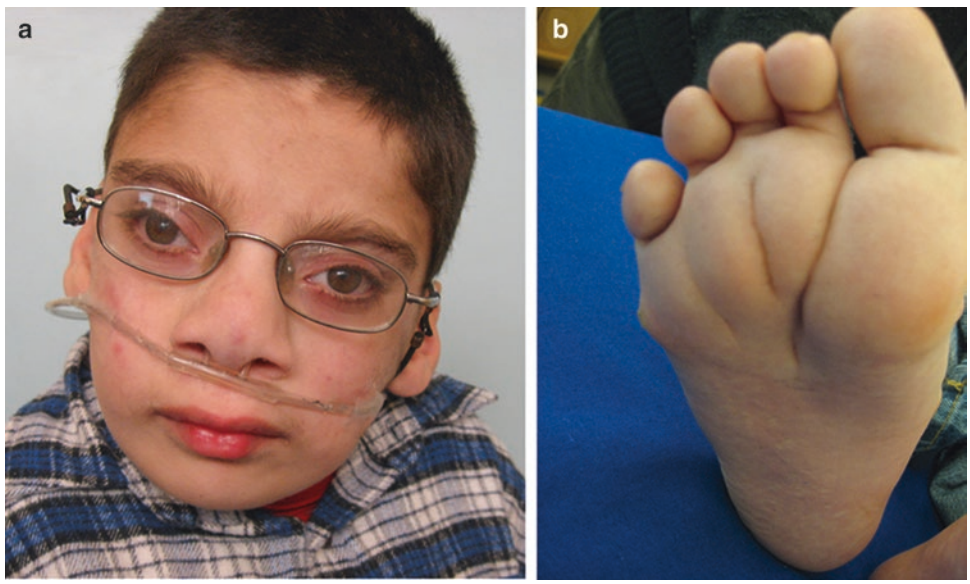

Fig. 6.5 (**a**) Patient with Trisomy 8 mosaic with mental retardation and dysmorphic facies characterized by prominent anteverted broad nasal tip, dysplastic ears and prominent lower jaw. Note patient also has hyperopia, exotropia, and telecanthus. (**b**) Deep creasesof the sole, and flexed digits 2 and 3 having equal length and turned towards midline of foot (courtesy of Mariana Aracena MD)

posture (flexed and turned towards midline of foot with digits 2 and 3 having equal length) (Fig. 6.5b), and deep furrows in the palms and soles [248]. Other typical features include cleft or high palate, sacral dimple/spina bifida occulta, congenital heart disease, clinodactyly/long fingers, slender pelvis, abnormal ears, hip dysplasia, everted lower lip, sternum abnormalities, or abnormal nails [248]. Seizures and gastrointestinal anomalies such as anus abnormalities are less frequent [248]. Birth weight is usually normal [248]. Patients with trisomy 8 can present temper tantrums. Hemihyperplasia and a discordant bone age of both hands have also been reported [249]. Trisomy 8 mosaicism is frequently found in patients with acute promyelocytic leukemia [250, 251].

Ophthalmic Manifestations

Trisomy 8 is usually associated with abnormal slanting [248]. Strabismus is frequent, with esotropia being most common [248]. Duane syndrome has also been described [252], perhaps due to duplication of the DURS1 locus at 8q12-13. One author reported bilateral asymmetrical corneal opacities consistent with choristoma [253]. Other findings include cataract, corneal clouding, nasolacrimal duct obstruction, microcornea, iris heterochromia, ptosis, microphthalmia and macular hypoplasia. There is a report of Axenfeld-Reiger spectrum but with no glaucoma [254]. One patient with congenital pendular nystagmus and macular hypoplasia was reported. Electrodiagnostic tests confirmed cone function [252]. A pre term patient (8 months gestation) had congenital cataract and retinopathy of prematurity. He later developed acute angle closure glaucoma in one eye, and chronic uveitis, band keratopathy, posterior embryotoxon and small optic disc in the other eye [248].

Chromosome 8 Inversion

One female patient with inv(8)(q21.3q24.13) who had Moebius syndrome was reported [255].

Ring 8

Craniofacial anomalies, growth and mental retardation, epicanthal folds, deep set eyes and hypertelorism have also been observed in ring chromosome 8 [256, 257].

Chromosome 9

Deletion 9p

Definition and Epidemiology

Deletion 9p syndrome is a rare structural chromosomal disorder. Estimated frequency is 1 in 50,000 births. Deletion of the distal portion of chromosome 9p is associated to a characteristic phenotype. Frequent breakpoints are at 9p21 or 9p22 and arise *de novo*. Patients derived from a parental balanced translocation carrier more commonly involve 9p24 region [258].

Systemic Manifestations

Clinical features include severe mental retardation, craniosynostosis/trigononcephaly, midfacial hypoplasia, posterior rotated poorly formed ears, foot positioning defects, long middle phalanges, cardiac abnormalities, inguinal and umbilical hernia, scoliosis, cryptorchidism, and choanal atresia [257, 259].

Ophthalmic Manifestations

One patient with congenital glaucoma was reported having del(9)(p23pter) associated with dup(1)(q41qter) [46]. One author reported a case of congenital glaucoma associated with del(9)(p22.3) [257]. These reports may suggest a gene implicated in this condition. Other ophthalmic findings include epicanthal folds and up-slanting palpebral fissures [259, 260]. Exorbitism and esotropia have also been described [260].

Deletion 9q

Definition and Epidemiology

The chromosome 9q subtelomeric deletion syndrome is the most common clinically recognizable phenotype [261]. Most patients have deletions of the 9q34.3 that range from <400 kb to >3 Mb [262]. More than 50 cases have been reported.

Systemic Manifestations

Clinical characteristics of del(9)(q22q32) include hirsutism, brachycephaly, dysmorphic ears, urogenital abnormalities, finger and toe anomalies, cardiac abnormalities, psychomotor retardation, seizures, dilation of cerebral ventricles and cerebral atrophy [263]. Reported phenotypic features of 9q subtelomeric deletion syndrome are mental retardation hypotonia, autism, sleep disturbances, epilepsy, urogenital abnormalities, obesity, microcephaly, brachcephaly, flat facies, mid facial hypoplasia cardiac defects, abnormalities of hands and feet, deafness, abnormalities of the teeth, and anal atresia [262, 264]. A newborn with del(9)(q34.1) from a paracentric inversin had malformed ears, micrognathia, bilateral webbing of the neck, widely spaced nipples, and complex heart anomalies [265]. Mental retardation, dental hypoplasia and deafness have been described as well [266]. In a 16 year old female patient with del(9)(q34.11q34.13), demonstrated severe intellectual disability, congenital hydrocephalus, cleft lip and palate, talipes equinovarus, epilepsy, kyphoscoliosis, severe short stature and facial dysmorphism were reported [267].

Ophthalmic Manifestations

Patients with interstitial del(9)(q22q32) have been associated to supraorbital ridge hypoplasia, synorphrys, hypertelorism, telecanthus, hypotelorism, downward slanting, narrow palpebral fissures, epicanthal folds, ptosis, strabismus, and sclerocornea [263]. Deep set eyes, hypertelorism, synophrys, arched eyebrows/straight eyebrows, long lashes, down or upslanted palpabral fissures, and hypertropia have been reported with del(9)(q34.3) [262]. Blepharophimosis and ptosis has also been reported [266]. In a female patient with del(9)(q34.11q34.13) with several systemic findings, strabismus was reported [267]. A patient with del(9)(q34.1) presented hypertelorism [265].

Duplication 9p

Definition and Epidemiology

It has been suggested that 9p22 could be a critical region for the duplication 9p syndrome [268]. More than 150 cases have been reported in the literature.

Systemic Manifestations

One patient had *de novo* dup(9)(p22p24) with mental retardation, small stature, microcephaly/brachycephaly, globular nose, down turned mouth, low set ears, single palmar crease, hypoplasia of some phalanges, nail dysplasia or hypoplasia [268]. Vocal cord paralysis has also been associated with dup(9)(q34) [269].

Ophthalmic Manifestations

An individual with a *de novo* dup(9)(p22p24) presented with down-slanting palpebral fissures, deep set eyes and hypertelorism [268].

Duplication 9q

Definition and Epidemiology

Duplication 9q has been infrequently described. Significant breakpoints include 34.1-34.3 segment [270]. One individual with dup(9)(q34) was reported with 18 year follow up [271].

Systemic Manifestations

Duplication of proximal 9q has been associated with microcephaly and developmental delay, whereas dup(9)(q34) has been reported with vertebral abnormalities and large low-set ears [272]. Variable findings have been observed in patients who present dup(9)(q32): deep-set eyes, beaked nose, micrognathia, long fingers, and stiff joints. Mental retardation, dolicocephaly, microstomia, retrognathia, arachnodactyly, and camptodactyly are clinical manifestations of dup(9)(q34.1q34.3) [270].

Ophthalmic Manifestations

Esotropia, epicanthal folds, narrow palpebral fissures, synophrys, and deep-set eyes are variably present. One patient with dup(9)(q12q33), had all these findings [272]. Microphthalmia, deep set eyes, small and narrow horizontal palpebral fissures and hypotelorism were described in a female patient with dup(9)(q33.3q34.1) [271].

Trisomy 9

Definition and Epidemiology

Trisomy 9 is rare in live born children. In fact, it may be that many live born children actually have cryptic mosaicism with non mosaic cases succumbing prenatally [273]. This severe chromosomal aberration is not consistent with survival beyond the neonatal period. Over 50 cases have been reported in the literature.

Systemic Manifestations

Live born infants with trisomy 9 may present with intrauterine growth retardation, skeletal abnormalities, congenital heart disease, congenital kidney disease and genitourinary malformations [273]. Other reported minor abnormalities include rocker bottom feet, joint contractures, overlapping fingers, and hypoplastic nails. Described craniofacial malformation include low set ears with possible absent external canals, cleft/arched palate, migrognathia, bulbous nose, wide fontanelles, and small mouth [273]. Less frequently, abnormalities of the palmar crease, low hairline, anomalies of the gall bladder or diaphragmatic hernia, and microcephaly have been described [273].

Ophthalmic Manifestations

Microphthalmia is the most common ocular manifestation of trisomy 9 (61%) [273–275]. Bilateral microphthalmia, cataracts, corneal clouding, deep-set eyes and a depressed right globe were described in one live born infant with trisomy 9 [273]. Although not described further, the latter may be related to the facial asymmetry seen in approximately one third of affected babies. Microphthalmia is less frequently seen in patients with mosaic versus non mosaic trisomy 9 [274, 276]. One case reported on the ocular pathology in a patient with mosaic trisomy 9 had sclerocornea, no recognizable anterior chamber, colobomatous ciliary body on one side, and detached and dysplastic retina and atrophy of optic nerve [277].

Ring Chromosome 9

Definition and Epidemiology

This is a rare condition with less than 30 patients ever reported in the literature. Most break points are found in 9p24-p22 and 9q33-q34. Estimated frequency is 1 in 50,000.

Systemic Manifestations

Ring chromosome 9 has been associated with growth defects, failure to thrive, patchy skin pigment changes, developmental delay, facial dysmorphism, microcephaly, genital abnormalities, cardiac malformations and limb and skeletal anomalies.

Ophthalmic Manifestations

Reported ophthalmic findings include upslanting and small palpebral fissures, epicanthal folds and hypertelorism [278].

Chromosome 9 Inversion

Definition and Epidemiology

Systemic Manifestations

There is a report in a 3 month old female with esotropia, nystagmus and optic nerve hypoplasia, associated with inv(9)(p12q13) and facial dysmorphism, including frontal bossing, cupped ears and prominent deep set eyes [279] MRI confirmed an arachnoid cyst in a perimesencephalic cistern with no other brain abnormalities [279]. This inversion can be found in more than 1 % of general population, making this finding most likely a coincidence rather than an effect of the chromosomal abnormality.

Ophthalmic Manifestations

The patient with inv(9)(p12q13) had an MRI that showed optic nerve hypoplasia [279].

Chromosome 10

Deletion 10p

Definition and Epidemiology

10p deletion is a rare chromosomal condition. The deletion results in a variable phenotype depending on the size of the deletion. A frequent breakpoint is 10p13, although the deletion may include only the terminal 10p15 band, or extend towards the centromere to 10p14. Less than 50 cases have been reported.

Systemic Manifestations

Interstitial del(10)(p13) present a facies similar to DiGeorge sequence (more typically associated with del22q11). Other malformations include posterior cleft palate, tracheomalacia, ventricular septal defect, and a small thymus [280]. Finger contractures can also be present. Hypoparathyroidism, sensorineural deafness, and renal dysplasia have also been associated with del(10)(p13) [281]. One case of a *de novo* del(10)(p11.21p12.1) microdeletion had copper beaten skull (gyral impressions on the inner table of the skull) and pseudoarthrosis of the clavicle [282].

Interstitial del(10)(p11.23p12.1) is associated with developmental delay, mild craniofacial abnormalities, and cryptorchidism [283]. This region involves three genes: *MKX*, *ARMC4*, and *MPP7*. Previous reports suggest that haploinsufficiency of the *MKX* gene may affect the developmental process during testis migration or serve as a genetic susceptibility locus for cryptorchidism.

Ophthalmic Manifestations

Del(10)(p13) has been associated with down-slanting short narrow palpebral fissures, deep set eyes, epicanthal folds and hypertelorism [281, 284]. Del(10)(p11.21p12.1) has been associated with myopia with astigmatism, optic nerve hypoplasia, abnormal eletroretinogram and delayed visual evoked potential responses [282].

Deletion 10q

Definition and Epidemiology

Deletion (10)(q23.2q24.1), involving the *PTEN* gene, can cause a spectrum of phenotypes including PTEN Hamartoma Tumor syndrome, Bannayan-Riley-Ruvalcaba síndrome and Cowden disease. Mutations of this gene are known to cause manifestations including macrocephaly, intellectual disability, mucocutaneous abnormalities, and hamartomatous neoplasms [285].

Systemic Manifestations

Deletion (10)(q23.2q24.1) associated features may include midfacial hypoplasia, prominent forehead, developmental delay and hypotonia. Dermatologic lesions particularly characteristic of Cowden disease include facial tricholemmas in the majority of cases, as well as acral keratosis and papillomas. Skin lesions usually do not occur until adulthood [285].

Patients with del(10)(q26pter) show microcephaly, brachycephaly, broad nasal bridge, malformed ears, webbed neck, micrognathia, congenital heart defects, urinary tract anomalies, hypertonia, respiratory distress, growth retardation and mental delay [286].

A novel interstitial del(10)(q24.3q25.1) is associated with lobar holoprosencephaly, cleft lip and palate, and hypoplastic kidneys [287].

Ophthalmic Manifestations

Hypertelorism and strabismus with del(10)(q11.1q21.1) have been reported [288]. Hypertelorism may be associated with midfacial hypoplasia in del(10)(q23.2q24.1) [285]. Pseudopapilledema is a typical finding of del(10)(q23.2q24.1). Anisometropia has also been associated to this deletion [285]. Patients with del(10)(qter) present hypertelorism, down-slanting palpebral fissure and strabismus [286].

Duplication 10p

Definition and Epidemiology

The majority of duplication 10p cases result from translocation . There are few reports of isolated pure trisomy [289]. A common proximal is 10p11 [289]. Approximately 60 cases have been described in the literature.

Systemic Manifestations

Duplication 10p has a variable clinical spectrum. Hypotonia, high-arched/cleft palate, frontal bossing, clubfoot, and nasal anomalies have been oftenly reported. Dolichocephaly, delayed suture closure, and mouth abnormalities are seen in less than half of cases [289]. Cardiac malformations and cystic dysplasia of the kidney are seen less frequently [289]. Agenesis of the gallbladder can also be present [289]. From all these findings, hypotonia has been associated with isolated trisomy of the largest trisomic segment (10)(p11pter) [289]. High arched/cleft palate and clubfoot are frequently present in pure trisomy.

Common findings in full trisomy 10p include developmental delay, dolicocephaly, low birth weight, ear abnormalities, micrognathia, cleft palate, club foot and renal and cardiac malformations [290]. One case with facio-auriculo–vertebral syndrome and dup(10)(p14p15) had complete absence of external ear, hemifacial microsomia and high arched palate [290].

Ophthalmic Manifestations

Approximately 20 % of trisomy 10p individuals have ocular abnormalities. A common finding is colobomatous microphthalmia [289]. Oculofacial findings, such as epicanthal folds and/or down-slanting palpebral fissures have been reported in about one third [289]. Hypertelorism has been seen in a patients with trisomy 10p [291, 292].

Duplication 10q

Definition and Epidemiology

Proximal 10q duplication is a well-defined, but rare syndrome and is often derived from a balanced translocation in a parent. Frequent breakpoints include 10q11q22 or 10q21q22 regions [293]. Less than 50 cases of duplication 10q have been reported in the literature.

Systemic Manifestations

The partial proximal trisomy 10q consists of mild to moderate developmental delay, growth retardation, microcephaly, prominent forehead, upturned nose, bow-shaped mouth, micrognathia, thick and flat helices of the ears and long, slender limbs. Other findings of dup(10)(q11q22) are anteverted nares, ear pits and/or hearing loss [293]. Duplication size has not been associated to any particular phenotype. A patient with an inverted terminal dup(10)(q25.1qter) had a flat occiput, flat face, small nose and mouth, congenital hip dislocation, abnormal thumbs, developmental delay, microcephaly, and hypotonia [239].

Ophthalmic Manifestations

Dup(10)(q11q22) has been associated to small deep set eyes [293]. Epicanthal folds have been reported in dup(10)(q11.2q22.3) [293], although proximal duplications to q11.2 region has been associated to strabismus. One patient with dup(10)(q11.2q22.3) had downslanting palpebral fissures [293]. Iris coloboma and retinal dysplasia are infrequent findings [293]. Blepharophimosis has also been reported in patients with dup(10)(q21q22) [293]. Dup(10)(q25.1qter) is associated with upslanting palpebral fissures and epicanthal folds [239].

Ring Chromosome 10

Definition and Epidemiology

Ring chromosome 10 is a rare condition, with few cases reported. Breakpoints at p13-15 and q26 have been reported.

Systemic Manifestations

One newborn with ring 10 presented with aganglionic megacolon, renal hypoplasia, stubby nose, long philtrum, micrognathia, ear abnormalities, short neck, pectus excavatum, severe hypotonia, seizures, hypocalcaemia and progressive renal failure [294].

Ophthalmic Manifestations

The patient had down-slanting palpebral fissures, hypertelorism and microphthalmia (no further description is provided) [294].

Chromosome 11

Deletion 11p

Definition and Epidemiology

Wilms tumor, Aniridia, Genitourinary anomalies, and Retardation characterize WAGR syndrome. It is a contiguous gene deletion syndrome at 11p13 region involving *PAX6* and extending distally into the Wilms tumor gene, *WT1*. Patients with deletion of *PAX6* and *WT1* have a 50 % risk of developing Wilms tumor. The reported prevalence of WAGR syndrome ranges from 1 in 500,000–1,000,000.

Systemic Manifestations

Hypotonia, trigonocephaly, hearing deficits, midline brain anomalies, and minor abnormalities of the fingers have been reported. Patients with del(11)(p) had genitourinary abnormalities, mental retardation, Wilm's tumor, short neck,

dysmorphic facies, ear abnormalities, cranial asymmetry, scoliosis, inguinal hernia, and clinodactyly [295]. Other systemic features are mental retardation, facial asymmetry, asymmetric calcification of coronal sutures, skeletal anomalies, heart defects and anal stenosis [293]. A 1.6 Mb critical region has been described in del(11)(p13) for severe developmental delay and autistic features characteristic of WAGR syndrome [296]. If the deletion does not involve *WT1* then there is no risk of Wilm's tumor.

Potocki-Shaffer syndrome is a contiguous gene deletion syndrome caused by hemizygous del(11)(p11.2p12) and includes multiple exostoses, hypotonia, developmental delay, intellectual disability, micropenis and dysmorphic features. A patient with a 137 kb deletion in the Potocki-Shaffer syndrome interval on 11p11.2 presented with developmental delay and hypotonia, providing a possible critical region for those features [297].

Ophthalmic Manifestations

The most recognized ocular manifestation of del(11)(p13.3) is aniridia which is caused by involvement of the *PAX6* gene. Aniridia is a panocular disorder that may present with a any combination of cataracts, macular hypoplasia, glaucoma, keratopathy and nystagmus. Dry eyes and ptosis have also been observed [298]. Isolated ocular disorders associated with *PAX6* mutations, such as autosomal dominant keratitis, macular hypoplasia, cataract and Peters anomaly, would not be expected in del(11)(p13.3) as they occur due to point mutations. One group reported aniridia, cataract, nystagmus and gonadoblastoma but no Wilm's tumor in a patient with del(11)(p12p13) [299]. Severe myopia, strabismus and nystagmus have been associated to 11p deletion syndrome [300]. Del(11)(p15.1p13) has been seen with aniridia, ptosis, cataract, glaucoma, nystagmus and pale optic nerve [295]. A patient with a del(11)(p11.2) was noted to have epicanthal folds [297].

Deletion 11q

Definition and Epidemiology

The eponym Jacobsen syndrome is often used for all cases of terminal 11q deletion with a breakpoint including or distal to 11q23. It has been suggested that deletion of 11q24.1 is critical for the full phenotype [301–304]. Although the original report described the deletion in the setting of a familial 11;21 translocation, over 85 % of terminal deletions occur *de novo* [305], and 15 % cases arise as a result of parental translocations. Jacobsen síndrome has a female predominance of 2:1. Usually, the deletion size varies from 7 to 20 Mb in size but could be as small as 2.9 Mb in some patients. The significance of a breakpoint at 11q23.3 (nearly 80 %) has been attributed to a fragile site (*FRA11B*) at this locus [306, 307]. It has been suggested that cases presumed to be terminal deletions may have some preservation of telomeric sequences [306, 308]. A frequent translocation also involves a breakpoint at 11q23.3 and 22q11.2 [309]. The incidence of Jacobsen syndrome has been estimated at less than 1 in 100,000 [308]. Fewer than 40 cases of interstitial deletions of 11q have been described. The phenotype tends to be less severe than terminal deletions [310, 311].

Systemic Manifestations

Patients with Jacobsen syndrome present with distinctive clinical findings. Terminal deletions from 11q23 frequently present with developmental delay, trigonocephaly, a flat bulbous nose, depressed nasal bridge, ear abnormalities, micrognathia with or without abnormal palate, carp-shaped mouth (Fig. 6.6), pre- and postnatal growth retardation, cardiac abnormalities, and minor distal limb anomalies or joint contractures [302, 303, 307, 308, 310, 312–319]. Transient thrombocytopenia or pancytopenia can also be seen in less than 40 % of cases. The *KIRREL3* gene has been proposed as a candidate gene for neurocognitive delay and autism spectrum disorder in the setting of a small deletion of 11q [320]. This is based in a child with clinical manifestations consistent with Jacobsen syndrome who had a 2.899 Mb del(11)(q24.2q24.3). Pseudoachondroplasia was observed in a patient with del(11)(q21q22.2) [312]. Other findings are less commonly seen in patients with Jacobsen syndrome. One case of mosaic del(11)(q21) presented with characteristic findings but also with holoprosencephaly, cyclopia and arhinencephaly [321].

About 25 % of patients with Jacobsen syndrome die before 2 years of age [308].

Fig. 6.6 Girl with Jacobsen syndrome and del(11)(q23.3), having developmental delay, a flat bulbous nose, depressed nasal bridge, and telecanthus (courtesy of Mariana Aracena MD)

It has been suggested that recurrent respiratory infections could be related to the hematologic abnormalities that are seen in these patients [305, 317, 322] This can be a significant cause of mortality. Other important morbidity associated to death is cardiac abnormalities.

There was an attempt to define the critical regions in patients with terminal deletions including or distal to 11q23, but the findings were not absolute as the particular regions did not have the expected clinical manifestation [308]. Deletion size was correlated with the severity of dysmorphism and developmental delay. Other uncommon findings, such as minor structural brain defects and genitourinary abnormalities are correlated with more proximal deletions [305, 307, 308, 315]. Deafness has been reported in del(11)(q22qter) [322].

Interstitial deletions phenotype is variable. One patient with del(11)(q14q22) [323] had transient hypocalcemia, hypotonia, severe growth and developmental retardation, dolichocephaly, anteverted nares, flat nasal bridge, high palate, carp-shaped mouth, micrognathia, recurrent respiratory infections and a normal immunologic evaluation.

Patients with more distal breakpoints to Jacobsen's critical region show milder phenotypes [308, 324]. For example, an individual presented with del(11)(q24.2qter), developmental delay minimal structural brain anomalies, but no other systemic findings [324].

Ophthalmic Manifestations

Patients with terminal deletions including 11q23 usually have telecanthus and/or hypertelorism, ptosis, and epicanthal folds [305, 310, 313–316, 322, 325, 326]. Hypertelorism can be present when the deletion starts at the 11q24.1 critical region [304]. Bilateral Peters anomaly was reported in an individual with del(11)(q14q22) [325]. Interstitial del(11)(q14q21) has been associated to strabismus, myopia and optic nerve colobomas [327]. One patient reported with subterminal deletion had also exorbitism [310]. Another individual with del(11)(q23) presented with hypoplastic orbital roofs [318], which was previously described [305]. Bilateral optic atrophy has been reported in del(11)(q23q25) [328].

Epicanthus has not been associated to a particular breakpoint [302, 304, 305, 308, 313, 315, 317, 319, 322, 326, 329] whereas ptosis can present in deletions that include 11q23 [302, 305, 308, 313, 319, 322, 326]. The ptosis may be mild, unilateral or bilateral, with or without levator function [314, 318, 330]. Downslanting [307, 317, 322, 329] or upslanting [302, 303, 305, 308, 315, 318, 319, 330] of the palpebral fissures has also been reported. Ectropion has been described in del(11)(q23qter) [308]. Lid colobomas with normal eyes were present in a child with del(11)(q22qter). Short or long eyelashes have been reported in del(11)(q23) as well. Del(11)(q23.3) has been associated to exotropia, hyperopia and chorioretinal coloboma [311].

Other reported ocular abnormalities seen in terminal deletions are unilateral or bilateral coloboma with or without microphthalmia with del(11)(q23) [305, 308, 316, 318, 322, 331], correctopia with del(11)(q23) [313], nuclear cataract del(11)(q23) [305, 331], and persistent pupillary membrane del(11)(q23) [331]. Juvenile glaucoma [305], and strabismus has been associated to del(11)(q23) [308, 317, 318], del(11)(q23.3) [319], and del(11)(q24.1) [308].

Retinal findings are unusual. The first reports of Jacobsen syndrome reports describe a normal fundoscopy [315, 318]. One child with del(11)(q23.3qter) born after a full-term gestation had peripheral avascular temporal retina, temporal dragging of retinal vessels, and peripheral vasculopathy [319]. Familial exudative vitreoretinopathy (FEVR) was suspected. Autosomal dominant FEVR has been mapped to this region (11q13-q23), which is proximal to the breakpoint for terminal deletions [332]. Both the *FZD4* and *LRP5* genes, which when mutated can result in FEVR, are located in this region.

One patient with interstitial del(11)(q14q22) had telecanthus and bilateral ptosis with normal globe examination [323]. Patients with breakpoints distal to 11q24.1 may have hypertelorism, ptosis, esotropia, and hypertrichosis of the eyebrows [308, 324].

Duplication 11p

Definition and Epidemiology

Complete or partial trisomy of 11p are rare conditions, with few cases reported. Most of cases result from unbalanced segregation of a balanced familial rearrangement [333]. An important breakpoint is 11p12-p13.

Systemic Manifestation

Described clinical manifestations of trisomy 11p are growth retardation, hypotonia/hypertonia, prominent forehead, broad nasal bridge, abnormal ears, cleft lip/ palate, overriding toes, clinodactyly, absent or hypoplastic thumbs, cardiac abnormalities, hernia, omphalocele, urogenital abnormalities, intestinal malrotation and cryptorchidism [333]. Majority of patients usually die early in childhood.

Ophthalmic Manifestation

Patients with trisomy 11p have been associated with different oculofacial findings, such as flat supraorbital ridges, epicanthal folds, hypertelorism, small down-slanted palpebral fissures, as well as other clinical manifestations, including strabismus, nystagmus, anophthalmia, microphthalmia, myopia, hyperopia, eccentric fixation, eccentric pupils, conjunctival telangiectasia, "Brushfield-like" spots, retinal detachment and rod dysfunction [333].

Duplication 11q

Definition and Epidemiology

Partial Trisomy 11q syndrome is a rare disorder. Band q23.3 contains a fragile site that predisposes to breaks and recombination between chromosomes. Few patients with "pure" 11q duplication have been reported.

Systemic Manifestations

Clinical manifestations in individuals with trisomy 11q are prominent occiput, hearing loss, micrognathia, café-au-lait spots, brain abnormalities, inguinal hernia, and thrombocytopenia. One patient with dup(11)(q11q13.3) presented with multiple craniosynostoses, congenital heart defect and developmental delay [334]. Dup(11)(q13.3q11.21) has been observed in individuals with mental retardation, microcephaly, abnormal ears, high arched palate, congenital heart disease and micrognathia [335]. A patient with dup(11)(q22qter) and a phenotype that resembled Pitt-Rogers-Danks syndrome, presented with manifestations not seen in that condition, such as severe kyphoscoliosis, prognathism, severe leg edema, hypertonicity, and spina bifida occulta [336].

Ophthalmic Manifestations

Dup(11)(q13q25) has been associated to bilateral iris coloboma and myopia, dup(11)(q13.5q21) with arched eyebrows, and dup(11)(q11q13.3) with blue sclera, strabismus and nystagmus [334]. Epicanthal folds, short palpebral fissures and strabismus have been seen in patients with dup(11)(q21q23.1) [335], and ptosis with dup(11)(q23) [337]. One case reported with dup(11)(q22qter) had mild ptosis and hypertelorism [336].

Ring 11

Definition and Epidemiology

Reports of ring chromosome 11 are rare. There are cases that resembled Jacobsen syndrome phenotype. Patients usually die early in infancy.

Systemic Manifestations

One case with del(11)(q24qter) had trigonocephaly, heart defects, micrognathia and minor ear anomalies [301], although this breakpoint is distal to Jacobsen's critical region. Another patient with breakpoints at 11p15 and 11q25 had prenatal growth and psychomotor retardation, micrognathia, arched palate, microbrachycephaly, short nose, low nasal bridge, low-set ears, heart anomaly, genital anomaly, short neck, café au lait spots, hirsutism and deformity of nails, and pancytopenia [338]. Short neck has also been described in del(11)(q23.1qter) [303].

Ophthalmic Manifestations

Narrow downslanting palpebral fissures, telecanthus, epicanthus hypertelorism, telecanthus, and exotropia have been reported [301, 338].

Pericentric Inversion of Chromosome 11

Definition and Epidemiology

This condition is rare, with few cases reported in the literature.

Systemic Manifestations and Ophthalmic Manifestations

One family had pericentric inv(11)(p15:q12). All affected members had congenital glaucoma and two also presented epithelial and stromal corneal opacities with peripheral pannus [339].

A 12 month old boy had inv(11)(p11p23) and sporadic unilateral retinoblastoma. His father had the same chromosomal inversion but no retinal findings [340]. The 11q23 breakpoint has been associated to several malignant hematological diseases and may be relevant in malignant transformations [340]. Chromosome 11 aberrations have been associated with leukemia, Wilms' tumor, malignant lymphoma and Ewing sarcoma [341].

Chromosome 12

Deletion 12p

Definition and Epidemiology

Monosomy for the distal short arm of chromosome 12 is rare [342].

Systemic Manifestations

A 15 year old patient and his mother had a del(12)(p13.33). After a normal karyotype analysis, FISH study revealed a 1.65 Mb terminal deletion. Clinical manifestations were microcephaly, facial dysmorphism, developmental and growth delay, dental anomalies and digital anomalies. The boy also had ventricular septal defect, attention deficit disorder, kyphoscoliosis and behavioral problems [342].

Ophthalmic Manifestations

The patient with del(12)(p13.33) had deep set eyes and strabismus [342].

Deletion 12q

Definition and Epidemiology

Few cases with deletion of 12q have been reported in the literature [343, 344].

Systemic Manifestations

Del(12)(q12q13.12) has been associated to mental and psychomotor retardation, intrauterine growth retardation, dental abnormalities, micrognathia, cleft palate, low set ears, sparse hair, short and webbed neck, widely set nipples, chest anomalies, mild scoliosis, and clinodactyly of the fifth finger [345]. Del(12)(q15q21.2) has been reported with intrauterine growth retardation, facial dysmorphism, developmental delay, delayed speech, ectodermal abnormalities, cleft palate, micrognathia, sacrococcygeal anomalies, and cardiac and renal anomalies [343]. An individual del(12)(q24.31q24.33) had developmental delay, tracheomalacia, coarse facial features, ambiguous genitalia, hypotonia, and apnea triggered by feeding or airway manipulation [346].

Reported findings of 12q subtelomeric deletions are developmental delay, food seeking behaviour, obesity, abnormal hair whorl pattern, brachydactyly and clinodactyly, short stature, mild dysmorphic facial features, polycystic kidneys and unilateral cryptorchidism [347]. In siblings with del(12)(q13.13q13.2) partially involving the *HOXC* gene cluster, minor facial dysmorphic features and developmental delay have been reported [348]. Deletion completely the entire *HOXC* gene cluster have skeletal abnormalities [348]. One girl with del(12)(q24.31) presented with intellectual disability, seizures and facial dysmorphisms [349].

Ophthalmic Manifestations

One case was reported with del(12)(q12q13.12). The patient had bilateral ptosis, hypertelorism, strabismus, downward slant of the palpebral fissures and epicanthal folds [345]. Del(12)(q15q21.2) has been associated to hypertelorism, downslanted/upslanted palpebral fissures, arched eyebrows and crescent shaped eyes [343]. Short palpebral fissures and ptosis were also reported in a case with del(12)(q24.31q24.33) [346]. In a patient with del(12)(q13.13q13.2) partially involving the *HOXC* gene cluster, deep eye sets and epicanthal fold have been reported [348].

Duplication 12p

Definition and Epidemiology

Pallister-Killian syndrome (PKS) is a rare, sporadic, condition that often has highly distinctive features. It is caused by mosaic tetrasomy of chromosome 12p often due to a supernumerary isochromosome 12p [350–356]. It is a dysmorphic disorder involving most systems, but also has a tissue-limited mosaicism in which most fibroblasts have 47 chromosomes with an extra small metacentric chromosome, while the karyotype of lymphocytes is normal. The grade of mosiacism in peripheral blood does not correlate with severity of the phenotype [353]. Estimated prevalence is 1 in 20,000. About 150 have been reported in the literature [356]

Systemic Manifestations

Patients with PKS present with coarse facial features, broad high forehead with sparse anterior hair, ear abnormalities, macrostomia, and a short broad nose with anteverted nares and a flat bridge [351–353]. They also have profound developmental delay, seizures and hypotonia in addition to pigmentary anomalies of the skin [350, 353]. Other features may include anogenital abnormalities, thin upper lip and protruding lower lip, finger anomalies, hearing loss, cleft palate, and hemihypertrophy. Mosaicism may be associated to streaks of hyper/hypopigmentation [351]. If multiple organ malformations are present, patients die in early infancy. Dup(12)(p11.2p13.3) has been reported with craniofacial dysmorphy, cleft palate, mental deficiency, severe mental and motor delay, hypotonia, seizures, corpus callosum agenesis, preaxial polydactyly and diabetes insipidus [355].

One mosaic patient with Pallister-Killian syndrome had a 12p triplication and dysmorphic features, poor tone, respiratory distress, brachycephaly, and premature balding. The tetrasomy of 12p was only diagnosed by cultured skin fibroblasts [357].

Ophthalmic Manifestations

Hypertelorism is a usual feature of PKS [350–352]. Approximately half of duplication 12p patients present epicanthal folds [350]. Other lid abnormalities are ptosis, lower lid entropion, and up-slanting or down-slanting of the palpebral fissures. About 30 % of individuals with PKS show sparse hair (particularly bitemporal alopecia), as well as sparse eyebrows. Patients with strabismus usually have exotropia although there are reports of esotropia [350, 352]. Other ophthalmic findings include myopia [350, 352], coloboma [353], cloudy corneas [353] nystagmus [352], patchy fundus hypopigmentation (as an expression of chromosomal mosaicism) [352].

A publication including 59 affected individuals with PKS, showed that 87 % had ophthalmological involvement, (most frequent were up-slanting or down-slanting of the palpebral fissures in 72 %) and other less frequent findings (proptosis, ptosis, epicanthal folds, telecanthus) [356].

One author reported depressed supra orbital ridges, possible microphthalmia, upslanting palpebral fissures and epicanthal folds with dup(12)(p11.2p13.3) [355].

One mosaic patient with Pallister-Killian syndrome had a 12p triplication and upslanting palperbral fissures [357].

Duplication 12q

Definition and Epidemiology

Duplication 12q is a rare condition with few cases reported in the literature.

Systemic Manifestations

One patient with a phenocopy of Wolf-Hirschhorn syndrome was reported with dup(12)(q13.3q14.1). Clinical manifestations were hypotonia, weak cry, developmental delay, tall forehead, receding anterior hair line, prominent glabella, highly arched eyebrows, hypertelorism, wide palperable fissures, prominent eyes, and a bulbous nasal tip with wide nasal bridge suggesting the Greek warrior helmet facies [358]. Dup(12)(q13.2q13.3) was reported in a patient that presented dysmorphism, developmental delay, seizures and hypospadias [359].

Low set ears, downturned mouth, micrognathia, short neck with loose skin at the nape, wide set nipples, palmar crease, subluxation of hips, sacral dimple, cryptorchidism, heart defects, and ulnar deviation of hands with clinodactyly have been reported with dup(12)(q24.1q24.5) [360].

Ophthalmic Manifestations

Epicanthal folds [359] and hypertelorism have been reported with dup(12)(q24.1q24.5) [360].

Trisomy 12

Definition and Epidemiology

Few cases of live born patients with trisomy 12 have been reported.

Systemic Manifestations

One case had dysmorphic features including malar hypoplasia, linear pigmented streaks on the forearms and lower legs, normal mental development, motor delay, short stature, scoliosis, and cardiac anomalies. Other reported features were infertility and situs inversus [361] Chromosome analysis of blood showed low incidence of trisomic cells (0.4 %) but cultured fibroblast presented trisomy 12 in 9 % and 13 % of cells from two skin biopsies [361].

Ophthalmic Manifestations

No ocular findings were reported in this case [361].

Chromosome 13

Deletion 13q

Definition and Epidemiology

The long arm of Chromosome 13 has several tumor suppressor genes, many of them involved in different types of malignancies such as breast cancer (*BRCA2*), alveolar rhabdomyosarcoma (*FOXO1A*) and retinoblastoma (*RB1*). 13q deletion has a wide clinical spectrum, and therefore, there has been a special interest in defining genotype-phenotype correlations. Depending on the size and position of the deleted region, partial deletion of 13q leads to distinct phenotypes [362–364]. The q32 region is a reference point for is categorizing 3q deletions into 3 groups: Group 1, proximal deletions usually not involving 13q32; Group 2, distal deletions involving at least part of 13q32; and, Group 3, with more distal deletions involving 13q33-34. In addition, some of the phenotypic differences may also be due to imprinting [364].

Systemic Manifestations

Various phenotypic findings can be mapped to deleted loci: short stature with del(13)(q31.3), microcephaly with del(13)(q33.3q34), cortical development malformations with del(13)(q33.1qter), Dandy Walker malformation with del(13)(q32.2q33.1), corpus callosum agenesis with del(13)(q32.3q33.1), meningocele/encephalocele with del(13)(q31.3qter), cleft lip/palate, lung hypoplasia and thumb aplasia/hypoplasia with del(13)(q31.3q33.1) and distal limb anomalies with del(13)(q31.3q33.1). Patients with del(13)(q21qter) showed similar facial dysmorphic features. Prominent nasal collumella is mapped between [13](q31.3q33.3), and micrognathia between [13](q21.33q31.1) [363].

In Group 1 patients, there is mild or moderate mental retardation, growth retardation, hypotonia, and variable minor anomalies although microcephaly may also occur. In addition, several gastrointestinal anomalies have been reported, including Hirschprung disease with del(13)(q13q22) and del(13)(q14.1q22.3), jejunal atresia with del(13)(q14q21), agenesis of colonic mesenteries with del(13)(q14q31), duodenal and jejunal atresia with del(13)(q21.2q22), and jejunal and ileal atresia with del(13)(q14) [365–367].

In Group 2, there can be one or more major malformations, in particular microcephaly, brain malformations such as anencephaly or encephalocele, cardiac malformations, absent distal limb abnormalities, and gastrointestinal tract malformations. Posterior encephalocele, holoprosencephaly, absent thumbs and genitourinary tract malformations have also been reported [364]. In Group 3, there is severe mental retardation without major malformations and usually without growth retardation.

Thumb and /or big toe anomalies are associated with deletion of 13q32 as is Hirschsprung disease. It appears that there may be more than one locus on 13q that affect limb development and colonic innervation. The *EDNRB* gene, which when mutated causes recessive Hirschprung disease, is located at 13q22. Minor dysmorphic abnormalities such as large ears, beaked nose, facial asymmetry, and protruding upper incisors occur in patients from both groups 2 and 3 [364].

Ophthalmic Manifestations

Retinoblastoma is caused by inactivation of the *RB1* gene, a tumor suppressor located on 13q14.2 region. Patients with a 13q deletion involving this region often have pleiotropic

manifestations. Group 1 have minor anomalies such as hypertelorism and iris heterochromia with or without retinoblastoma. Patients with Moebius syndrome with del(13)(q12.2q13), Axenfeld-Rieger spectrum with del(13)(q14), retinoblastoma with del(13)(q14.2), and Wilson disease with del(13)(q14.3q21.1) have been reported [365]. Strabismus has been observed with del(13)(q12.3) [366]. Hypertelorism, deep set eyes, strabismus and hypermetropia have been reported with del(13)(q32.3qter) [363]. Bilateral retinoblastoma (Fig. 6.7) have been reported with del(13)(q13q22) and del(13)(q14.1q22.3), bilateral retinoblastoma with del(13)(q14q21), unilateral retinoblastoma with del(13)(q14q31), bilateral optic nerve hypoplasia with del(13)(q21.2q22), and bilateral microphthalmia with del(13)(q14) [367]. Group 2 present minor anomalies including hypertelorism, down-slanting of the palpebral fissures and major ocular malformations including fixed and dilated pupils, microphthalmia and retinal coloboma have been reported [364] Group 3 present minor oculofacial findings, such as hypertelorism.

Large deletions involving 13q have also been observed. Rieger syndrome, nasolacrimal duct obstruction and mild dysplastic optic nerve heads have been associated with del(13)(q14q31). Optic nerve hypoplasia and retinal dysplasia have also been described [368] A patient with del(13)(q14q32) had bilateral microphthalmia, bilateral iris and fundus coloboma, and bilateral retinoblastoma. In a large series of retinoblastoma patients (n = 1265) only 0.3 % had microphthalmia [369]. Iris heterochomia, iris stromal hypoplasia and depigmentation of retinal pigment epithelium were seen in a case with del(13)(q21.1q31.3) [370]. One patient with del(13)(q21.2q32) was reported with features of Waardenburg syndrome [371]. Anophthalmia/microphthalmia spectrum has been associated to del(13)(q31.3qter) [363].

Fig. 6.7 Patient with del(13)(q12.3q22) and bilateral low grade retinoblastoma, hypotonia and partial dysgenesis of corpus callosum (courtesy of Diego Ossandón MD and Federica Solanes MD)

Duplication 13q

Definition and Epidemiology

Partial 13q duplication cases can be classified as either proximal (pter-q22.1) or distal (qter-q22.2) Duplication of the proximal part of chromosome 13 is more phenotypically variable. Few cases have been reported.

Systemic Manifestations

Partial trisomy for the segment 13pter-q14 is characterized by a nonspecific pattern of malformations. Patients with partial trisomy for the distal segment of 13q have severe mental deficiency and a characteristic facies. One patient with dup(13)(q31.3q32.3) had developmental delay, autistic spectrum disorder, unexplained muscle cramp, dysmorphic appearance, elongated columella, bilateral low-set ears, short-webbed neck. One author reported a female patient with tetrasomy 13q mosaicism in the form of an inverted dup(13)(q21). The patient had developmental delay, pigmentary abnormalities known as phylloid hypomelanosis and precocious puberty [372].

Ophthalmic Manifestations

One patient with dup(13)(q31.3q32.3) presented elongated and wide palpebral fissures. A case with 13q mosaicism had hypertelorism [372].

Trisomy 13

Definition and Epidemiology

Trisomy 13, also known as Patau syndrome, has a significant frequency of congenital ocular malformations at birth. The incidence of trisomy 13 in live born infants is approximately 1 in 20,000 [373–375]. Like many other trisomies, increased maternal age is associated. Trisomy 13 mosaicism is characterized by a less severe phenotype with a wide variation of clinical findings.

Systemic Manifestations

Central nervous system anomalies have been described in up to 50 % of patients [376]. Holoprosencephaly is the single most common cephalic disorder [376]. Seizures and severe mental deficiency are also very common. Abnormal facies and head and neck anomalies can be seen in up to 90 % of patients (Fig. 6.8). Microcephaly is frequently observed, particularly with wide sagittal suture and fontanelles. Cardiovascular abnormalities occur in about 80 % of patients, cleft lip and/or palate in 60 %–80 % of cases, and external ears anomalies with/without deafness in nearly 50 %. Capillary hemangiomas, particularly affecting the forehead, have been observed. Localized scalp defects in the parieto-occipital area may be seen. Other frequent reported findings

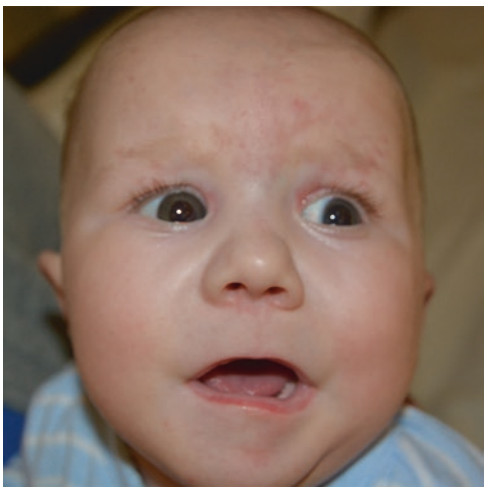

Fig. 6.8 Patient with trisomy 13 mosaicism. Note mild facial findings such as, low-set ears and capillary hemangioma

infants include intrauterine growth retardation, polydactyly, cryptorchidism, bicornuate uterus, a single umbilical artery, and persistence of embryonic and/or fetal hemoglobin. Polycystic kidneys and other genitourinary abnormalities have been described.

Full trisomy 13 is usually a lethal condition. One study reported that 28 % of surviving newborn infants die in the first week of life, 44 % within 1 month and 86 % in infancy [377]. Another study reports a median of survival of 10 to 26 days [378, 379], with a 3 month survival of 18 % [379]. One year survival for live births with trisomy 13 mosaicism was 80 % and for those with partial trisomy 13 was 29 % [379]. One child survived 146 months [380]. Although there is a very high frequency of congenital heart disease, these malformations are usually not lethal. One publication suggested that primary apnea was the most common cause of death [375].

Ophthalmic Manifestations

Ocular malformations have been found in almost 80 % of patients with trisomy 13 [381, 382]. These abnormalities are frequently severe and incompatible with vision. Because of the poor systemic prognosis, treatment of ocular conditions has to be carefully pondered.

Bilateral manifestations are seen in nearly all children. Trisomy 13 is the most common chromosomal aberration associated with microphthalmia or anophthalmia [276]. Although the first report describes apparent anophthalmia [383], severe microphthalmia as colobomatous microphthalmia is a known presentation of trisomy 13, in up to 60 % [378, 384]. Intraocular cartilage or other choristomatous tissue may be associated to iris and ciliary body coloboma. Anterior segment malformations are also common, occasionally similar to Axenfeld-Rieger spectrum or less frequently, Peters anomaly. Secondary glaucoma to angle dysgenesis may also occur. The cornea can be vascularized and with dysgenesis of Descemet or Bowman membranes. Cataract is a frequent feature. Optic nerve hypoplasia has also been described. Retinal dysplasia can be present, with features that include folds or intraocular cartilage. Full trisomy 13 is often associated with persistent ocular fetal vasculature [384]. A premature infant with trisomy 13, confirmed by karyotype analysis had microphthalmia, extensive colobomata, retinal dysplasia, and a heterotopic ciliary body [381].

Less common ocular and oculofacial findings are shallow supraorbital ridges, slanting palpebral fissures, absent eyebrows, hypertelorism, hypotelorism, synophthalmos and cyclopia. Congenital unilateral facial paralysis have also been reported [385]. The first patient reported by Patau had a non-elevated simple capillary hemangioma involving the upper eyelids [383].

Ring 13

Definition and Epidemiology

Ring chromosome 13 is a rare genetic aberration in which the loss of genetic material determines the phenotype. Ring 13 is often incompatible with live birth.

Systemic Manifestations

A patient with r(13)(p11q32) had microcephaly, absent and hypoplastic thumbs, ambiguous genitalia, anal stenosis, congenital heart disease, agenesis of the corpus callosum, skeletal abnormalities, turricephaly with an abnormal ventricular system, and severe developmental delay [386]. Other dysmorphic features were low-set ears, flat nasal bridge, micrognathia, and arched palate. The patient died at 3 years [386].

Ophthalmic Manifestations

The patient with r(13)(p11q32) had microphthalmia and iridochorioretinal coloboma, blepharophimosis with epicanthus, down-slanting palpebral fissures and hypertelorism [386].

Chromosome 14

Deletion 14q

Definition and Epidemiology

Few patients have been reported with interstitial deletions in the long arm of chromosome 14 [387–396]. They have a broad spectrum of clinical manifestations caused by loss of different segments of 14q. The proximal region includes the gene *NRXN3*, which is associated with cognitive and neurological defects.

Systemic Manifestations

A patient with del(14)(q11.2) presented with autistic features, obesity and dysmorphisms reminiscent of Wolf-Hirschhorn syndrome [391]. Deletion of 14q12 could be associated with *FOXG1* syndrome, that includes microcephaly, severe intellectual disability and agenesis of corpus callosum [392]. Del(14)(q24.1q24.3) has been associated with congenital heart defects, brachydactyly and mild intellectual disability [393]. Pituitary hypoplasia with hypogonadism and hypothyroidism have been reported with del(14)(q22q23) [387]. Patients with del(14)(q32q32) had hearing loss, congenital inguinal hernia, joint contractures, cardiorespiratory anomalies, and gastrointestinal and genitourinary abnormalities [390]. Clinical manifestations of 14qter deletions include microcephaly, high forehead with lateral hypertrichosis, broad nasal bridge, long philtrum, short bulbous nose, single palmar crease, short neck, micrognathia, high arch palate, epicanthal folds, hypotonia, mild to moderate mental retardation and developmental delay. One female patient with mosaic del(14)(q32.3qter) was reported with mental retardation, tracheoesophageal fistula, intestinal malrotation, low-set ears, midfacial hypoplasia, maxillary hypoplasia, and coronal synostosis [388].

Ophthalmic Manifestations

Multiple genes are found on 14q which when mutated are associated with microphthalmia: *BMP4* at 14q22-23, *SIX6* at 14q23, *CHX10* at 14q24.3, and *CMIC* at 14q32. One case with bilateral anophthalmia due to del(14)(q22.1-22.3) has been reported [394]. Others authors reported a case with bilateral anophthalmia and del(14)(q22.1q23.2) [395].

One patient with del(14)(q11.2) presented with highly arched eyebrows, down-slanted palpebral fissures and ptosis [391]. Patients with 14qter deletion syndrome have been reported to have hypertelorism [389, 393], blepharophimosis, ptosis, epicanthal folds, down-slanting palpebral fissures, and bushy eyebrows [390, 396]. Deletion of 14q12 may result in strabismus [392]. A patient with mosaic del(14)(q32.3qter) had a unilateral nuclear cataract, small orbits, and down-slanting palpebral fissures [388].

Duplication14q

Definition and Epidemiology

Duplication of the long arm of chromosome 14 has been reported in approximately 60 patients, from which 20 cases are pure duplication of 14q, mostly involving from q12 to q35 region. Most of them result from the meiotic segregation of a parental balanced translocation. Patients with partial trisomy 14q have variable clinical manifestations, which is associated to the size of duplicated segment of the chromosomal arm 14q, and sometimes, to associated monosomy.

Systemic Manifestations

Short stature, developmental delay and facial dysmorphism has been described in dup(14)(q32.2qter) [397]. Dup(14)(q28q35.2) has been associated to hypertonic syndrome, microcephaly and facial dysmophism, including broad nasal bridge, prominent beaked nose with anteverted nostrils, low-set malformed ears, high arched palate, and micrognathia. The patient also had slight bilateral contractures of the knee, congenital heart defect (foramen ovale) and immunodeficiency syndrome. One patient was reported with dup(14)(q11.2) and short stature, hypogetinalism and mental retardation [398]. One child with inverted dup(14)(q22q24.3) and CHARGE phenotype was reported. The patient had congenital heart disease, choanal stenosis, mental and growth retardation, minor genital abnormalities, and hearing loss [399]. He also had clubfoot, pyloric stenosis, gastroesophageal reflux, and recurrent otitis media and sinusitis due to hypogammaglobulinemia. Other findings were prominent forehead, anteverted nares, bulbous nasal tip, low set posteriorly rotated ears, micrognathia, and brachydactyly with syndactyly of the second and third toes. The phenotype in distal trisomy (14)(q22qter) is variable. Majority of patients present growth retardation, micrognathia, and ear abnormalities. Nearly half have facial anomalies with prominent forehead, finger anomalies and hypotonia . Less commonly, congenital heart defects, genital hypoplasia, and foot anomalies have been reported [400].

Oculoauriculovertebral spectrum has been described in a family with dup(14)(q23.1) [401]. Main clinical features were oral defects, mandibular alterations and vertebral abnormal development. The duplication was 1.34 Mb in size and segregated with the phenotype. This described region contains *OTX2*, a known gene associated to oculoauriculovertebral spectrum, which is involved in the development of the forebrain, eyes, and ears.

Ophthalmic Manifestations

Dup(4)(q28q35.2) has been described with to antimongoloid slanted palpebral fissures, epicanthic folds, strabismus, and bilateral coloboma of optic papilla. One child with inverted dup(14)(q22q24. 3) had hyperopic astigmatism and bilateral iris colobomas [399]. Hypertelorism was seen in 72% of patients with trisomy (14)(q22qter) [400]. One author reported hypertelorism, epicanthal folds, downslanting palpebral fissures, pale optic nerve and atrophic choroidal and retinal blood vessels in a patient with dup(14)(q24q32) [402].

Ring 14

Definition and Epidemiology

Ring chromosome 14 syndrome is a rare chromosomal anomaly. About 70 cases have been reported in the literature.

Systemic Manifestations

Clinical manifestations of patients with ring 14 chromosome include mental retardation, seizures, flat nasal bridge, upturned nostrils and short neck [403, 404]. Other described features are microcephaly, psychomotor delay, hypotonia, feeding and growth difficulties, recurrent respiratory infections, prominent forehead, an elongated face with puffy cheeks, and low-set ears. Seizures are generally of variable types and are typically hard to treat.

Ophthalmic Manifestations

Described manifestations are widely spaced eyes, blepharophimosis, epicanthus, retinal dysplasia, downslanting palpebral fissures, and epicanthal folds. Abnormalities in retinal pigmentation have been described, although no further description was provided [390].

Chromosome 15

Deletion 15p

We are unaware of any published reports of pure live born with deletion 15p for which ophthalmic manifestations have been reported.

Deletions 15q

Definition and Epidemiology

The most significant 15q deletion involves 15q11-q13. This region contains genes with maternal imprinting, others with paternal imprinting, and some that are not imprinted. Any alteration that prevents maternal allele expression of *UBE3A* gene results in Angelman syndrome, while preventing the paternal expression of *SNRPN* causes Prader-Willi syndrome. These syndromes may also result from uniparental disomy or intragenic mutation in children with normal karyotypes. The majority of Prader-Willi syndrome cases occur sporadically. These include interstitial deletions, unbalanced translocations, and maternal uniparental disomy. About 70 % of Prader Willi and Angelman patients are due to del(15)(q11q13). There could be intrachromosomal aberrations, such as balanced translocations, in the parental alleles which contribute to creation of a deletion in their offspring [405]. A minority of patients have *de novo* unbalanced translocations. It should be noted that the previous name for Angelman syndrome, happy puppet syndrome, has been discarded along with the pejorative names of many other syndromes (e.g., trisomy 21).

Systemic Manifestations

Clinical manifestations of Prader-Willi syndrome include neonatal hypotonia and feeding difficulties followed later by obesity, developmental delay, and in some occasions, hyperphagia that may be associated with behavior problems. Other features include small hands and feet, narrow bifrontal skull, and primary hypogonadism with cryptorchidism and small genitals. Mega cisterna magna, horseshoe kidney and pulmonary interstitial glycogenosis have also been reported [406]. Patients with Angelman syndrome present more severe developmental delay and seizures, which may involve inappropriate bouts of laughter and ataxic jerky movements of the extremities. They do not present obesity.

Patients with del(15)(q11.2) flanked by *BP1* and *BP2* of the Prader-Willi/Angelman syndrome region have recently been associated to intellectual disability, speech and language delay, motor delay, autism spectrum disorders, epilepsy, and schizophrenia. Distal del(15)(q25.2), is also associated with neurodevelopmental and neuropsychiatric disorder [407]. Array CGH analysis of 14,605 patients found that 83 patients (0.57 %) carried the 15q11.2 (BP1-BP2) deletion. Those patients had significantly more prevalent developmental delay, motor delay, and speech and language delay [408].

Ophthalmic Manifestations

Approximately 1 % of patients with either Prader-Willi or Angelman syndrome due to del(15)(q) will present oculocutaneous albinism due to contiguous deletion that includes the Prader-Willi or Angelman locus as well as the *P* gene. Mutations in the P gene, which is required for melanocyte maintenance, a gene that is not affected by imprinting, have type 2 oculocutaneous albinism. Patients with del(15)(q) and OCA2 have a concurrent mutation in their remaining copy of the gene. Iris transillumination and a higher frequency of blue iridies may be seen in Prader-Wills and Angelman even in the absence of albinism when the patient has del(15)(q) involving *the P* gene but a normal copy of *the P* gene on their other allele.

In Prader-Willi syndrome the palpebral fissures are often described as “almond shaped”. Strabismus has been reported in del(15)(q25.2) [407]. Patients with del(15)(q13.3) have been reported with lack of eye tracking, optic nerve pallor, electronegative b wave in the context of convulsive encephalopathy and “congenital blindness” [409]. These findings were attributed to deletion of *TRPM1* at 15q13-14. When mutated, *TRPM1* results in autosomal recessive congenital stationary night blindness. High hyperopia and exotropia have been reported in Angelman syndrome.

Duplication 15p

We are unaware of any published reports of pure live born with duplication 15p for which ophthalmic manifestations have been reported.

Duplication 15q

Definition and Epidemiology

Duplication 15q is a rare condition with few cases reported in the literature. BP1–BP5 are five frequent breakpoints in the 15q11.2-q13 region, which often define the boundaries of both deletions and duplications. At least 50 cases of duplication of regions 15q21-15q26.3 have been reported.

Systemic Manifestations

Patients with duplication 15q can present with autism spectrum disorders, epilepsy, and schizophrenia. Developmental delay, hypotonia, and minor dysmorphic features have been described, including low-set ears, "coarse" facial features, and hypopigmented areas of the skin. Distal 15q duplication is characterized by minor craniofacial anomalies, congenital heart disease, mental retardation, and genital anomalies, particularly in males.

Ophthalmic Manifestations

Minor oculofacial findings include down-slanting palpebral fissures, and epicanthal folds. Because of the use of vigabatrin for severe epilepsy, some patients with duplication 15q have to be followed carefully.

Trisomy 15

Definition and Epidemiology

Trisomy 15 is considered to be incompatible with life [410]. Only a few cases of mosaic trisomy 15 in live born infants have been described in the literature. This chromosomal aberration is frequently associated with advanced maternal age.

Systemic Manifestations

There are no consistent phenotypic features although multiple congenital anomalies are usually present. These include intrauterine growth retardation, craniofacial abnormalities and facial dysmorphisms, and cardiac disease.

Ophthalmic Manifestations

Retinal dysplasia and Bergmeister papilla have been reported with trisomy 15 [383]. Orbital hemangiopericytoma has been associated to mosaic trisomy 15.

Chromosome 16

Deletion 16p

Definition and Epidemiology

Alpha-thalassemia-mental retardation (ATR-16) is a contigous gene deletion syndrome associated to del(16)(p13.3), which includes the alpha1 and alpha2 globin genes [411]. Usually the deletions are large (1–2 Mb). ATR-16 is a rare condition, with few cases reported in the literature.

Systemic Manifestations

ATR-16 syndrome is characterized by the presence of both alpha thalassemia and developmental delay. Other features may include midfacial hypoplasia, capillary hemangioma, club foot, and less commonly, patent ductus ateriosus, inguinal hernia, hypospadius, cryptorchidism, and speech problems [412]. Other described dysmorphisms include a high forehead, prominent nasal root and bridge, flattened maxilla, high-arched palate, and anterior frenulum. Structural brain anomalies include reduced periventricular white matter volume and thin corpus callosum.

A recurrent *de novo* pericentromeric del(16)(p11.2p12.2) was reported in four individuals with developmental disabilities, flat facies, malformed ears, orofacial clefting, micrognathia, heart defects, frequent ear infections, short stature, minor hand and foot anomalies, feeding difficulties, hypotonia and cognitive and developmental delay [413]. Del(16)(p13.11) has been reported with severe microcephaly [414].

Ophthalmic Manifestations

Oculofacial findings in patients with ATR-16 syndrome include mild hypertelorism, up and down-slanting palpebral fissures and epicanthal folds. One patient had del(16)(p13.3pter) associated to scarce eyebrows with hypoplastic superior orbital ridges and shallow orbits have also been reported [412]. One author reported blepharophimosis with del(16)(p11.2) [413].

A patient with del(16)(p13.2), involving *TMEM114*, had developmental delay and cataract. His healthy father had same deletion, but examination revealed no cataract [415].

Deletion 16q

Definition and Epidemiology

Interstitial deletions of chromosome 16 long arm are rare aberrations with approximately 20 cases described. Clinical manifestations are associated with the extension and location of the deleted regions. Del(16)(q12.1q13) and del(16)(q22) are associated with a similar phenotype.

Systemic Manifestations

Frequent manifestations of 16q deletions are severe growth and developmental disorders, and craniofacial and musculoskeletal abnormalities. Patients also present psychomotor retardation, autistic like behaviour, hypotonia, low-set ears and club foot [416]. Microcephaly, congenital heart defect, renal cystic dysplasia, micrognathia, high arched cleft palate, broad flat nasal bridge, short neck, narrow thorax, flexed fingers, bilateral palmar creases, and malpositioned toes and broad first toe, have been associated with del(16)(q11.1q22)

[417]. Del(16)(q22) present failure to thrive, poor growth, delayed psychomotor development, hypotonia, and dysmorphic features, including large anterior Fontanelle, high forehead, diastasis of the cranial sutures, broad nasal bridge, hypertelorism, low-set abnormal ears, and short neck. Congenital heart defects, mainly septal defects and anomalies of the outflow tract, are commonly seen in del(16)(q22), and with a lower frequency, kidney malformations and anterior anus have also been reported. A 4 year old patient with del(16)(q23.1q23.3) was reported with nephrocalcinosis [418]. High forehead, coarse hair have been seen in del(16)(q13q22) [419].

Ophthalmic Manifestations

Del(16)(q13q22) has been associated with short palpebral fissures, ptosis, esotropia, prominent eyebrows, long lashes, mild synophrys and mild microphthalmia have been reported with [419]. A patient with del(16)(q23.1) had synophrys, hypertelorism, short and upslanting palpebral fissures, unilateral iris coloboma, and bilateral cataract with many small drop-like precipites [416]. Cataracts seen with del(16)(q) may also be nuclear, anterior polar and stellate [416]. The boy with del(16)(q23.1q23.3) and nephrocalcinosis had normal ophthalmic examination, although other patients with overlapping deletions in that region were reported with bilateral iris coloboma and congenital cataract [418]. The heat shock factor gene *HSF4*, mutations in which result in childhood cataract, is located at 16q21-22.1.

Duplication 16p

Definition and Epidemiology

Duplication 16p is a rare chromosomal imbalance with less than 20 cases reported, from which only 7 of the reported patients have a "pure" duplication. Most cases are due to familial balanced translocation.

Systemic Manifestations

Duplication of the short arm of chromosome 16 present with severe pre and postnatal growth retardation, dolichocephalus, clinodactyly and hypoplastic thumbs. Reported clinical manifestations of dup(16)(p11.2p12) have included a characteristic round face with flattened occiput, long philtrum, cleft palate, posteriorly rotated low-set ears, short neck, eczema, truncal hypotonia, hyporeflexia, and developmental delay [420]. A single umbilical artery is seen in half of patients [420]. Dup(16)(p13.1pter) has been associated to autistic spectrum disorder [421].

Ophthalmic Manifestations

One patient with dup(16)(p11.2p12) had tremor-like movements and ocular abnormal movements lasting several seconds without loss of consciousness that, in the absence of seizure activity on EEG, were attributed to a behavioral disturbance with autistic features [420]. The child had several oculofacial findings, including sparse eyebrows, narrow palpebral fissures, hypertelorism and epicanthus, and also had strabismus and microphthalmia.

Chromosome 17

Deletion 17p

Definition and Epidemiology

Smith-Magenis syndrome (SMS) is usually related to del(17)(p11.2) [422]. Homologous recombination of flanking repeat gene clusters has been described as one of the mechanisms for this contiguous gene deletion syndrome [313]. 70 % of SMS patients have a common deletion interval spanning 3.5 Mb. The critical region is 17p11.2, where the gene *RAI1* is located.

Systemic Manifestations

Patients with SMS have a specific phenotype that includes developmental delay/mental retardation, self-injurious behavior, hyperactivity, and severe sleep disturbance [422, 423]. Individuals have a flattened midface, brachycephaly, broad nasal bridge, short stature, prominent supraorbital ridges, synophrys, prominent mandible, hoarse deep voice, infantile hypotonia, and brachydactyly [423–425]. Most of patients present peripheral neuropathy, while cardiac defects, renal abnormalities, thyroid anomalies, low levels of immunoglobulins, and seizures are found in less of 40 % of patients with SMS [425].

One child with a del(17)(p11.2) that did not involve the entire SMS region, had a phenotype that resembled Smith-Lemli-Opitz syndrome. The patient had micropenis, hypogonadism, laryngomalacia, polydactyly, craniofacial dysmorphism, midface hemangioma, and syndactyly, but normal cholesterol levels [426]. The child died at 2 years old.

Two patients with SMS were reported with abnormal brain MRI. One had subependymal periventricular gray matter heterotopia, and the second had a thin corpus callosum, a thin brain stem and hypoplasia of the cerebellar vermis [427]. Periventricular nodular heterotopia, has also been described in SMS. It is variably associated with other brain malformations, epileptic seizures and intellectual disability [428].

Del(17)(p13.1) phenotype includes cognitive disability, facial dysmorphism, intellectual disability and epilepsy, but a defined syndrome has not been described [429]. It has been described in 16 patients [429].

Ophthalmic Manifestations

One patient with a mosaic del(17)(p11.2) and a phenotype consistent with SMS, had epicanthal folds, Brushfield-like iris spots, and mild myopia that progressed to −6.00 sphere in 4 years [422]. A slight upward slant of the palpebral

fissures and exotropia have also been described [422, 430]. Other findings include microcornea, iris anomalies such as Wolfmann-Kruckmann spots, and cataracts [424, 425]. One case had esotropia, amblyopia, and mild optic nerve hypoplasia. Anisocoria has been also described [424]. High myopia with retinal detachment has been observed in non mosaic patients [423]. Epicanthus may also be present [426]. Iris coloboma is an unusual finding. Del(17)(p13.1) has been described to have nystagmus and deteriorated fixation, pursuit and saccadic movements [429].

Deletion 17q

Definition and Epidemiology

Deletion 17q is an infrequent chromosomal aberration. Del(17)(q21.31) has been recently described as a recognizable dysmorphic síndrome. It is estimated that 1 in 16,000 individuals may be affected. *MAPT* gene within the deleted region appears a good candidate for the learning disabilities seen in this condition. Other recognized breakpoints are 17q12 and q23.1q24.2.

Systemic Manifestations

Del(17)(q12) has been associated with variable clinical findings, including renal cysts, childhood onset type 2 diabetes, autism spectrum, Alagille syndrome-like facial dysmorphism and learning problems [431]. Del(17)(q21.31) has been associated to cardio-facio-cutaneous syndrome, and shows considerable overlap with Noonan and Costello syndromes. Many individuals with del(17)(q21.31) also present features of ectodermal dysplasia, pulmonary stenosis, and macrocephaly. Variable degrees of developmental delay have been reported in patients with del(17)(q21.31). Del(17)(q23.1q24.2) has been reported with the Hunter-McAlpine syndrome phenotype: craniosynostosis (coronal, lamboidal, metopic) with developmental delay, down-turned mouth, short stature, and minor skeletal anomalies [432]. Other reported clinical manifestations are polydactyly, club foot, genitourinary anomalies, ankyloglossia, seizures, thin upper lip, dental anomalies, microcephaly, round face, hypertelorism, micrognanthia, symphalangism and low-set simple ears [433]. Mortality has been associated to congenital heart defects [433].

Ophthalmic Manifestations

Del(17)(q12) has been associated with arched eyebrows, telecanthus, blepharophimosis and ptosis [431]. Almond shaped palpebral fissures are one of the most significant ophthalmic findings of the Hunter-McAlpine phenotype. One patient with del(17)(q23.1q24.2) had hyperopia, esotropia, short palpebral fissures, and amblyopia [432].

Duplication 17p

Definition and Epidemiology

Few cases of partial trisomy of short arm of chromosome 17 has been reported.

Systemic Manifestations

Clinical manifestations associated with trisomy of the entire arm of chromosome 17p are facial dysmorphism, microcephaly, growth retardation, hypotonia, short webbed neck, congenital heart defect, minor abnormalities of the hands and agenesis of the corpus callosum [434]. Heart defects and aortic anomalies have also been described. One case showed respiratory dysfunction and poor weight gain due to severe feeding difficulties [434]. Mortality of these patients is associated to cardiorespiratory failure and respiratory infections occurring primarily in the neonatal period [434]. Two cases with dup(17)(p12p11.2) had few facial anomalies and only mild developmental delays compared with the usual anomalies of trisomy 17p. They had growth retardation, club feet, delays in expressive speech, hypoplasia of the maxillary and zygomatic bones, smooth philtrum, thin upper lip, posteriorly angulated and prominent ears, high-arched palate with thick palatine ridges, short ramus, short sternum, and a triangular face [435]. One individual with dup(17)(p13.1p13.2) presented with intellectual disability and obesity [436].

Ophthalmic Manifestations

The ophthalmologic assessment of one patient with full arm trisomy 17p showed miotic, irregular, and eccentrically positioned pupils, irides with little pigmentation and iristransillumination in both eyes [434]. Downslanted palpebral fissures were also described in the case with the dup(17)(p12p11.2) [435]. In a patient with 17q25.3 partial tetrasomy, deep set eyes and strabismus was reported [437]. One patient with dup(17)(p13.1p13.2) had wide palpebral fissures [436].

Duplication 17q

Definition and Epidemiology

Duplication 17q is an uncommon chromosomal aberration, with few cases reported in the literature.

Systemic Manifestations

Dup(17)(q12) have been described with different phenotypes, including renal diseases, maturity onset diabetes, developmental delay, general hypotonia, seizures and structural brain abnormalities [438]. Three cases with dup(17)(q24q25.1) were described with familial transmission from a mosaic mother to two children. Clinical features in the children were short stature, microcephaly, thin upper lip, highly

arched palate, malaligned teeth and mild mental retardation. One of them had bulbous nose, a short philtrum, and attached ear lobes [439]. The three patients had shortening of the metacarpal and metatarsal bones. One case with dup(17)(q24.5q24.3) had similar findings as the patients described above, however, the patient also presented saddle nose, down-turned corner of the mouth, low set and malformed ears, webbed neck, lowered posterior hairline, shield chest, small hands and feet, and systemic hirsutism [440]. A patient with (17)(q25.3) partial tetrasomy was reported to have severe intellectual disability, West syndrome (severe epilepsy syndrome composed of the triad of infantile spasms, an interictal EEG pattern termed hypsarrhythmia, and mental retardation), Dandy-Walker malformation and syndactyly [437].

Ophthalmic Manifestations

Dup(17)(q12) has been reported with upslanted palpebral fissures and strabismus [438]. One of the cases with dup(17)(q24q25.1) had mild exotropia and nystagmus [439]. One patient with dup(17)(q24.5q24.3) exhibited blepharophimosis [440].

Chromosome 18

Deletion 18p

Definition and Epidemiology

Deletion of the short arm of chromosome 18, is an uncommon syndrome. Nearly 150 cases have been reported. Its estimated prevalence is 1 in every 50,000 live births and its phenotypic variability makes it difficult to diagnose. Female to male ratio is 3:2. Nearly 85 % of the cases have originated from a *de novo* deletion and less often from familial cause.

Systemic Manifestations

This rare syndrome characteristically presents with variable mental retardation, growth retardation, low height, pectus excavatum, craniofacial malformations including long ear, microcephaly and short neck. There are some cases with alobar holoprosencephaly, and single nostril. The severity of holoprosencephaly is variable. It can present as cyclopy to facial malformations. Four genes has been associated to holoprosencephaly: *SHH* (7q36), *ZIC2* (13q32), *SIX3* (2p21) and *TGIF*. Gonodal dysgenesis, menstrual and fertility disorders have also been reported. Other abnormalities such as mid-facial hypoplasia, flat face, renal hypoplasia, cardiopathy, cebocephaly, dystonia can be observed. Orofacial findings observed in this syndrome can be long philtrum, microstomy, malocclusion, dental hypoplasia, and down-turned corners of mouth. A patient with 18p deletion (18p11.2pter) presented with mental retardation, and white matter abnormalities.

Ophthalmic Manifestations

Abnormalities described with deletion 18p include blepharoptosis, and hypertelorism. A patient with del(18)(p11.2pter) had tilted optic nerves with tortuous vessels in the context of myopia.

Deletion 18q

Definition and Epidemiology

Although the original description of de Grouchy syndrome seems to be associated with deletions distal to and including 18q21 region [441], the eponym is often used to describe all deletions of the long arm of chromosome 18. Proximal deletions are less frequent and have different clinical manifestations.18q deletion syndrome occurs in an estimated 1 in 40,000.

Systemic Manifestations

Clinical manifestations of del(18)(q) include severe mental and motor retardation,, failure to thrive, short stature, palmar creases and abnormal external ears [147, 441–451]. Postsynaptic hearing loss can be observed, as well external ear anomalies [443]. Some individuals with deletions distal to the proximal portion of 18q21.3 present mild developmental delay [443]. Microcephaly and severe mental retardation has been associated to the region 18q21.2q21.3, abnormal brain on MRI to 18q21.2-22.2, and dysmorphic features with extremity abnormalities and hypotonia distal to 18q22.2 region [15].

Other reported manifestations include microcephaly, delayed secondary sexual features, cleft lip and palate, cutaneous hemangiomas, congenital heart disease, club feet, and minor distal skeletal anomalies [442, 443]. A typical facies may includes a large down-turned mouth [442, 443].

Although much less common, patients have been reported with deletions proximal to the region associated with the de Grouchy phenotype [147]. One case had severe developmental delay and a transverse palmar crease [147]. The patient differed from the de Grouchy phenotype because of an anteverted nose, protruding upper lip, retrognathism, cryptorchidism, polymicrogyria, an anomalous pectoral muscle, and bronchopulmonary anomalies. One case with del(18)(q21q32) had chronic granulomatous disease [442]. The myelin basic protein gene has been mapped to 18q22.3 and patients with deletions involving this region have abnormalities in brian myelination [123, 444, 445]. IgA deficiency is found in almost 25 % of del(18)(q) patients [446]. Broad nasal bridge has been described in 26 % of cases [446].

Ophthalmic Manifestations

The first patient reported by de Grouchy was described with “poor visual responses” at 1 year, nystagmus, mild optic atrophy, and a possible tapetoretinal degeneration [441], although an electroretinogram was not performed.

This report was the first to suggest that a locus for a tapetoretinal degeneration could be located on 18q. Cone-rod dystrophy has been mapped to 18q21.1-22.2. There is a report of a case with del(18)(q21.1qter) who presented hand motion vision, lateral gaze nystagmus, high myopia and retinal changes consisting of marked vessel attenuation, optic atrophy, absent foveal reflexes, and "pale and tigroid" retinas without typical pigmentary clumping or "bone spicule" pigmentation [443]. An electroretinogram showed cone-rod dystrophy. The authors suggested that the retinal abnormalities were not attributable to patholgic myopia, which might independently alter the electroretinogram. In addition, they comment that the patient's hearing deficit was postsynaptic and therefore not consistent with Usher syndrome. Three other patients presented in the same report with deletions not involving 18q21.1 had normal retinas [443]. Ishihara color vision testing was normal, but electroretinograms were not done on these other patients. A locus for myopia has also been reported on 18q.

Common abnormalities found in deletion 18q are nystagmus (35 %) and optic atrophy (28 %) [446]. One review reported that 29 % of patients had fundus abnormalities, but clinical and cytogenetic correlation are not provided [447]. One case with "ocular fundoscopic anomalies" and strabismus was observed, but the specific breakpoint was not given [448]. One author reported 9 of 21 patients with 18q deletion and optic atrophy [449]. Other authors have also cited optic atrophy and retinal abnormalities [450]. Some children with involvement of the critical region may be too young to demonstrate evidence of the retinal disorder. Patients with deletions distal to 18q21.1 region may be diagnosed with retinal dystrophies even well into adulthood [451]. In addition, visual loss may occur as a consequence of abnormalities in visual pathway myelination or gliosis when 18q22 is involved [123, 445, 451]. Either the retinal dystrophy or the visual pathway disorder might be the cause of nystagmus seen in some patients with breakpoints for deletion in the 18q21 region [147, 326].

One patient with del(18)(q21) had esotropia, epicanthus, myopia (−7.00 sphere and −5.00 sphere), microcornea (8 and 5 mm), unilateral opacification of the inferior half of the cornea, iris hypoplasia with full thickness defects and corectopia, peripapillary staphylomas, and straightening of the retinal vessels [444]. Other author reported a patient who also had microcornea (10 mm) associated with del(18)(q23) along with mild nystagmus, and mild bilateral ptosis [443]. Ptosis, exotropia, and mild microcornea have also been reported in other patients with deletions involving this region [147, 443]. Another case with del(18)(q22.3qter) had microcornea with opaque corneas but an otherwise normal eye at autopsy. In a patient with del(18)(q21.3) there was strabismus but no myopia [443]. Patients with terminal or subterminal deletions sharing a del(18)(q21.3) with proximal breakpoints varying from 18q21.3 to 18q21 were reported [147]. No refractions are cited and electroretinograms were not done. In four of the six patients, fundus examinations was described as normal [147]. One case with a normal retina also had nystagmus and strabismus [147]. Another had ptosis with Brushfield-like spots [147]. One child had optic atrophy associated with nystagmus [147]. The only child whose deletion extended proximally to involve 18q21.1 was described to have a normal fundus at 1 year of age but poor visual responses [147]. Choroidal coloboma was present in one child with del(18)(q21qter) [326].

Epicanthus is reportedly variable with other more distal loci [123]. One case had mild exophthalmos, esotropia, ptosis, and epicanthal folds but lacked anterior chamber anomalies and retinal dystrophy suggesting that the patient's deletion did not involved q21.1 [147]. A typical facies may include mild hypotelorism [443].

Duplication 18p

We are unaware of any published reports of pure live born with duplication 18p for which ophthalmic manifestations have been reported.

Duplication 18q

We are unaware of any published reports of pure live born with duplication 18q for which ophthalmic manifestations have been reported.

Trisomy 18

Definition and Epidemiology

Trisomy 18, also known as Edwards syndrome, has a frequency of about 1 in 6000 live births. It is more common in females (3:1). It is associated with increased maternal age [452].

Systemic Manifestations

Almost every organ system is affected. Trisomy 18 is usually lethal. One study reported a 9 % survival at 6 months and 5 % at 1 year, but majority of reports show no survival at 1 year [453].

Frequent anomalies include intrauterine growth retardation, prematurity or post-maturity, congenital heart disease, and a single umbilical artery. Affected patients have an unusual head shape with prominent occiput, narrow bifrontal diameter, and narrow forehead. The mouth is small with micrognathia and a narrow palatal arch. The external ears may be low-set and malformed. Other reported features include inguinal or umbilical hernia, short sternum, small nipples, redundant skin, cryptorchidism, flexion contractures,

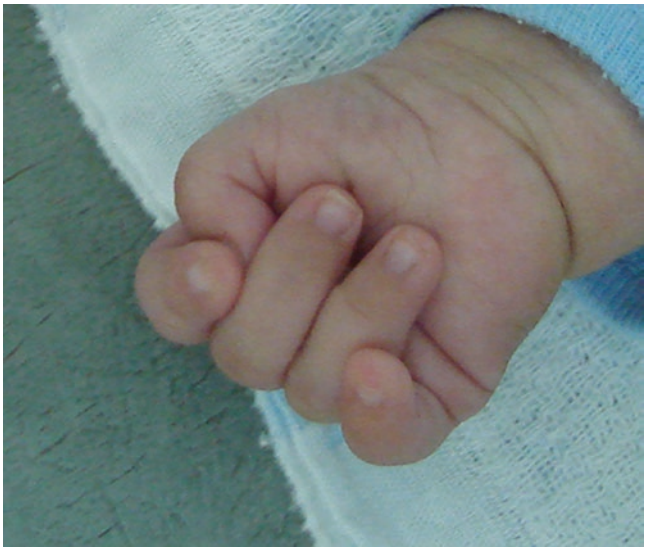

Fig. 6.9 Patient with Trisomy 18 demonstrating clenched hands with overlapping of the index finger over the third and fifth finger, and hypoplasia of the nails (courtesy of Guillermo Lay-Son MD)

scoliosis, clenched hands with overlapping of the index finger over the third and fifth finger, and hypoplasia of the nails (Fig. 6.9) [454].

Ophthalmic Manifestations

Ocular malformations in trisomy 18 are common. The most frequently reported periocular abnormalities include hypoplastic supraorbital ridges, ptosis, blepharophimosis, epicanthus, and hypertelorism. Ankyloblepharon may rarely be seen [455]. Nystagmus, anisocoria, and strabismus have been reported. Common globe abnormalities include corneal opacities, uveal and optic nerve colobomas, optic nerve hypoplasia or gliosis, cataract, ciliary process abnormalities (frequently associated with persistent fetal vasculature), microphthalmia, myopia, and retinal folds. Congenital glaucoma and anterior chamber anomalies have also been observed. Defects of the iris pigment, stroma, sphincter, and dilator can also be present. Hypopigmentation of the retinal pigment epithelium along with focal areas of retinal dysplasia have been observed [456]. Dysplastic retinal rosettes have been reported in an aphakic eye [457]. Choroidal and optic nerve coloboma were present in both the aphakic and microphthalmic phakic eye, the latter having an otherwise normal anterior segment. Congenital unilateral facial paralysis may rarely occur [384].

Trisomy 18 is frequently associated with microphthalmia/anophthalmia [275]. One case had bilateral microphthalmia, unilateral primary congenital aphakia and a markedly dysplastic anterior segment [457]. The cornea had the microscopic appearance of sclera with no surface epithelium, Bowman layer, Descemet membrane, or endothelium. Histopathologic examination showed a grey nodule of fibrous tissue at the ciliary body with vitreous strands attached which the authors suggest might represent a form of persistent hyperplastic primary vitreous (PHPV). Less common findings, such as PHPV and persistent hyaloid artery/tunica vasculosa lentis, retinal dysplasia and Bergmeister papilla have also been reported [383, 458].

Chromosome 19

Deletion 19p

Definition and Epidemiology

Overall, deletions of chromosome 19 are rare [459]. 19p13 is a significant breakpoint.

Systemic Manifestations

Three cases with del(19)(p13.3) presented with hypotonia, cardiac defect, and facial dysmorphism [460]. Del(19)(p13.12) has been associated to multiple congenital anomalies including deafness, bilateral cervical sinuses, congenital cardiac defects, hypoplasia of the corpus callosum, and hypoplasia of the cerebellar vermis [461]. One case with del(19)(p13.3) and Peutz-Jeghers syndrome presented with intellectual disability, hypotonia, and distinctive facial features, including prominent mandible, smooth philtrum, and malformed ears. The 19p13.3 region encompass *STK11*, suggesting an association with this distinctive phenotype [462]. Loss of this gene function induces gastrointestinal polyps. *STK11*-deficient mesenchymal cells produces less TGF-beta, which is associated with epithelial proliferation.

Ophthalmic Manifestations

Three cases with del(19)(p13.3) had mild ptosis and downslating palpebral fissures [460]. Del(19)(p13.12) has been described with lacrimal duct stenosis and strabismus [461].

Deletion 19q

We are unaware of any published reports of pure live born with deletion 19q for which ophthalmic manifestations have been reported.

Duplication 19p

Definition and Epidemiology

Rearrangements involving chromosome 19, either duplications or deletions, have rarely been reported in the literature. Seven patients with pure 19q trisomy, and 28 patients with other chromosome aberrations, have been published [463].

Systemic Manifestations

Main clinical manifestations in partial 19q trisomy include low birth weight, short stature, abnormal ears, short neck, intellectual disability and seizures [463]. One case of interstitial dup(19)(p13.13p13.2) [459] had developmental delay and severe congenital heart defects. Occipital flattening, bifrontal prominences, a wide and high nasal bridge with an obtuse frontonasal angle, and absence of the fleshy inferior border of the nostrils were among the facial anomalies. Mild retrognanthia, along with a prominent vertical ridge at the mental symphysis, and a raised midline ridge on the anterior tongue were also reported. Toe and finger nails appeared to be short and convex, while both clinodactyly and camptodactyly of the toes existed. One patient with dup(19)(q13.33qter) had recurrent urinary tract infections, bronchopneumonia episodes, urolithiasis and anemia [463]. She also had moderate neuromotor developmental and speech delay, seizures, and non-quantified intellectual disability. Her main dysmorphic features were short stature, ocular hypertelorism, downturned corners of mouth, posteriorly rotated ears, prominent antihelix, short neck, clinodactyly of the 5th fingers, and thoracolumbar scoliosis [463].

Ophthalmic Manifestations

The patient with dup(19)(p13.13p13.2) presented with scant eyebrows, upslanted palpebral fissures, S-shaped lower eyelids, prominent globes with blue sclera, and intermittent exotropia [459]. The case with dup(19)(q13.33qter) had ocular hypertelorism [463].

Duplication 19q

We are unaware of any published reports of pure live born with duplication 19q for which ophthalmic manifestations have been reported.

Chromosome 20

Deletion 20p

Definition and Epidemiology

Alagille syndrome, also known as arteriohepatic displasia, is an autosomal dominant single gene disorder, due to mutations in the *JAG1* gene located at 20p11.23-12 region. Approximately 7 % of patients with Alagille syndrome will have a demonstrable del(20)(p11.23p12) [464]. The estimated prevalence of Alagille syndrome is 1 in 70,000 newborns.

Systemic Manifestations

Three of the following five primary clinical criteria are needed to diagnose Alagille syndrome: cholestasis, characteristic facies, posterior embryotoxon, butterfly vertebrae (hemivertebrae), and cardiac malformation (most frequently pulmonary tree stenosis) [464]. When deletions are present, all five findings are usually present [464], and also hearing disorders and developmental delay. The characteristic facies includes triangular chin, prominent forehead, long straight nose with flat tip, and flat midface. Notched nasal alae may also be observed [464]. Renal and neurodevelopmental anomalies are less frequent. The cholestasis may require surgical intervention.

Ophthalmic Manifestations

When the Alagille phenotype is associated to del(20)(p11.23p12), distinguishing features may include posterior embryotoxon, iris adhesions, and pigmentary retinal dystrophy. Ophthalmological examinations of three Japanese siblings, a 14-year-old girl, an 11-year-old boy, and a 9-year-old girl with revealed that they had posterior embryotoxon, refractive error, retinochorodial degeneration, and electrophysiological abnormalities. The two sisters had retinochoroidal degeneration and unilateral high myopia while the brother showed marked retinochoroidal degeneration with extensive pigment clumps. Visual fields showed moderate concentric contraction in the two sisters and marked concentric contraction in the brother. Amplitudes of the single flash electroretinogram were moderately reduced in the sisters, the test was nonrecordable in one eye and extensively reduced in the other eye of the brother. Visual evoked cortical potential were abnormal in the high myopic eye in each of the two sisters [465]. The IDH3B gene, which when mutated caused autosomal recessive retinitis pigmentosa is located outside the Alagille region at 20p13. A candidate gene in the Alagille region, *Plcb4*, is known to block invertebrate phototransduction leading to a retinal degeneration [464]. Irregularly shaped and sized pupils, and coloboma of the iris consistent with Axenfeld-Rieger spectrum, may be seen [466]. Strabismus can occur. Facial features include deep-set eyes, hypertelorism and short, downslanting palpebral fissures with epicanthal folds[464, 467]. Progressive bilateral chorioretinopathy with severe deterioration in visual acuity have been reported [468].

Deletion 20q

Definition and Epidemiology

Pure deletion of the long arm of chromosome 20 is uncommon.

Systemic Manifestations

Anomalies associated with del(20)(q11.2q12) include asymmetric intrauterine growth retardation, bilateral inguinal hernias, and bilateral talipes equinovarus [469]. Individuals may also have recurrent vomiting, regurgitation, and choking.

Facial dysmorphies include a large and high forehead, mild metopic ridging, a small triangular face, depressed nasal bridge, hypertelorism, protruding well-formed ears, mildly prominent anteverted nose with hypoplatic alae nasi and a long and smooth philtrum [469]. Neurological abnormal manifestations include mildly exaggerated deep tendon reflexes and an increased muscle-tone around the hips leading to difficulty in hip extension. Brain atrophy with enlargement of the cerebral spinal fluid spaces and hypomyelination have also been described [469]. One case with del(20)(q13.33) had speech delay, joint laxity, flat feet, and was overanxious [470]. One patient with del(20)(q11.21q11.23) presented with feeding problems and skeletal abnormalities [471].

Ophthalmic Manifestations

Microphthalmia and bilateral Duane syndrome have been observed with del(20)(q11.2q12) [469]. The *SALL4* gene, which whne mutated results in Duane syndrome, is located at 20q13.2. The patient with del(20)(q13.33) presented with esotropia, hyperopia, and astigmatism [470]. One patient with del(20)(q11.21q11.23) presented with retinal dysplasia [471].

Ring 20

Definition and Epidemiology

Mosaic Chromosome 20 ring is a chromosomal aberration that has been associated with a rare syndrome characterized by a typical seizure phenotype [472, 473]. Over 60 cases have been reported in the literature, mostly sporadic. The pathogenic mechanism underlying the seizures disorder in chromosome 20 ring syndrome is still unknown. Epilepsy genes *CHRNA4* and *KCNQ2* have been proposed as candidates [472, 473].

Systemic Manifestations

Complex partial seizures, a particular electroclinical pattern, cognitive impairment, behavioural problems and absence of a consistent pattern of dysmorphology defines chromosome 20 ring. The development is generally normal or mildly delayed but it can be followed by cognitive and behavioural declinement after seizures indicating that the clinical manifestations could be interpreted as an epileptic encephalopathy. The ring chromosome 20 syndrome represents a good example of a chromosomal aberration in which epilepsy can be the only expression of the disorder which can be easily diagnosed by molecular techniques. Epilepsy manifests in more than 90 % of cases, an it presents as refractory complex partial seizures, nocturnal frontal lobe seizures and non-convulsive status epilepticus. Rare cases of chromosome 20 ring present microcephaly, plagiocephaly, synophrys, genital hypoplasia, micrognathia, cauliflower-shaped ears, and coarse facial features [472, 473].

Ophthalmic Manifestations

Eyelid myoclonia and slanting eyelids have been reported in patients with chromosome 20 ring [472, 473].

Chromosome 21

Deletion 21p

We are unaware of any published reports of pure live born with deletion 21p for which ophthalmic manifestations have been reported.

Deletion 21q

Definition and Epidemiology

Pure deletion 21q is uncommon, with few cases reported in the literature.

Systemic Manifestations

Facial dysmorphism in 21q1 monosomy presents with beaked nose, high nasal bridge, wide glabella, micrognathia, midline alveolar notching, cupped ears, preauricular tags, and a midline raphe through the philtrum. Congenital heart disease, genitourinary anomalies, rib malformations, and vertebral abnormalities may also be seen. Mild abnormalities of the hands, in particular a hypertonic overlapping of the fingers have been reported [474]. A patient with del(21)(q22.3) presented with frontonasal dysplasia, callosal agenesis and basal encephalocele [475].

Ophthalmic Manifestations

Severe microphthalmia has been reported 21q1 monosomy. One case with del(21)(q22) had severe microphthalmia and cloudy corneas [474]. A patient with del(21)(q22.3) presented with hypertelorism and ptosis [475].

Duplication 21p

We are unaware of any published reports of pure live born with duplication 21p for which ophthalmic manifestations have been reported.

Trisomy 21

Definition and Epidemiology

Trisomy 21, also known as Down syndrome, is the most common chromosomal aberration in living children. The term "mongolism" is no longer accepted. It was originally used to describe patients due to their facial similarity to individuals of

Mongoloid descent and a erroneous concept about a racial association [476]. The most frequent cause of Down syndrome is trisomy of chromosome 21 (92 %–95 %), followed by translocation involving choromosome 21 (3 %–4 %) and mosaicism (1 %–4 %) [476, 477]. In complete trisomy 21, the origin of the extra chromosome is almost always maternal. Approximately 50 % of all translocations that lead to Down syndrome are spontaneous events whereas the reminder are due to balanced translocation [476]. The critical area associated with Down phenotype is 21q22 region although there are several genes in this region.

Down syndrome occurs approximately 1 in 800 live births [476, 477]. Congenital ocular abnormalities at birth are frequent [1]. The recurrence risk for parents who already have an affected child is empirically estimated to be 1 % [477]. Increasing maternal age is associated with an augmented risk of having a child with trisomy 21.

Systemic Manifestations

Spontaneous abortion occurs in approximately 75 % of affected fetuses. Survival rate for liveborns with trisomy 21 is variable, depending mostly on the presence of comorbities. The highest chance of death occurs in the first year of life (9 % overall, 24 % of those with congenital heart disease) [478, 479]. Survival is lower than that of other mentally retarded patients [478]. Less than 50 % of children with congenital heart disease will be alive at 30 years. Nevertheless, if a patient with trisomy 21 and congenital heart disease survives beyond 10 years, the rate of subsequent mortality does not differ from those without heart disease [478]. With care improvement, children with Down syndrome now have an improved life expectancy, and the total population is expected to grow substantially. The median age at death of individuals has risen significantly from 25 years in 1983 to 49 years in 1997 [479]. The fall in mortality has been associated to the successful early surgical treatment of congenital heart disease and to the improved treatment of congenital anomalies of the gastrointestinal tract.

The most identifiable features of Down syndrome are the characteristic facies and variable degree of mental retardation. Patients typically have a flattened facies with midfacial hypoplasia and depressed nasal bridge, small ears and mouth, prominent tongue (true macroglossia is infrequent although the normal tongue is relatively large compared to the airway), brachycephaly, flattened occiput, and a narrow palate with prominent ridges. Children with trisomy 21 could also have redundant skin on the nape of the neck, brachydactyly with fifth finger clinodactyly, a single palmar crease and abnormal dermatoglyphics [476, 479]. Affected patients tend to have short stature and alternative growth charts are available for comparison [476, 479]. Other neurologic problems can occur as well, including seizures and Tourette syndrome [476, 479]. Psychiatric disorders may occur in adolescence. Affected individuals with Down syndrome also have a predisposition to the development of Alzheimer disease in the fourth and fifth decade of life.

Congenital heart disease is the main life threatening systemic manifestation of Down syndrome, although many children are not symptomatic as neonates [476, 479, 480]. It occurs in about 40 %–50 % of patients, of which approximately 30 %–60 % have a complete atrioventricular canal and an additional half will have other malformations, including atrial septal defects, ventricular septal defects, and/or atrioventricular valvular abnormalities [476, 479, 480]. Patent ductus arteriosus, tetrology of Fallot, and mitral valve prolapse also occur with greater frequency [476, 479].

During the first year of life, common causes of death are congenital anomalies, respiratory infection, particularly pneumonia, systemic infections of other origin or perinatal complications [477, 479]. Between 1 and 10 years of age, congenital heart disease and respiratory infection still are the major causes of death [477, 479]. Leukemia [481], and lymphoma, can also occur in this age range where they have their highest effect on mortality rates [476, 480]. Other conditions such as diabetes mellitus, intestinal obstruction, and renal disease may also contribute to morbidity and mortality during adolescence [472, 479].

Gastrointestinal problems include duodenal atresia, tracheoesophageal fistula, Hirschsprung disease, and imperforate anus. These must be suspected in children with feeding problems or constipation. Genitourinary anomalies include obstructive hydronephrosis, renal dysfunction, hypospadias and cryptorchidism [476, 479]. Children with trisomy 21 have an increased risk of autoimmune conditions, such as thyroiditis or alopecia areata [476, 479]. Congenital hypothyroidism may also be seen.

Airway problems are also important and may present issues during anesthesia. Obstructive sleep apnea and chronic daytime fatigue may occur [476]. The airway, and the spinal cord, may also be at risk because of cervical subluxation or dislocation due to ligamentous laxity and hypotonia (atlantoaxial instability). Pulmonary hypertension with or without cardiac disease may occur as well. Dental anomalies and malocclusion are not infrequent.

Ophthalmic Manifestations

In a prospective cohort of 90 infants with Down Syndrome, up to 50 % had ocular abnormalities [482]. Upward slanting of the palpebral fissures and epicanthal folds are almost always present. In one study, epiphora was described in 15 % of patients, but only one third of these had evidence of nasolacrimal duct obstruction [483]. Epiphora may be related to orbicularis hypotonia thus creating and inefficient pump mechanism [484]. Other causes of epiphora include floppy lid syndrome, blepharitis or lacrimal sac fistula. Chronic xeroderma can be present in up to 90 % of children [476] and chil-

dren with dry skin or eczema affecting the periorbital area and eyelids have also been described. Syringoma may be observed with greater frequency in patients with trisomy 21 [476].

Children with trisomy 21 have a high frequency of refractive error. Approximately 20 % of affected children will have greater than one diopter (D) of astigmatism, 20 % will have greater than 1D of myopia, and 20 % will have greater than 3D of hyperopia [477]. In one study, 2 % of patients with Down syndrome had high astigmatism (>3D), 8.5 % had high myopia (>5D), and 5 % had high hyperopia (>5D) [483].

Strabismus is also frequent in patients with Down syndrome (33 %–57 %) [483, 485]. Of the children with strabismus, about 15 % have anisometropia. Approximately 80 % have esotropia and 5 %–20 % show exotropia [483]. Although the majority of exotropic patients may be hyperopic (35–50 %), up to 12 % are high myopes [483]. Exotropic patients may be either myopic or hyperopic. High accommodative convergence to accommodation ratio has also been described. Hypertropia occurs in approximately 5 % of individuals and may be due to congenital superior oblique palsy, dissociated vertical deviation, or Brown syndrome [486]. Anisometropia and an A or V pattern are also frequent. Other studies describe head tilts in 19 % of children with Down syndrome of which only 17 % had vertical deviations [483]. Twenty-five percent of patients had an abnormal head posture in another large cohort [487]. Anomalous head positions may be due to strabismus, nystagmus or cervical neck issues. The results of standard medical and surgical strabismus treatment in children with Down syndrome are the same as those with normal children. In a 17 patient cohort, good surgical outcomes were achieved in children with esotropia and Down syndrome compared with those with esotropia but without Down syndrome using the same surgical technique [488].

A prospective cross-sectional study investigated the association between visual acuity deficits and fixation instability in children with Down syndrome and nystagmus. Visual acuity was 0.2–0.9 logMAR (20/30-20/174 Snellen equivalent) and corresponded to a 0.4 logMAR (4 lines) mean age-corrected visual acuity deficit. Fixation stability ranged from poor to mildly affected. They concluded that nystagmus alone could account for most of the visual acuity deficit in patients with Down syndrome [489]. A 29 % incidence of nystagmus was described in an outpatient ophthalmology setting, but nystagmus was not characterized [483]. A recent review reports nystagmus in 11 to 29 % [479].

Down syndrome patients may develop keratoconus [490]. Keratoconus is rare in childhood but develops later in life [479]. One study used videophotokeratoscopy to describe subclinical signs of keratoconus in almost all, perhaps suggesting the presence of a genetic predisposition to the development of keratoconus [491] although it have been suggested that the etiology may be related to eye rubbing perhaps associated with atopy. One study measured corneal thickness and found that these children had lower corneal thickness compared to controls, hypothesizing that this could be an early sign of keratoconus [492]. The superoxide dismutase gene, *SOD1*, which when mutated is a cause of autosomal dominant keratoconus, is located at 21q22.1 region.

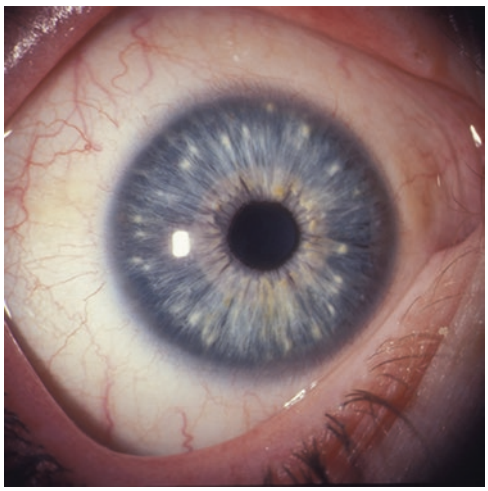

Fig. 6.10 Brushfield spots of iris in patient with trisomy 21 (Courtesy of Dr E. Jaeger)

One of the most characteristic ocular findings of Down syndrome are Brushfield spots (Fig. 6.10). These occur in approximately 30 % of patients, being more prevalent in those with blue or hazel irides [490]. Peripheral iris stromal hypoplasia has also been noted in Down syndrome with or without Brushfield spots [490].

The risk of cataract in children with Down syndrome is about 300 times higher than the general population [493]. The cumulative incidence of all types of lens opacities is approximately 20 % [490], but there is a wide variability in opacity type ranging from visually significant dense total congenital cataract to visually insignificant cortical cataract in adulthood [490] (Fig. 6.11). In a large surveillance study, the incidence of cataract at birth was 2.9 per 1000 patients with Down syndrome [493]. One study described cortical "snowflake" opacities in 10 % of their patients and dense cataracts in 2 % [477]. Posterior lenticonus has also been reported [494]. Bilateral lens subluxation may rarely occur [483]. Premature development of nuclear sclerosis may occur as part of the overall precocious aging seen in these children. A recent review reports congenital cataract 4–7 % of patients with Down syndrome and acquired cataract in 3–15 % [479].

Other ocular malformations and retinal findings are less common. There have been isolated reports of retinal detachment (without refraction data) as well as unilateral optic atrophy with accompanying clinical signs of unilateral retinitis pigmentosa [490]. No further details are given to allow analysis and this may represent an chance association. A characteristic "spoke wheel" optic nerve head may be observed in some patients (Fig. 6.12). The vessels radiate out from the disc at multiple clock hours. There is also an increased

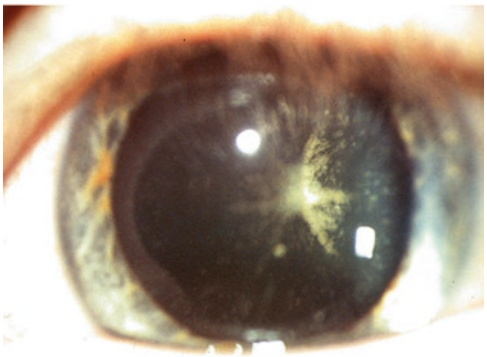

Fig. 6.11 Note snowflake cortical cataracts characteristic of Down syndrome and also posterior subcapsular cataract

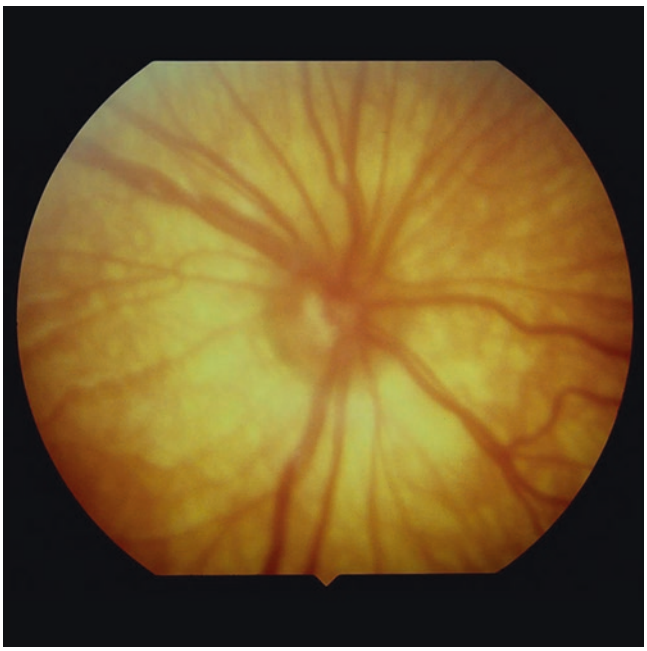

Fig. 6.12 Down syndrome optic nerve. Note straightening and radial configuration of vessels with increased number crossing disc edge

number of vessels crossing the disc edge due to early branching. Optic nerve hypoplasia, pseudopapilledema/crowded disc, and myopic tilted disc may also be seen. Microphthalmia or anophthalmia may rarely happen [275].

Cosmetic intervention has generated much controversy over the years and may or may not result in improved appearance, developmental functioning, behavior, or social/family acceptance [476]. The appearance of the eyes affects parental perception of syndromic status more than any other feature except the relative macroglossia and articulation [495]. Lateral canthoplasty to lower the position of the lateral canthal tendon and thus normalize (or "Westernize") the palpebral fissure slant is usually successful in improving parental perception of appearance although 50% of the operating surgeons in one study were dissatisfied with the result [495].

Based on the high prevalence of ophthalmic abnormalities, the American Academy of Pediatrics [496] recommend that within the first 6 months of life, patients should be referred to evaluate for strabismus, cataracts, lacrimal duct obstruction and nystagmus. Between years 1–5, patient should be seen annually because children with Down syndrome have a 50% risk of refractive errors that lead to amblyopia between 3 and 5 years of age [496]. Addressing refractive errors and strabismus at an early age can help prevent amblyopia and encourage normal visual development. Between 5 and 13 years old, an ophthalmologic evaluation should be performed every 2 years [496]. Finally, above 13 years old, at least an evaluation every 3 years, to check for onset of cataracts, refractive errors, and keratoconus, which can cause blurred vision, corneal thinning, or corneal haze and is typically diagnosed after puberty [496].

Ring 21

Definition and Epidemiology

Ring 21 can be explained because of asymmetric breakage and reunion of 21q sequences from an intermediate isochromosome or Robertsonian translocation chromosome.

Systemic Manifestations

One patient with ring 21 had facial dysmorphism, low set ears, hypotonia, wide spaced nipples, and skin alterations [497].

Ophthalmic Manifestations

Peters' anomaly was reported in a child with ring 21 [497]. Other reported eye abnormalities have included enophthalmos, down-slanting palpebral fissures, strabismus, microphthalmia, anterior segment dysgenesis, and epicanthal folds.

Chromosome 22

Deletion 22p

We are unaware of any published reports of pure live born with deletion 22p for which ophthalmic manifestations have been reported.

Deletion 22q

Definition and Epidemiology

A 3 Mb deleted region at 22q11.2 is known to be associated with a spectrum of phenotypes including DiGeorge sequence (DGS), velocardiofacial syndrome (VCFS), conotruncal

anomalies face syndrome (CTFA), Sedlackova syndrome, CHARGE and Cayler syndrome. Variable expression can occur even within the same family [498–500]. The prior acronym for this deletion, CATCH 22 (cardiac, abnormal facies, thymus hypoplasia, cleft palate, hypocalcemia) syndrome, should not be used, as it may be perceived as pejorative.

Del(22)(q11.2) is the most common chromosomal aberration other than trisomy 21 seen in clinical cytogenetic laboratories examining specimens on live patients. 22q11.2 deletion syndrome affects an estimated 1 in 4000 newborns.

Systemic Manifestations

The DiGeorge sequence includes absent or hypoplastic thymus, hypocalcemia due to hypoparathyroidism, conotruncal heart anomalies, a characteristic facies (Fig. 6.13a, b), and possible developmental delay. VCFS involves velopalatal insufficiency and/or cleft palate, conotruncal heart anomalies, facial dysmorphism, and learning disability. CTAF describes patients with only conotruncal heart anomalies, facial dysmorphism, and developmental delay. Sedlackova syndrome consists of a congenitally short palate, while Cayler syndrome indicates the association of asymmetric crying facies with heart anomalies. The common facial appearance in these disorders is characterized by mildly dysplastic ears, a laterally built-up nose with bulbous tip, and small jaw [500]. Phenotypes range from lethal DGS to individuals with only mild developmental delay and subtle facial dysmorphism with other more serious malformations. Long tapered fingers and other minor limb malformations may be seen [500–502]. An arthropathy may be associated as well [503].

Del(22)(q11.2) is one of the most common microdeletion syndromes. Loss of *TBX1* is considered an important cause of the phenotype. A few patients with smaller, overlapping deletions distal to *TBX1* locus have been described, where the *CRKL* gene is located. Haploinsufficiency of *CRKL* alone has also been associated in del(22)(q11.2) syndrome. One study reviewing 52 patients reports that the prevalence of congenital heart anomalies and the frequency of *de novo* deletions in patients with a central deletion are substantially lower than in patients with del(22)(q11.2). Renal and urinary tract malformations, developmental delays and cognitive impairments seem to be equally frequent as in patients with a common deletion. Patients with a deletion that also encompasses *MAPK1* have a more severe phenotype, characterized by a higher frequency of congenital heart anomalies, growth restriction and microcephaly [504]. A case with del(22)(q11.2) syndrome presented with craniosynostosis, microcephaly, midface hypoplasia, broad nasal bridge, high palate and low set ears, imperforate annus and hypoplastic thumb [505].

Ophthalmic Manifestations

The facial appearance of del22q11 includes "lateral displacement of the outer canthi" (increased outer canthal distance in the absence of hypertelorism) [500]. In one study, 90 patients with del(22)(q11.2) had ophthalmological assessment. The authors found posterior embryotoxin (49 %), tortuous retinal vessels (34 %), upper eylid "hooding" malformation (20 %), strabismus (18 %), ptosis (4 %), amblyopia (4 %) and tilted optic nerves (1 %) [506]. Autoimmunity is a known phenomenon in del(22)(q11.2), although uveitis is very rare [507].

One patient with Waardenburg syndrome resulting from del(22)(q12.3q13.1) involving *SOX10* had iris heterochromia in addition to developmental delay, profound bilateral sensorioneural hearing loss, hypotonia and bilateral finger contractures [508]. A patient with del(22)(q11.2) presented with proptosis and sparse eyebrows [505].

Duplication 22p

We are unaware of any published reports of pure live born with duplication 22p for which ophthalmic manifestations have been reported.

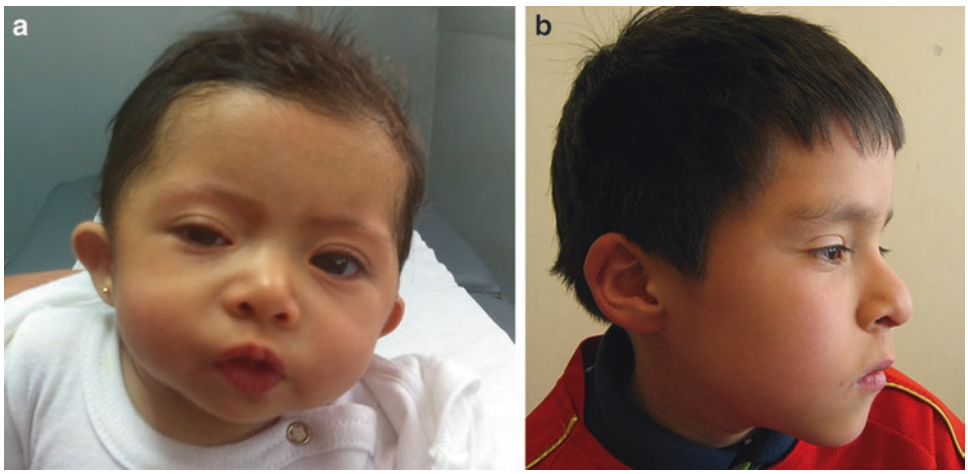

Fig. 6.13 (**a**), (**b**) Two patients with common facial appearance in del(22)(q11), characterized by mildly dysplastic ears, a laterally built-up nose with bulbous tip, and small jaw (courtesy of Guillermo Lay-Son MD and Mariana Aracena MD)

Duplication 22q

Definition and Epidemiology

22q duplication is an infrequent chromosomal abnormality. Duplications of the proximal segment of chromosome 22q causing cat eye syndrome, and 22q11.2 microduplication syndrome are more common than 22qter duplication.

Systemic Manifestations

One case with dup(22)(q13.2qter) had hypotonia, retarded growth, cleft lip and palate, hearing loss, seizures, developmental delay and abnormal teeth [509]. MRI showed mild abnormalities.

Ophthalmic Manifestations

Dup(22)(q13.2qter) may also result in hypertelorism [509]. Exotropia was present in one child with dup(22)(q13.2qter) [509].

Trisomy 22

Definition and Epidemiology

Complete trisomy of chromosome 22 must first be distinguished from partial trisomies, in particular the Cat Eye syndrome (CES), which may have similar ocular findings [500]. Mosaicism may also occur fluid [501]. Pericentric inversion may result in partial trisomy for the distal end of 22q [509]. Trisomy 22 is responsible for almost 2 % of all chromosome aberrations associated with microphthalmia [275]. Less than 16 cases of mosaic trisomy 22 have been reported.

Systemic Manifestations

Trisomy 22 is most often lethal either antepartum or in the immediate post partum period [510]. Only one of every 1450 fetuses conceived with trisomy 22 is carried beyond 20 weeks of gestation [510]. Congenital cardiac anomalies and related respiratory disease are the most common cause of death, usually in infancy [36].

With complete trisomy, the fetus usually exhibits intrauterine growth retardation and premature birth [510]. In live born children, abnormal facial features characteristically include dysmorphic ears, small ovoid mouth, preauricular pits, and cleft palate. Rocker-bottom feet, ankyloglossia, hypoplastic nails, and single palmar creases have also been reported. Variable cardiac, gastrointestinal, pancreatic, genitourinary, and central nervous system malformations have been reported although these brain abnormalities are not constant findings despite the usual presence of microcephaly.

Children with mosaicism may also be severely affected. One small-for-gestational-age infant was reported with pulmonary stenosis, developmental delay microcephaly, and dysmorphic features including preauricular pits, protruding upper lip, and hypoplastic toenails [511]. Unexplained eosinophilia was also present.

Ophthalmic Manifestations

In complete trisomy 22, the major reported malformation is retinochoroidal coloboma with or without microphthalmia [510]. The optic nerve is often involved and may be hypoplastic.

Epicanthal folds, hypertelorism, and proptosis have been described in one infant [510] and are seen in over 40 % of mosaic infants. Both down-slanting or up-slanting fissures have been reported along with synophrys, ptosis [512].

Other uncommon reported findings include defects in Bowman membrane with thin epithelium and stroma, stromal vascularization, limbal dermoid, anomalous angle morphology, cataract, inferior lens subluxation, and ris hypoplasia [510]. One child had an unusual bifid iris with the posterior leaflet extending posteriorly into the retinochoroidal colobomatous cyst [510]. Retinal dysplasia with rosette formation may be present. PFV has been documented histologically [510].

Exotropia is observed in over 40 % of reported cases with mosaic trisomy 22 [512]. Double elevator palsy has also been noted [513].

Supernumerary 22q

Definition and Epidemiology

The cat eye syndrome (CES) phenotype is associated with a supernumerary marker chromosome derived from 22q with an inverted duplication in the marker resulting in tetrasomy of all or part of 22q [514]. Some patients can have a normal phenotype especially when only trisomic for 22q or when the marker only contains pericentric duplicated material [514].

Systemic Manifestations

The CES phenotype may include cleft palate, anorectal anomalies, preauricular pits, congenital heart disease (particularly Tetralogy of Fallot), sensorineural and conductive hearing impairment, hemivertebrae, cryptorchidism, and failure to thrive [514, 515]. One case with developmental delay and hypotonia and seizures [514]. One case was reported with an inverted duplicated extra chromosome 22 and some features thought to be part of CES [515]. However, this patient did not have anal atresia or coloboma. The patient had blood mosaism (40 %) for the marker chromosome (but 100 % affectation of skin fibroblasts). A patient with dup(22)(qter) presented with pituitary hypoplasia [516].

Ophthalmic Manifestations

The name of the syndrome reflects the frequent (but not absolute) association with iris coloboma. The coloboma can involve the posterior segment with or without iris involvement.

Oculofacial features include down-slanting palpebral fissures and epicanthal folds [506]. Various forms of Duane syndrome have been reported and suggest the possibility of an

important gene on 22q [514]. One case had poor fixation and following for age [505]. Esotropia has been also reported [517].

A patient with dup(22)(qter) presented with oculofacial findings, including deep set eyes and hypertelorism [516].

X Chromosome

Fragile X Syndrome (Martin-Bell Syndrome)

Definition and Epidemiology

Four fragile sites are associated on the X chromosome: FRAXA, FRAXD, FRAXE, and FRAXF. Fragile sites are caused by a hypermethylated expansion of either a CCG or CGG repeat the size of which determines the range from normality, to carrier, to affected. Hypermethylation switches off transcription of the gene [518, 519]. The same effect may result from a deletion of the gene or a mutation within the gene [520]. The concept "folate sensitive" is frequently applied to the fragile sites reflecting cytogenetic detection techniques which either limit the availability of folic acid or interfere with thymidylate production necessary for DNA replication [521]. A fragile site at Xq27.2 or lesions at Xq26 can be present in normal patients and developmentally delayed individuals under these conditions, but are not diagnostic of the syndrome [521]. Chromosome analysis for Fragile X syndrome (FXS) is obsolete in the clinical setting, replaced by molecular techniques to quantify the trinucleotides repeats. Approximately over 200 CGG repeats causes fragile X syndrome, as compared with 55 to 230 repeats in carriers and 5 to 54 repeats in unaffected individuals. In this section the term FXS will refer to FRAXA unless otherwise denoted.

FXS is the most common cause of hereditary mental retardation [522]. The incidence of FXS is between 1:1200 and 1:4000 [519]. Since males have only one X chromosome, they are more susceptible to the effects of fragile X. Nearly all cases of fragile X syndrome are caused by expansion of the CGG trinucleotide repeat in the *FMR1* gene, which encodes FMRP protein. As a result of CCG expansion, *FMR1* gene is methylated, which silences the gene and may lead to severe learning deficits or mental retardation, along with other clinical abnormalities seen in fragile X syndrome. Less than 1 % of all cases of fragile X syndrome are caused by point mutations or deletions affecting *FMR1* gene. Studies based on testing *FMR1* have estimated a prevalence of 16 to 25:100,000 males affected with the fragile X syndrome

Females may become heterozygotes for the fragile X by inheriting the abnormal chromosome from either parent. As female heterozygotes also have a normal X chromosome, they are more "protected" from the effects of the fragile X with a higher percentage of unaffected carriers than males [523]. Up to 70 % of females have a non penetrant fragile site [522]. The expression of the fragile X in females may be in part dependent upon Lyonization [523].

Systemic Manifestations

Fragile X syndrome has very variable expressivity. Nearly 10 % of prepubertal boys with fragile X may have IQ's in the borderline to low normal range [524]. However, some children will have IQ's below 20 [522]. Approximately one third of fragile X positive females may function as normal or borderline normal [523].

It has been described that more severely affected patients may present autism, attention deficit disorders, self abusive behavior, hyperactivity, temper tantrums and language anomalies [522–524].

Facial appearance in patients with fragile X syndrome is characterized by large ears, broad nasal bridge, long prominent chin, and narrow face. Dental anomalies and a flat occiput are also frequent findings [522]. Nearly 90 % of individuals present joint hypermobility. Males have large testes. In girls, the only physical characteristics are prominent ears and a long face [523].

FRAXE syndrome is characterized by borderline to mild developmental delay which may manifest with learning difficulties, regardless of whether it is caused by an *FMR2* deletion or a CCG expansion [518].

Ophthalmic Manifestations

Visual motor integration is delayed [524]. Several authors have reported "gaze avoidance" behaviors with poor eye contact [522, 524]. Patients with fragile X-associated tremor/ataxia syndrome may present with a progressive supranuclear palsy-like phenotype and other eye movement abnormalities [525] There are no consistent ocular malformations, although strabismus has been reported in up to one third of patients.

Monosomy X (Turner Syndrome)

Definition and Epidemiology

Turner syndrome, also known as gonadal dysgenesis, and 45,X, is a condition in which a female is partly or completely missing an X chromosome. The estimated incidence is 1 in 2500 girls.

Systemic Manifestations

Turner syndrome is characterized by short stature, ovarian hypofunction with infertility and amenorrhea, wide spaced nipples, cubitus valgus and webbed neck (30 %). The ovaries develop normally at first, but oocytes typically die prematurely and most ovarian tissue degenerates before birth. Many affected girls do not reach puberty unless they receive hormone therapy, and most of them are considered infertile. Other findings include low hairline at the back of the neck, infantile lymphedema of the hands and feet, skeletal abnormalities, or kidney problems. About 30 to 50 % of individuals with Turner syndrome are born with a heart defect, such

as coarctation of the aorta or aortic valve abnormalities. Most patients with Turner syndrome have normal intelligence, although developmental delays and behavioral problems are possible. There is also an association with gonadal tumors and neuroblastoma, diabetes, thyroid dysfunction and deafness [526–528].

Ophthalmic Manifestations

Reported ocular problems are cataract, ptosis, corneal opacity, "recurrent ocular infections" [529], nystagmus and glaucoma. In a literature review that included 274 patients with Turner syndrome, other ophthalmic findings were accommodative insufficiency (40 %), epicanthus (35 %), strabismus (33 %), amblyopia (29 %), hyperopia (27 %), ptosis (21 %), myopia (13 %), nystagmus (9 %), presenile cataract (3 %), blue sclera (2 %), and congenital glaucoma (1 %) [527]. The frequency of red-green color deficiency was comparable to that found in normal males [527]. Other reported findings have included conjunctival lymphedema, keratoconus, uveitis, anterior segment dysgenesis, exudative retinal detachment and subfoveal choroidal neovascularization [527, 530–532].

In a recent review, eye disorders were diagnosed in nearly 50 % of patients, with 35 % patients having multiple eye defects. Refractive problemas were the most common with 44 %, followed by strabismus in 21 % of cases. Less commonly, changes in the posterior eye segment (6 %), red-green colour deficiency (5 %), changes in the anterior eye segment (5 %) and nystagmus (4 %) were also described. Amblyopia was present in 13 patients (16 %). The most frequent combinations of ophthalmological defects were hypermetropia and astigmatism. The authors couldn't establish an association between the presence of eye defects and karyotype [533]. A 25-year-old woman with a history of Turner syndrome diagnosed at 15 years of age inferior conjunctivalization of the corneal epithelium consistent with limbal stem cell deficiency [534]. Another case, a 23-year-old woman with the Turner syndrome was referred for rosacea keratitis. An ocular assessment revealed significant conjunctivalization with epithelial scarring and opacity, also consistent with limbal stem cell deficiency [534]. Increased central corneal thickness (CCT) has also been described in patients with Turner syndrome [535] The mean CCT values were 582.0 ± 40.8 μm [489–547] in patients with Turner syndrome and 549.1 ± 34.6 μm (494–601) in the healthy group. The mean CCT value was significantly higher in the Turner syndrome group ($p < 0.05$) but there was no statistically significant difference between the 2 groups for intraocular pressure ($p > 0.05$) [535]. A 13-year-old girl with 45,X Turner syndrome had Axenfeld-Rieger spectrum [536]. A 6-year-old girl with Turner syndrome had left divergent strabismus and tractional retinal detachment in the left eye, with a temporal avascular area with neovascularization at the junction with the vascular area. Examination was characteristic of familial exudative vitreoretinopathy [537]. Four patients with mosaic Turner had anterior segment dysgenesis. Three presented with congenital glaucoma and the remaining child had a Rieger malformation [538].

Deletion X

Definition and Epidemiology

Any kind of genomic imbalance, deletions or duplications of an X chromosome have a much more severe consequence on males than females [539, 540]. In males, most frequent deletions of the X chromosome involve the terminal portion of Xp (Xp22.2-Xpter), which cause contiguous gene deletion syndromes. The clinical manifestations depend on the extent and position of the deletion, showing the variable association of apparently unrelated phenotypes such as Leri-Weill dyschondrosteosis (*SHOX*), chondrodysplasia punctata (*CDPX1*), mental retardation (*NLGN4*), ichthyosis (*STS*), Kallmann syndrome (*KAL1*), or ocular albinism (*GPR143*) [540]. The extent of terminal Xp deletions is defined by male lethal genes in Xp22.2 at approximately 10–11 Mb from the telomere [540]. The majority of the deletions in viable reported males extended to the *STS* or to the *KAL1* locus [540]. Larger Xp deletions extending beyond the *KAL1* or OA1 locus are very rare [540].

Systemic Manifestations

Two cases were reported having a del(X)(p22.2) and congenital nasal pyriform aperture stenosis, a rare malformation that may present with cyclic respiratory distress relieved with crying, noisy breathing, feeding difficulties and nasal drainage [539]. One 13 years old male patient had a 9.7 Mb terminal del(X)(p22.2), resulting in the absence of genes from the telomere of Xp to *GPR143* of Xp22. The boy had Leri-Weill dyschondrosteosis, chondrodysplasia punctata, mental retardation, ichthyosis, and Kallmann syndrome [540]. His sister, 11 years old, had only Leri-Weill dyschondrosteosis, and was treated with growth hormone therapy for 3 years [540]. A female infant with del(X)(p22.2pter) had raw linear skin lesions on the face and neck since birth, that turned into pigmented streaks [541].

Ophthalmic Manifestations

Ophthalmological finding in siblings with del(X)(p22.2) was ocular albinism [539]. This deletion encompasses a gene known to cause ocular albinism (*GPR143*). One 13 years old male patient had a 9.7 Mb terminal del(X)(p22.2), resulting in ocular albinism [540]. His sister did not present ocular findings [540]. A female infant with del(X)(p22.2pter) had left sided microphthalmia and bilateral sclerocornea [541].

Duplication Xq

Definition and Epidemiology

Dup(X)(q28) is quite variable in size, and usually includes the *MECP2* gene.

Systemic Manifestations

One patient with a small dup(X)(q28), not including *MECP2*, but including *IKBKG* had ectodermal dysplasia, immunodeficiency, recurrent infections, peripheral neuropathy, gastroparesis and various benign tumors, but no intellectual disability [542].

Ophthalmic Manifestations

The case with dup(X)(q28) had incontinentia pigmenti [542].

XXY (Klinefelter Syndrome)

Definition and Epidemiology

XXY is the most frequent sex chromosome abnormality in males and one of the more common chromosomal aberrations associated with male developmental delay. It is estimated that 1:1000 male live births are affected but many may be asymptomatic. It is suspected that is an under diagnosed condition because it may not be identified in patients with mild findings.

Systemic Manifestations

Affected patients frequently have small testes that do not produce enough testosterone. Low testosterone can lead to delayed or incomplete puberty, gynecomastia, reduced facial and body hair, and infertility. Some affected individuals also have cryptorchidism, hypospadias, or micropenis. Older patients with Klinefelter syndrome tend to be taller than their peers. Some individuals have been described as having a Marfanoid appearance, including tall stature and mild arachnodactyly [543]. Patients also have an increased risk of developing breast cancer and systemic lupus erythematosus. Patients affected by Klinefelter syndrome may have mild to moderate developmental delays, learning difficulties, introversion or social immaturity. Major malformations are not usually found. Minor facial dysmorphism may include low set ears and asymmetric facies [543].

Ophthalmic Manifestations

Eye abnormalities are unusual. Microphthalmia and coloboma of the iris and choroid have been reported [275, 543, 544]. Ectopia lentis has also been described [543]. Other anterior segment abnormalities are occasionally observed. A 2-month-old infant with Klinefelter syndrome had microphthalmia, cataracts, and malformed pupils [545]. One case presented superior superficial corneal pannus and prominent corneal nerves with an unusual corneal dystrophy consisting of peripheral radial linear double-lined corneal stromal opacities which originated 2 mm from the limbus but did not involve the visual axis [543]. This patient also had a bilateral deepened anterior chamber, anterior stromal hypoplasia, miotic pupils, asymmetric optic discs with situs inversus, and optic disc anomalies consistent with mild colobomas as well as dyschromatopsia and visual field abnormalities. No electrophysiologic studies were performed.

Mild unilateral congenital ptosis, mild proptosis, long palpebral fissures and foreshortened inferior conjunctival fornices have been reported [543]. X-linked red green color deficiency occurs in 0.4 to 7.8 % of patients with Klinefelter syndrome [543]. Esotropia with convergence insufficiency has also been reported [543].

47, XYY

Definition and Epidemiology

47, XYY syndrome is a common sex chromosome aneuploidy in males occurring in approximately 1/1000 male newborns.

Systemic Manifestations

Patients characteristically show a weight, height and head circumference above average starting at birth. Speech delay, language disabilities, increased frequency of attention deficit problems as well as hyperactivity and impulsiveness can also be present.

Ophthalmic Manifestations

One 7 month old male patient presented with 47,XYY and morning glory syndrome has been reported [546]. Previously, this condition has been associated with myopia and iris coloboma.

Triploidy

Definition and Epidemiology

Triploidy is defined by the presence of three sets of each chromosome in all or some cells. Triploidy occurs in 1 % of all conceptions and in 15 % of all chromosomally abnormal fetuses [547]. Most triploid fetuses spontaneously abort. Only 1 of 10,000 liveborn infants are triploid [547].

Systemic Manifestations

Type I triploidy usually results from inheritance of an extra haploid set of paternal chromosomes whereas Type II is usually due to maternal inheritance [547]. In Type I triploidy, fetal death usually occurs before 8 weeks. Type II triploidy results in intrauterine growth retardation and macrocephaly.

Other anomalies may include hydrocephalus, agenesis of the corpus callosum, congenital heart disease, myelomeningocele, adrenal hypoplasia, cryptorchidism, hypogonadism, and intestinal malrotation. Malformed low-set ears, large bulbous nose, and micrognathia with or without cleft lip and palate characterize facial dysmorphism. Minor skeletal abnormalities include vertebral malformations, clubfoot and syndactyly of the third and fourth fingers may occur [548].

Ophthalmic Manifestations

Coloboma and microphthalmia have been reported [548]. Hypotelorism can also be present.

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Ocular Manifestations of Craniofacial Disorders

7

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Skull and Facial Development

The formation of the human face begins very early during development, with migration of neural crest cells forming the frontonasal processes around gestational weeks 4–5. Proliferation into the paired medial and lateral nasal, maxillary, and mandibular processes follows during weeks 5–6, with fusion of these structures during weeks 7 and 8 into the mature structures of the lip, nasal cavities, palate, and mandibular and maxillary arches [1]. Development of these structures is influenced by both genetic and environmental factors. An interruption in cell migration during this time may result in a cleft lip and/or palate or other craniofacial malformation. Similarly, abnormalities in the development of the infant skull, particularly premature fusion of the cranial sutures, is a process that is influenced by both genetic and environmental factors and results in growth restrictions of the skull and the face, depending on the affected region. This chapter describes craniofacial anomalies that involve craniosynostosis or clefts, focusing on the ocular manifestations of these disorders.

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Craniosynostosis

Introduction

Craniosynostosis is a condition affecting approximately 1:2000 live births in which the fibrous structures that divide the bones of the infant skull ossify and fuse prematurely [2]. Craniosynostosis can be isolated (with no underlying genetic syndrome) or syndromic (usually involving more than one suture and associated with a known genetic syndrome). Isolated craniosynostosis usually involves only one suture, but occasionally patients manifest multisuture involvement with no associated genetic syndrome, termed "complex" nonsyndromic craniosynostosis. Treatment of craniosynostosis includes surgical cranial vault remodeling during infancy to prevent problems associated with increased intracranial pressure and maximize developmental potential.

The calvaria, or the top of the skull, is made up of the frontal, occipital and parietal bones. As illustrated in Fig. 7.1, the major sutures of the infant skull are the sagittal, coronal, metopic, and lambdoidal sutures. The sagittal suture runs along the length of the skull, from the anterior to the posterior fontanel, separating the right and left parietal bones. The metopic suture begins at the anterior fontanel and makes a vertical line inferiorly, bisecting the frontal bone. The bilateral coronal sutures originate at the anterior fontanel and separate the frontal from the parietal bones. The lambdoid sutures originate at the posterior fontanel and separate the occipital bone from the parietal bones. Normally the major sutures of the infant skull should remain patent until the third decade of life, with the exception of the metopic suture, which normally fuses between 3 and 9 months of age [3]. There are also sutures in the skull base, the inferior portion of the skull which forms the floor of the cranial cavity. The skull base is comprised of many sutures including the frontosphenoid, squamosal, and intraoccipital, one or more of which may also fuse prematurely. When the skull base sutures fuse prematurely, the results are characteristic midface abnormalities

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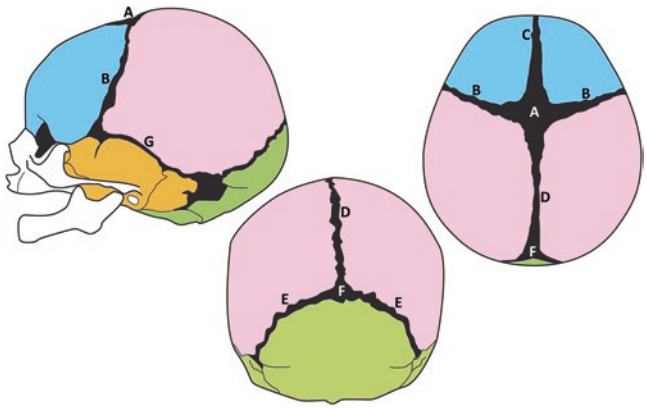

Fig. 7.1 Illustration of infant skull showing sutures and bones from side, top, and back. *Blue*: frontal bones; *pink*: parietal bones; *green*: occipital bone; *yellow*: temporal bone. (**a**) anterior fontanel, (**b**) coronal sutures, (**c**) metopic suture, (**d**) sagittal suture, (**e**) lambdoid sutures, (**f**) posterior fontanel, (**g**) squamosal suture

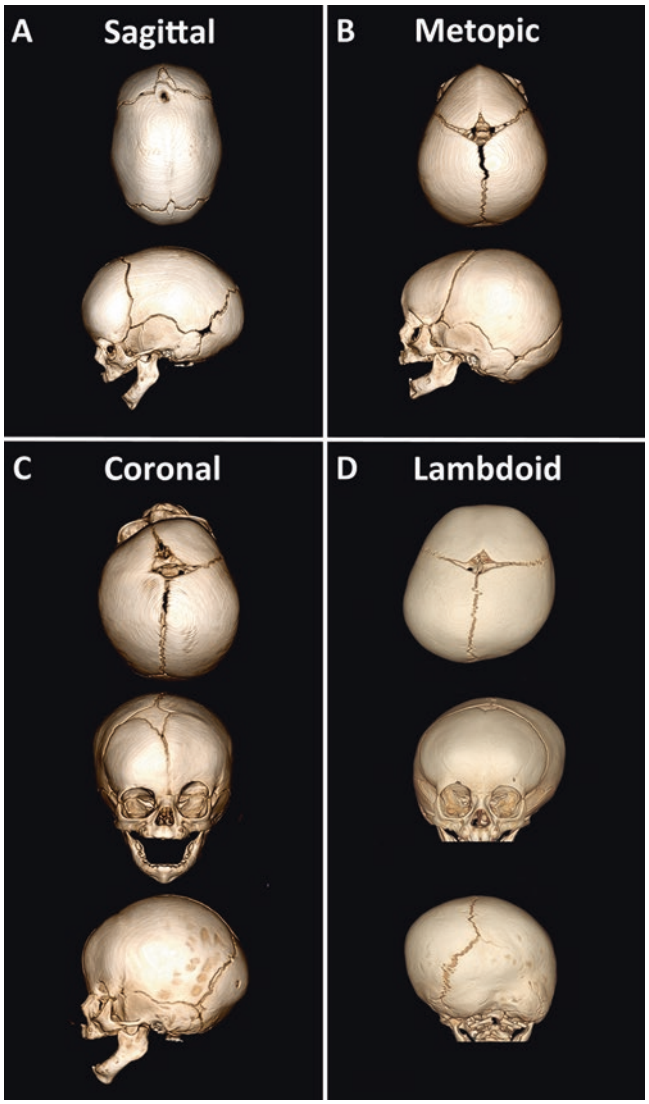

Fig. 7.2 3D CT reconstructions from infants with single suture craniosynostosis. (**a**) Sagittal synostosis: top view shows fusion of sagittal suture with elongated skull and narrow biparietal width. Side view shows elongation with prominent occiput and frontal bones. (**b**) Metopic synostosis: top view shows trigonocephaly with orbital exposure. (**c**) Coronal synostosis: top view shows fusion of the left coronal suture, exposure of the orbit on the left side; frontal view shows orbital asymmetry and facial twist to the right side; side view shows fusion of the left coronal suture. (**d**) Lambdoid synostosis: top view shows skull asymmetry with prominence of the left parietal and occipital bones; front view also shows asymmetry; back view shows fusion of the right lambdoid suture, asymmetry of the skull base, and a right mastoid bulge. Note that the metopic suture has fused normally in this patient because of age, not pathologically associated with metopic craniosynostosis

that can be recognized on physical exam: midface hypoplasia, exorbitism, beaked nose, narrow and high-arched maxillary arch, and relative mandibular prognathism.

When a calvarial suture fuses prematurely, the result is a characteristic and abnormal head shape that can be recognized on physical exam. The shape of the calvarium is determined by brain growth exerting an outward force on the skull. If a suture has fused prematurely (which usually occurs in utero), calvarial growth cannot occur in the intended direction and the result is compensatory growth in a predictable direction, typically perpendicular to the direction the fused suture would have allowed growth if patent (Virchow's law). For example, if the sagittal suture (which normally allows the skull to become wider over the parietal bones) has fused prematurely, the resultant head shape is scaphocephaly, or "boat-shaped" skull: anterior-posterior elongation with narrowing over the parietal bones and a prominent occiput and forehead (Fig. 7.2). Metopic craniosynostosis results in trigonocephaly because of the same principle. If the metopic suture has fused prematurely, the frontal bones are not able to grow anteriorly, resulting in a triangular shape of the frontal bones with lack of orbital protection from the brows, hence the term trigonocephaly (Figs. 7.2 and 7.3). In unilateral coronal craniosynostosis, the frontal bone on the affected side cannot grow anteriorly, resulting in ipsilateral forehead flattening or retrusion, superior orbital rim retrusion and a wider inter-palpebral fissure (Figs. 7.2 and 7.4). In addition, the "normal" contralateral side is affected, resulting in forehead protrusion and orbital depression. Unicoronal synostosis, in the older literature, was termed frontal or anterior plagiocephaly, which means oblique skull. Lambdoid craniosynostosis, also known as posterior plagiocephaly, results in asymmetry of the skull base, with the ipsilateral ear appearing lower than the unaffected side, flattening of the ipsilateral occiput and compensatory forehead asymmetry on the contralateral side (Fig. 7.2).

Not all abnormal skull shapes are due to craniosynostosis. Positional (also termed deformational) plagiocephaly describes a head shape that results from an external force, not craniosynostosis, and does not require surgical intervention. This condition is usually caused by positioning

Fig. 7.3 Patient with metopic suture synostosis and trigonocephaly

Fig. 7.4 (**a**) Patient with left unilateral coronal suture synostosis, status post frontal orbital advancement on the left as a baby. Note higher orbit on the left compared to the right, retruded left forehead compared to right, and secondary facial asymmetry with nose and chin deviated toward the non-synostotic side

(usually excessive time spent on the back of the head causing flattening of the occiput on one side) or torticollis with a strong preference to sleep on one side of the skull during infancy. This can be distinguished from craniosynostosis because the principles of compensatory growth seen in synostosis are not seen with positional plagiocephaly. The skull base remains symmetric, the widest point of the skull remains over the parietal bones, and the ipsilateral ear on the side of the flattened occiput is often anteriorly displaced, which can only occur if the lambdoid suture is patent. Positional plagiocephaly typically resolves with position changes (e.g., increasing tummy time, physical therapy if needed for torticollis), but in severe cases helmet therapy can hasten the improvement of skull shape.

Multisuture craniosynostosis is associated with different calvarial shapes, but follows the same principle of restricted growth in areas where sutures have fused and compensatory growth where sutures are patent. Bilateral coronal craniosynostosis results in a frontal bone that cannot grow anteriorly, often resulting in brachycephaly (a shortened anterior-posterior distance of the skull) or oxycephaly/turricephaly (increased vertical height of the skull). Mercedes craniosynostosis results from fusion of the sagittal and bilateral lambdoid sutures. The resultant head shape has anterior turricephaly and an indentation inferior to the posterior fontanel where the lambdoid sutures meet the sagittal suture [4]. Cloverleaf skull, also known as kleeblattschädel, usually results from fusion of the sagittal, coronal, and lambdoid sutures. It is characterized by a trilobar skull shape. Children with multisuture craniosynostosis also often have skull base suture fusion which leads to shallow orbits, exorbitism, midface hypoplasia, and narrow or clefted palates. Midface hypoplasia is often associated with upper airway obstruction, sometimes requiring tracheostomy in more severe cases. Multisuture craniosynostosis may also be associated with increased intracranial pressure, often requiring early cranial vault reconstruction.

The management and treatment of all children with complex syndromic craniosynostosis should be conducted by an experienced multidisciplinary team consisting of plastic surgery, neurosurgery, orthopedic surgery, orthodontics, ophthalmology, otolaryngology, genetics, anesthesiology, neuroradiology, pediatrics, audiology, speech pathology, occupational and physical therapy, neuropsychology, and social services [5].

Causes

Among patients with craniosynostosis, 15–25 % are syndromic, and display other physical abnormalities in addition to the synostosis. In most patients, genetic testing will identify a specific mutation. Most craniosynostosis syndromes show autosomal dominant inheritance.

The remaining 75–85 % of cases of craniosynostosis are non-syndromic [2]. These patients may or may not have an identifiable germ lime gene mutation causing the craniosynostosis. Yet, approximately 8 % of non-syndromic craniosynostosis is familial, usually with autosomal dominant transmission [6].

Because of differences in male–female ratios and proportions of cases that are familial among different sutures, there is likely a distinct etiology of both genetic and environmental factors that determine each sutural synostosis, and each sutural fusion is probably a distinct process with varying recurrence rates. For example, a study evaluating maternal nutrition during pregnancy and associated risk of craniosynostosis found that folic acid intake was not associated with craniosynostosis. Women who had higher intake of riboflavin and vitamins B6, E, and C had a significantly lower risk of having an infant with sagittal craniosynostosis.

Women with higher intakes of choline and vitamin B12 had a higher risk of having an infant with metopic synostosis. Women with higher intake of methionine and vitamin C had a significantly lower risk of having an infant with coronal synostosis [7]. Maternal thyroid disease (particularly Graves disease) has been shown to have an association with craniosynostosis; mothers of infants with craniosynostosis are more than twice as likely to report thyroid disease or treatment compared with mothers of control infants [8]. While first trimester use of selective serotonin-reuptake inhibitors (SSRIs) has been shown to have no significant associated risk of craniosynostosis, the use of valproic acid during pregnancy is associated with an adjusted odds ratio of 6.8 (95 %, CI 1.8–18.8) for having an infant with craniosynostosis [9, 10]. Exposure to other antiepileptic drugs has shown similar associations. Fetal constraint has also been studied as a potential risk factor for craniosynostosis. A large case–control trial from the National Birth Defects Prevention Study found that being a twin or first born child was associated with a twofold increased risk of metopic craniosynostosis, and macrosomia (birth weight >4000 g) was associated with twice the risk of developing coronal craniosynostosis [11]. However, this study also found that prematurity and low birth weight were associated with craniosynostosis. Other studies using animal models have shown that induced fetal head constraint results in altered morphology of the chondrocytes with resulting craniosynostosis [12].

Similar to the sutural specificity seen with environmental exposures in isolated craniosynostosis, the genetic causes of nonsyndromic craniosynostosis also have some suture specificity. Recurrence rates among relatives with craniosynostosis vary by suture. First degree relatives of probands with metopic craniosynostosis have the highest incidence of synostosis (6.4 %), followed by probands with lambdoid (3.9 %), sagittal (3.8 %), and coronal (0.7 %) craniosynostosis [13]. Although there is relatively little known about the genes involved in single-suture craniosynostosis, a large study analyzing whole genome array comparative genomic hybridization (CGH) from 186 patients with craniosynostosis found that 7.5 % had at least one deletion or duplication that had not been previously reported in patients without craniosynostosis [14]. The genes identified in this cohort are potential candidate genes for craniosynostosis and further studies are ongoing. Another study found that 26 % of children with presumed isolated craniosynostosis had genetic alterations (either single-gene mutations or chromosomal abnormalities.) [15] This group may have found a higher percentage of patients with a gene mutation because they included patients with bilateral coronal synostosis (3 %) and complex synostosis (5.5 %).

About 5 % of cases of nonsyndromic craniosynostosis are complex synostosis. Patients with complex synostosis are more likely to have symptoms related to synostosis and to require more surgeries than with other forms of nonsyndromic craniosynostosis. Patients with complex craniosynostosis have a higher incidence of ear infections, hearing problems, palate abnormalities, and incontinence compared with patients with single suture involvement [13]. Patients are also more likely to have Chiari malformation (particularly when the lambdoid suture is involved) and may have more developmental delays compared with patients who have other suture involvement [16].

Genetics

The eight most common craniosynostosis syndromes are associated with mutations in fibroblast growth factor receptors (*FGFRs*). *FGFRs* are receptor tyrosine kinases with an extracellular ligand-binding domain, a transmembrane domain, and an intracellular kinase domain. Fibroblast growth factors (*FGFs*) play various roles during development. *FGFs* are involved in induction and differentiation of cells during development, cell growth and migration, bone growth and development, differentiation of neurons, wound healing, and tumorigenesis [17]. *FGF1* and *FGF2* are expressed in both embryonic and adult tissues, while *FGF3-9* are primarily expressed only in embryonic tissue. *FGFR2* mutations are associated with the majority of craniosynostosis syndromes. *FGFR3* mutations are associated with various skeletal dysplasias as well as a few craniosynostosis syndromes. Other craniosynostosis syndromes are associated with mutations in *TWIST1* or other genes.

Heterozygous *FGFR2* mutations are typically missense substitutions with gain-of-function properties. They have an autosomal dominant pattern of inheritance. Mutations in different regions of *FGFR2* result in the three classic craniosynostosis syndromes: Apert, Pfeiffer and Crouzon. As described below, each has specific phenotypes but they share some features of presentation. These infants usually have multiple sutures fused at birth, characteristic facial features, and variable anomalies in extremities and developmental delay [18]. Two specific missense mutations in *FGFR2*, either Ser252Trp or Pro253Arg, are found in 98 % of patients with Apert syndrome. Variations are associated with the specific mutation (e.g., mutation at 252 is more likely to have cleft palate but milder syndactyly.) [19] Furthermore, studies in mice suggest that the Ser252Trp mutation causes loss of control of osteogenesis, causing proliferation and differentiation of cells within the sutural mesenchyme [20]. Most cases of Pfeiffer syndrome are caused by mutations in *FGFR2*, although a small number of cases have a mutation in *FGFR1*. Crouzon syndrome is caused by *FGFR2* mutations at numerous sites. There is considerable overlap in the mutations causing Crouzon and Pfeiffer, but most result in constitutive activation of the receptor. Of note, there have been cases reported of identical mutations resulting in Crouzon or

Pfeiffer syndrome, suggesting that there is further influence from epigenetic factors [21].

FGFR3 mutations are commonly associated with skeletal dysplasias, but also craniosynostosis syndromes: Muenke syndrome and Crouzon syndrome with acanthosis nigricans, both of which result from mutations in *FGFR3*. Muenke syndrome is caused by a Pro250Arg substitution. Patients with Muenke can present with unilateral coronal, bilateral coronal, pansynostosis, or no craniosynostosis [21]. There can be phenotypic variability among family members, and some individuals have the mutation causing Muenke but no features of the syndrome. Crouzon syndrome with acanthosis nigricans is associated with the Ala391Glu substitution in *FGFR3*. The phenotype is similar to the *FGFR2*-associated Crouzon syndrome at birth, with acanthosis nigricans developing later in life.

Saethre-Chotzen syndrome is caused by mutations in *TWIST1*, which encodes a basic helix-loop-helix (bHLH) transcription factor. Saethre-Chotzen syndrome is characterized by coronal craniosynostosis (either unilateral or bilateral) and a characteristic facies. Mouse models have demonstrated abnormal migration of neural crest cells within the coronal suture associated with mutations of TWIST1 [20]. Exome sequencing of patients with isolated unilateral coronal craniosynostosis identified mutations in *TCF12*, an E-protein that heterodimerizes with bHLH proteins such as TWIST1 [22]. *TCF12* and *TWIST1* have been shown to act synergistically, and loss-of-function mutations of both genes results in a more severe phenotype in mouse models.

Nonsyndromic Craniosynostosis

Sagittal Suture

Definition

Sagittal craniosynostosis is due to a disorder of the mesenchyme wherein there is intramembranous ossification of the suture causing premature fusion [23]. This results in scaphocephaly, or "boat-shaped" skull, characterized by anterior-posterior elongation with narrowing over the parietal bones and a prominent occiput and forehead (Fig. 7.2a).

Epidemiology

Sagittal craniosynostosis is the most common type of single suture synostosis and is associated with a strong male predominance (M:F ratio of 3.5:1). Sagittal synostosis comprises 40–58 % of craniosynostosis cases and has a prevalence of 1.9–2.3 per 10,000 births [24]. It has been associated with in utero exposure to maternal smoking and possibly intrauterine head constraint [25].

Systemic Manifestations

Single suture synostosis involving the sagittal suture may be a component of a syndrome, such as cranioectodermal dysplasia, or seen in isolation. Isolated synostosis is frequently associated with Chiari I malformation, and rarely with partial agenesis of the corpus callosum [26, 27].

Cranioectodermal dysplasia, which is also known as Sensenbrenner syndrome, features ectodermal anomalies such as sparse hair and eyelashes, short nails, and abnormal teeth, as well as systemic manifestations including chronic kidney disease, hepatosplenomegaly, and short limbs and fingers [28]. Isolated sagittal synostosis has also been described in association with syndromic patients who had concurrent radioulnar synostosis, some of who also presented with hydrocephalus and Chiari I malformation [29, 30].

Ophthalmic Manifestations

Typically, the orbital development is not affected with sagittal craniosynostosis. There are ophthalmic risks, however, most significantly related to elevated intracranial pressure (ICP) and the possible development of papilledema. Patients with isolated sagittal suture synostosis have an estimated incidence of elevated ICP of between 4.5 and 24 %, and evidence of increasing frequency with age [31, 32]. Pattern visual evoked potentials (pVEP) have been reported to deteriorate in craniosynostosis patients with elevated ICP, even in the absence of papilledema. One study found in pathologic pVEPs in 53.8 % of patients with sagittal suture synostosis and may serve as another surveillance tool in the detection of elevated ICP [33].

Diagnosis

Diagnosis is typically made clinically, although can be confirmed with conventional radiographic imaging. With the advancement in ultrasound technology, premature sagittal closure can potentially be detected in utero. Postnatal ultrasound of the cranial sutures has also shown to be an accurate diagnostic tool [34]. While ultrasound is a preferable first-line modality as it limits radiation exposure in the growing child, computed tomography is still considered the gold standard in the diagnosis of synostosis and provides more detailed information that may be utilized in surgical planning.

Management

Ophthalmologic evaluations to monitor for signs of intracranial pressure are warranted, with surgical intervention as indicated. Surgical correction may also be pursued for improved cosmesis, especially with the advent of less invasive techniques, such as endoscopic strip craniectomies, which reduce surgical times and hospitalization [35]. Surgical repair is optimally performed before the patient is 1 year of age. After 1 year of age, the surgical procedure

involves more extensive calvarial remodeling and reconstructive intervention [36].

Metopic Suture

Definition

If the metopic suture has fused prematurely, the frontal bones are not able to grow anteriorly, resulting in a triangular shape of the frontal bones with lack of orbital protection from the brows, hence the term trigonocephaly (Figs. 7.2 and 7.3).

Epidemiology

Metopic craniosynostosis accounts for approximately 14 % of all craniosynostosis cases and has a male predominance (M:F ratio 3.3:1) [37]. The recurrence risk is 3.2 % [2].

Systemic Manifestations

Numerous studies have suggested that children with metopic craniosynostosis have an increased risk of cognitive, speech, language, or behavior problems, although the severity of trigonocephaly is not associated with severity of cognitive deficits [38].

Similar to sagittal synostosis, single suture synostosis involving the metopic suture may occur in isolation or as part of a syndrome, as in microdeletion 9q22.3 syndrome. This syndrome is associated with de novo mutations resulting in characteristic obstructive hydrocephalus, macrosomia, hypotonia, and global developmental or motor delay. Patients may also present with basal cell nevi, as the PTCH1 gene which is mutated in basal cell nevus syndrome is also located at position 22 of the long arm of chromosome 9 [39, 40]. Metopic synostosis has also been shown to be associated with polysyndactyly as a result of a mutation in GLI3 [41].

Ophthalmic Manifestations

Metopic suture craniosynostosis can also lead to hypotelorism, with resultant pseudoesotropia. Patients occasionally present with true strabismus, most commonly accommodative esotropia. The most common ocular manifestation of metopic synostosis is refractive, generally occurring in the form of astigmatism, which puts them at risk for amblyopia. The risk of amblyopia in this population, due to both strabismus and refractive factors, is higher than that in the general pediatric population (8.8 % vs. 0.74 %.) [42, 43]. Metopic suture synostosis carries a risk of increased intracranial pressure, reported range of 7–33 %, and secondary papilledema, reported incidence of 5.6 %, underscoring the fact that elevated intracranial pressure dose not always lead to papilledema [31, 32].

Diagnosis

Diagnosis is made clinically based on the phenotypic presentation, but imaging with ultrasound may be supportive, and is even possible in utero [40]. Much like with sagittal synostosis, CT may be more useful as part of a preoperative workup and should be used sparingly to limit radiation exposure in the pediatric population. If a patient presents with other syndromic findings, a genetic workup may be warranted.

Management

In cases of mild metopic synostosis, most craniofacial surgeons would elect for observation, whereas in moderate or severe synostosis where there are secondary craniofacial skeletal deformities or elevated intracranial pressure, most would pursue surgical intervention. Frontal bone remodeling is the procedure of choice for metopic craniosynostosis, and most surgeons delay operating until the patient is at least 6 months of age [44].

Given the increased risk of amblyopia in this population, thorough evaluation by ophthalmology to screen for amblyogenic risk factors is critical early in childhood, with the institution of patching or penalization therapies as indicated. Strabismus surgery should be deferred until after craniofacial operations, as long as there is not a significantly increased risk of strabismic amblyopia with delay of intervention. Lastly, ophthalmologic evaluations to monitor for signs of intracranial pressure are warranted.

Coronal Suture

Definition

Coronal craniosynostosis is the premature closure of one or both cranial sutures that lie behind the forehead and run from the top of the head to the ear. Unicoronal synostosis, was formerly referred to as frontal or anterior plagiocephaly, which means oblique skull.

Epidemiology

Unilateral coronal craniosynostosis is the second most common single suture craniosynostosis. Approximately 75 % of all cases occur in females. Family history is positive in 8–15 %. Approximately 20 % have an identifiable gene mutation [45]. The most common mutations are in *FGFR3*, followed by *FGFR2,* and *TWIST1*.

Systemic Manifestations

In unilateral coronal craniosynostosis, the frontal bone on the affected side cannot grow anteriorly, resulting in ipsilateral forehead flattening or retrusion, superior orbital rim retrusion and a wider inter-palpebral fissure, and forehead protrusion and orbital depression on the contralateral "normal" (Figs. 7.2 and 7.4). Bilateral coronal craniosynostosis, in contrast, results in retrusion of both sides of the frontal bone resulting in brachycephaly (a shortened anterior-

posterior distance of the skull) and/or oxycephaly/turricephaly (increased vertical height of the skull).

Nonsyndromic coronal synostosis is often associated with brain anomalies, frequently Chiari I malformation (27.3 %) or sella changes, such as an empty or j-shaped sella (27.3 %) [26, 27].

Syndromic associations of bilateral coronal synostosis include the rare Baller-Gerold syndrome, which is characterized by aplasia or hypoplasia of the radius with a radial ray defect, oligodactyly, aplasia or hypoplasia of the thumb, and growth retardation. This syndrome is associated with a mutation of the RECQL4 gene, and may be manifest in infants exposed to valproic acid in utero [46, 47].

Bilateral coronal synostosis is usually associated with midfacial hypoplasia, which puts patients at risk of upper airway obstruction. This frequently manifests as obstructive sleep apnea, and children should be monitored for snoring as well as daytime fatigue and irritability [48].

Ophthalmic Manifestations

With single coronal craniosynostosis, ipsilateral orbit growth is restricted, whereas the contralateral side correspondingly enlarges. This disproportionate orbit development can lead to orbital and ocular excyclotorsion, and in severe cases lead to an elevation of the superolateral corner of the orbit known as "harlequin" or "owl's eye" deformity [49]. Harlequin deformities commonly lead to large vertical facial asymmetry. Unilateral coronal craniosynostosis is reportedly associated with strabismus in 57.6 % of cases, mostly commonly with a superior oblique palsy. This manifests as an ipsilateral hypertropia which increases in opposite lateral gaze, inferior oblique overaction, and V-pattern strabismus [50]. Anomalous extraocular muscle anatomy, including superolateral translation of the superior rectus muscle pulley, may be found and account for complex strabismus patterns [51], similar to the abnormalities seen in some syndromic craniosynostoses as discussed later in this chapter. There is evidence orbital asymmetry from unilateral coronal craniosynostosis can lead to contralateral amblyogenic anisometropic astigmatism, usually with an axis parallel to the peaked orbit, presumably due to the disparate orbital and adnexal volume [52–54]. While there is risk of increased intracranial pressure (8.1 %) in coronal synostosis, it has not been shown to have an increased risk of papilledema [31, 32].

Diagnosis

Coronal synostosis is generally diagnosed clinically, but similar to the single-suture craniosynostoses discussed earlier, imaging is confirmatory.

Management

The most common procedure for coronal synostosis is fronto-orbital advancement, with the most common indication for surgery being cosmesis [50]. Recent literature has advocated for early intervention of unilateral craniosynostosis with an alternative method, endoscopic strip craniectomy, showing promising results with regards to the degree of postoperative V-pattern exotropia compared to the previous standard [55, 56].

Given the increased risk of ipsilateral strabismus and contralateral astigmatism, these patients are at increased risk of amblyopia in this population, periodic ophthalmic evaluations should be conducted throughout childhood. Lastly, ophthalmologic evaluations to monitor for signs of intracranial pressure are warranted.

Lambdoid Suture

Definition

Lambdoid craniosynostosis, also known as posterior plagiocephaly, results in asymmetry of the skull base, with the ipsilateral ear appearing lower than the unaffected side, flattening of the ipsilateral occiput and compensatory forehead asymmetry on the contralateral side (Fig. 7.2d).

Epidemiology

Lambdoid craniosynostosis is rare and is the least common isolated craniosynostosis accounting for only 2–4 % of all nonsyndromic craniosynostosis [57]. It has been associated with male gender, intrauterine restriction, and preterm labor [58].

Systemic Manifestations

Unilateral premature fusion of the lambdoid suture causes posterior plagiocephaly, whereas bilateral synostosis results in brachycephaly. Unilateral lambdoid craniosynostosis needs to be distinguished from a positional or deformational plagiocephaly [59]. These cranial changes are most commonly associated with ipsilateral anterior displacement of the ear, although other ear positions have also been reported [60].

Ophthalmic Manifestations

There is rarely if any involvement in orbital development and no reported ocular abnormalities.

Diagnosis

As opposed to other craniosynostoses where diagnosis is often made solely on exam findings, lambdoid synostosis frequently requires further investigation with ultrasound to distinguish it from positional plagiocephaly, which has a similar clinical picture [61].

Management

Whether or not to pursue surgical intervention is largely dependent on the severity of the deformity. Often, it is mild and can be observed. In more severe cases with unacceptable

cosmesis, surgical intervention by open posterior cranial vault reconstruction or endoscopic-assisted suturectomy can be performed with equivocal results [62].

Syndromic Craniosynostosis

Apert Syndrome

Definition

Apert syndrome manifests as congenital or early-onset synostosis of multiple sutures, with midface retrusion and syndactyly of the hands and feet. The most common sutures to be involved are the sagittal suture and both coronal sutures, leading to turri- and brachycephaly, retruded forehead and exorbitism. The anterior fontanel remains patent for a prolonged period due to a growing brain in the face of widespread sutural synostosis. In addition to exorbitism, skull base suture fusion causes midface retrusion or hypoplasia, beaked nose, highly arched palate with dental malocclusion, and relative mandibular prognathism (Fig. 7.5a, b). Patients with Apert syndrome display complex and severe syndactyly of the hands and feet, often with complete fusion of all the fingers and toes (Figs. 7.6 and 7.7). This feature distinguishes patients with Apert syndrome from other syndromic craniosynostosis that may have a similar craniofacial appearance, such as Crouzon and Pfeiffer syndromes.

History

M.E. Apert, a French physician, first described the syndrome in 1906.

Epidemiology

The frequency of Apert syndrome is estimated to be 1 in 65,000 births, and it affects males and females equally. Most cases of Apert syndrome are sporadic, but in hereditary cases it has been reported as an autosomal dominant disorder. Advanced paternal age is more common in patients with Apert syndrome [63, 64].

Systemic Manifestations

Neurologic abnormalities are common and include global developmental delay, absent or thin septum pellucidum and corpus callosum, cerebellar hypoplasia, jugular foramina stenosis, cerebral venous abnormalities, and Chiari type I malformation. Nonprogressive ventriculomegaly occurs in 35–93 % of patients, and likely reflects a global lack of white matter volume [65–67]. Hydrocephalus is less common (4–12 %) in Apert syndrome when compared to other syndromic craniosynostoses [65]. Intelligence may range from normal to significant mental deficiency. Patients with Apert syndrome tend to have more intellectual disability compared to other craniosynostoses, with a mean full-scale intelligence quotient (FSIQ) of 70.0–76.7 [68, 69]. Otologic abnormalities found in patients with Apert syndrome include chronic middle ear effusions and hearing loss [67]. They often have choanal stenosis and atresia with cleft palate, which combine with malacia of the larynx, trachea, and bronchi to put them at risk of airway compromise; one study showed that 38 % of patients suffered from mild airway compromise with 8 % suffering from severe obstruction [70, 71]. These airway abnormalities also put them at risk of difficulty feeding and failure to thrive [71]. Patients commonly have abnormalities of dentition, such as malocclusion, crowding, delayed eruption, and shovel-shaped incisors [3]. Common cardiovascular anomalies are septal defects of the ventricle and atrium, tricuspid atresia, patent foramen ovale, and mitral valve prolapse. There is also an association with urogenital defects such as hydronephrosis, nephrocalcinosis, inguinal hernias, hydroceles, and cryptorchidism. The majority of patients with Apert syndrome manifest hand syndactyly of digits 2–5

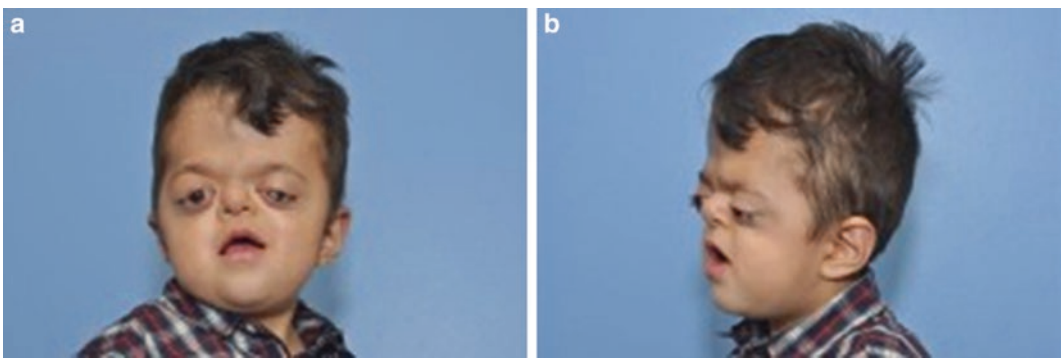

Fig. 7.5 (**a**), (**b**) Patient with Apert syndrome, revealing turricephaly (tower-shaped skull) and brachycephaly (shortened skull in the anterior–posterior dimension) with midface retrusion, exorbitism with corneal scar (left eye), tarsorraphies, and exotropia

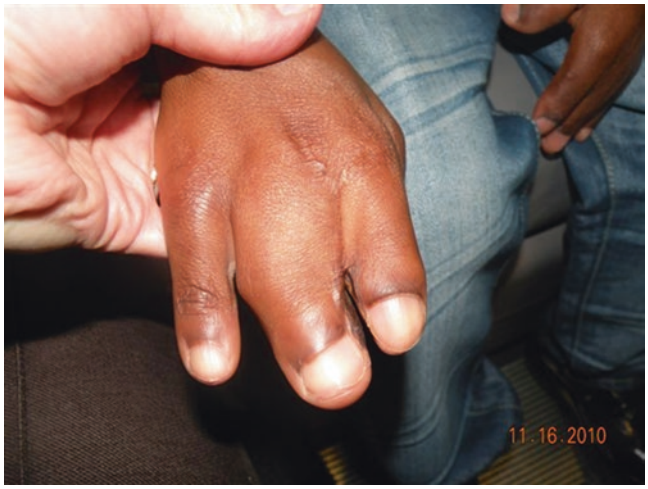

Fig. 7.6 Operated hand of the patient with Apert syndrome, complete syndactyly was present prior to hand surgery

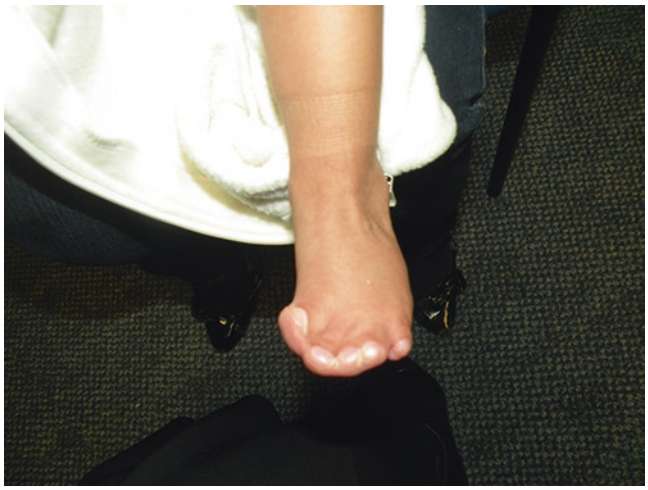

Fig. 7.7 Complete syndactyly of the toes in a patient with Apert syndrome

or 1–5, and foot syndactyly of all five digits. In addition to hand and foot anomalies, patients often have other skeletal abnormalities in the spine and limbs which result in limited mobility [72].

Ophthalmic Manifestations

Shallow orbits are a result of bilateral coronal suture synostosis and midface retrusion, leading to exorbitism and orbital hypertelorism. Exorbitism may lead to an incomplete blink during waking hours and nocturnal lagophthalmos, causing corneal exposure, abrasions, infections, and potentially blinding corneal scarring (Fig. 7.8). Patients with extremely shallow orbits may experience spontaneous globe luxation. In this situation, the globe appears to "pop" out of the orbit, with the eyelids falling behind the globe. When this occurs, intraocular pressure may elevate to extremely high levels, potentially leading to permanent optic nerve damage [73]. In

Fig. 7.8 Patient with Apert syndrome, exorbitism, down slanting fissues, left corneal scar secondary to resolved microbial corneal infection. Severe exorbitism lead to chronic exposure keratopathy and secondary infection

severe cases, the globe may become trapped in front of the lids, and rarely cannot be reduced manually.

Strabismus is common in Apert syndrome, with some form of deviation reported in 93 % of patients [74]. Patients may present with vertical and/or horizontal deviations that are often caused by anomalies of extraocular muscle position or structure. Patients with Apert syndrome are more likely to present with esotropia than exotropia, generally with a V-pattern [75]. Alternating hypertropias, with the adducting eye being hypertropic in lateral gaze, is common and mimics bilateral inferior oblique overaction. The cause of this typical motility disturbance is likely orbital abnormalities that arise from coronal suture synostosis. Coronal suture synostosis leads to ipsilateral restricted orbital growth, decreased orbital volume, extorsion of the orbit, and an extorted position of the globe and all the extra-ocular muscles. This muscle displacement may significantly alter the actions of the extraocular muscles [73]. In cases of orbital and globe extorsion, the medial rectus is superiorly displaced. This causes the medial rectus, a muscle that normally adducts the eye, to also elevate the adducted eye (Fig. 7.9). True inferior oblique overaction occurs as well, and may be secondary to superior oblique underaction or absence. Superior oblique underaction occurs secondary to the superior orbital rim retrusion induced by the coronal synostosis. Patients with syndromic craniosynostosis are at increased risk for a wide variety of other anomalies of the extra-ocular muscles including absent muscles (Fig. 7.10), muscles inserted too far anteriorly, doubled muscles, bifid muscles, and muscularized intermuscular septi [73, 76].

Patients with Apert syndrome are at higher risk for optic nerve abnormalities. Papilledema may arise secondary to elevated intracranial pressure, and is seen in 9 % of patients prior to first surgical intervention [74]. Elevated intracranial

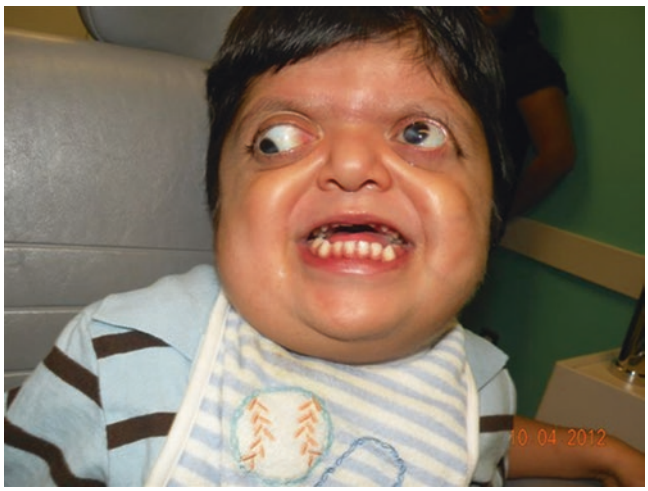

Fig. 7.9 Patient with Apert syndrome, looking into right gaze, the left eye elevates as it adducts. Note the left corneal scar (same patient as Fig. 7.6)

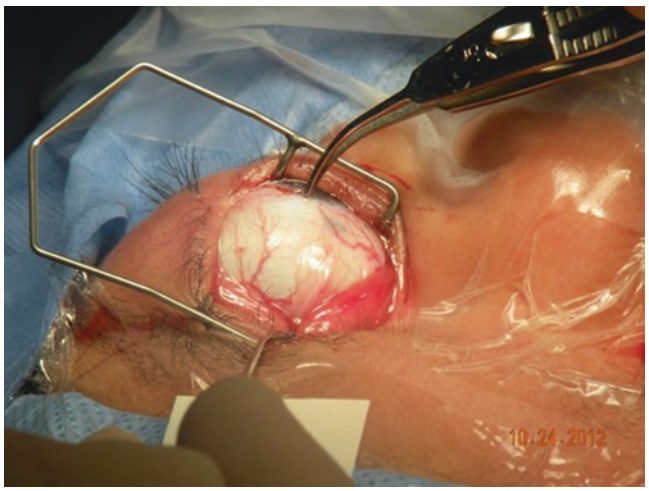

Fig. 7.10 Intraoperative photo of the superior portion of a globe the patient in Fig. 7.7, conjunctiva pulled back, revealing that the superior rectus muscle and superior oblique tendon are congenitally absent

pressure, has many potential causes: decreased cranial vault volume due to craniosynostosis, congenital cerebral venous outflow abnormalities including jugular foramina stenosis, obstructive sleep apnea and, infrequently, hydrocephalus. If the papilledema is moderate or severe, this may result in optic nerve atrophy with secondary permanent loss of vision and/or visual field. Optic atrophy is reported to be present in 16.7 % of patients with Apert syndrome [77].

One group has reported abnormal Goldman visual fields and pattern visual evoked potentials in children with syndromic craniosynostosis, speculated to be secondary to elevated intracranial pressure, with improvement after intracranial pressure is lowered (typically with cranial vault expansion) [78, 79].

Decreased visual acuity in one or both eyes affects up to 73 % of patients and may be secondary to: amblyopia (strabismic, isometropic, or anisometropic), uncorrected refractive errors, corneal opacity, optic atrophy, ptosis and rarely, cortical visual impairment. Unusual and/or asymmetric refractive errors (high near- or farsightedness, and high astigmatism) is common, found in one study to affect 93 % of patients [73, 80].

Diagnosis

The diagnosis is usually made clinically based on the constellation of findings listed above, but can be verified by molecular genetic testing. As mentioned earlier, the most common gene affected in Apert syndrome is FGFR2 [19, 81].

Management

Patients with Apert syndrome will typically undergo cranial vault expansion. As with the other forms of syndromic craniosynostosis, it is felt that early suture fusion leads to insufficient cranial volume that will impact brain growth and development. Therefore, in most craniofacial centers, cranial vault expansion is performed early in life in patients with multiple suture synostosis. The most common initial surgery is frontal orbital advancement, performed as early as 9–12 months of age, and may be repeated later in life. If expansion is required earlier than 9 months of age, posterior vault expansion can be performed. LeFort III midface advancement is typically performed in late childhood to early adolescence. This procedure advances the midface to significantly improve obstructive sleep apnea, exorbitism shallow orbits and appearance [82]. Airway obstruction may also be improved with supportive measures such as oxygen supplementation, infection prophylaxis, and positioning. More severe compromise may require use of nasopharyngeal or oropharyngeal airways, or endotracheal tubes for airway maintenance [71]. Patients should have an otolaryngology evaluation to assess hearing loss and predisposition to otitis media; prolonged antibiotic therapy or tympanostomy tubes may prevent further hearing loss. Treatment with hearing aids or cochlear implants may also be indicated [83].

Hand surgery is commonly performed in patients with Apert syndrome, with multiple procedures and revisions required throughout childhood. The feet rarely undergo surgery.

Ongoing ophthalmologic care is important because patients with Apert syndrome are at increased risk to experience significant vision and ophthalmic complications. Spectacles should be prescribed for significant refractive errors to improve vision and eye alignment, and to prevent amblyopia. However, the fit of the spectacles is problematic due to exorbitism and maxillary hypoplasia. Patients should be followed for the risk of development of amblyopia, with treatment regimens prescribed as necessary. Patients with a history of globe luxation may undergo lateral (and possibly

medial) tarsorrhaphy to prevent recurrence of the subluxation, with the risk that the forward pressure of the globe will result in breakdown of the tarsorrhaphy. Midface advancement surgery definitively expands orbital volume. Patients with exorbitism should use artificial tears throughout the day, and ointment at bedtime. Strabismus surgery can be successful in restoring alignment in primary gaze, but often cannot correct all eye movement abnormalities. Normal ocular alignment may be impossible to achieve in patients with very complex horizontal and vertical strabismus secondary to anomalous extraocular muscles and orbits. Fundoscopic exams, with vigilance for papilledema or optic atrophy, are critical.

Crouzon Syndrome

Definition

Crouzon syndrome is the most common type of craniosynostosis [84]. The craniofacial findings in Crouzon syndrome may be similar to those seen in Apert syndrome. Patients typically have multiple suture synostosis, most commonly bicoronal and sagittal, leading to turri- and brachycephaly, with a broad retruded forehead and exorbitism. The face and skull may be indistinguishable from Apert, but more mild phenotypes can occur, almost making the syndrome unrecognizable. Such mild phenotypes are not seen in Apert syndrome. Patients often are not born with cranial suture synostosis; rather, it is a progressive disease. Fusion of the coronal and sagittal sutures is seen within the first year of life, while lambdoid fusion occurs later [85]. Hypertelorism and exorbitism both occur, but the inferior orbital rim is more retruded in patients with Crouzon syndrome, resulting in more inferior scleral show, compared to Apert patients [86]. Skull base suture fusion leads to midface retrusion/hypoplasia, beaked nose, high arched palate with malocclusion and relative mandibular prognathism (Fig. 7.11a, b).

History

Louis Edouard Octave Crouzon, a French neurologist, first described the condition in 1912.

Epidemiology

While Crouzon syndrome is the most common craniosynostosis syndrome, it is still relatively rare, with an estimated frequency of 1 in 25,000 live births. Half of the cases are sporadic and the other half are autosomal dominant with complete penetrance and variable expression [75]. There is an equal distribution among sexes [87]. Crouzon syndrome has also been shown to be associated with advanced paternal age [88].

Systemic Manifestations

Unlike Apert syndrome, the hands and feet usually appear to be normal, although subtle abnormalities have been reported such as clinodactyly and carpal fusions producing only mild effects on the hands [89]. Neurologic abnormalities include seizures and nonprogressive ventriculomegaly, the latter reported to occur in 16–63 % of patients. These manifestations are less frequently seen in Crouzon than in Apert syndrome. Progressive hydrocephalus and severe airway obstruction, the latter due in part to retrusion of the maxillae, are both more commonly seen in Crouzon than in Apert syndrome (9–26 % and 15 %, respectively) [66, 71, 85]. It is reported that 70 % of Crouzon syndrome patients display chronic tonsillar herniation (Chiari 1), with approximately 50 % of these patients developing hydrocephalus. Jugular foramen stenosis and secondary venous outflow obstruction has also been suggested as a cause of chronic tonsillar herniation and elevated intracranial pressure [90, 91]. Patients generally have normal to slightly below normal intelligence, with a mean FSIQ of 92.3 [68]. Crouzon has also been found to have an association with acanthosis nigricans, a finding which is associated with a mutation in the FGFR3 gene [92]. Patients often have microtia and low-set ears, with the majority having hearing loss of conductive (60 %), sensorineural (11 %), or mixed (14 %) type [83].

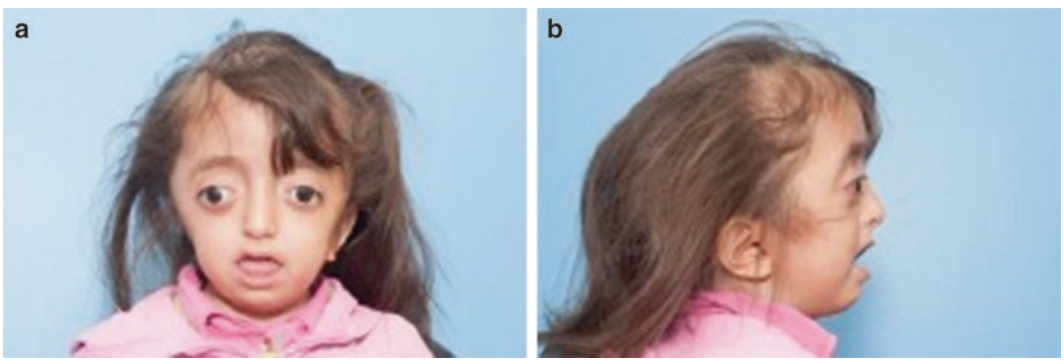

Fig. 7.11 (**a**), (**b**) Patient with Crouzon syndrome, revealing turri- and brachycephaly, broad retruded forehead, exorbitism, hypertelorism, midface retrusion/hypoplasia, beaked nose and relative mandibular prognathism. She also has exotropia

Ophthalmic Manifestations

Ophthalmic manifestations are frequent in Crouzon syndrome. Exorbitism results from shallow orbits secondary to bilateral coronal suture synostosis and midface retrusion. Like patients with Apert syndrome, they may experience spontaneous globe subluxation, exposure keratopathy, and exposure conjunctivitis. Strabismus is common in Crouzon syndrome, reported to occur in 39–76.6 % of patients. Unlike in Apert syndrome, these patients manifest exotropia more commonly than esotropia, although they, too, often demonstrate a V-pattern (Fig. 7.11a) [75, 86, 87]. Like patients with Apert syndrome, alternating hypertropias in lateral gaze is common [87]. Optic atrophy is more common in Crouzon syndrome than in Apert, and has been reported to occur in 7–22 % of patients. This finding is likely secondary to elevated intracranial pressure and papilledema [86, 87]. Decreased visual acuity is reported in 32–44 % of patients, secondary to amblyopia (strabismic, isometropic, or anisometropic), ptosis, corneal opacity, optic atrophy and/or uncorrected refractive errors, with amblyopia being the most common cause, occurring in 21–73 % of patients [80, 87]. Nystagmus is also associated with Crouzon syndrome and is seen in 8–11.5 % of patients [80, 86]. High refractive errors occur commonly, especially high astigmatism, occurring in up to 77 % of patients [75, 87].

Diagnosis

The diagnosis of Crouzon syndrome can be made clinically, or with genetic testing for a mutation in the FGFR2 gene as discussed earlier if the diagnosis is uncertain [18, 20].

Management

Patients with early onset craniosynostosis are candidates for vault expansion and midface advancement surgeries, in the same time course as patients with Apert syndrome [73]. Progressive hydrocephalus requires consultation with neurosurgery and consideration for ventriculo-peritoneal shunt [93]. Concurrent ophthalmologic follow-up is also necessary to monitor for associated disc edema and optic atrophy. Management of airway obstruction will depend on the severity, and while supportive therapies similar to those utilized for Apert syndrome may be successful, surgery is required more frequently in the management of these patients. Midface advancement helps to address the maxillary retrusion in the upper airway obstruction, but many patients ultimately require tracheostomy to maintain a patent airway [71, 94].

Patients with Crouzon syndrome experience similar ocular, oculomotor and visual complications to patients with Apert syndrome. The strabismus in Crouzon patients also may be complex, a combination of horizontal and vertical deviations with oblique dysfunction, with or without anomalous muscles or pulley systems. Use of imaging to identify anomalous muscle pulleys may be useful in surgical planning, as studies have shown this to be causative of V-pattern exotropia in this patient population [95, 96]. Strabismus surgery is successful in many, restoring normal alignment in the primary position (straight ahead gaze). Patients with very complex strabismus are less likely to achieve normal eye alignment. Even those patients who are successfully aligned in primary gaze, residual abnormalities in their ocular motility often persists [97].

Pfeiffer Syndrome

Definition

Pfeiffer syndrome is a disorder with physical characteristics similar to Apert syndrome: premature craniosynostosis involving multiple sutures, midface retrusion, abnormalities of the hands and feet (namely broad thumbs and broad great toes, often medially deviated,) and varying degrees of brachydactyly and partial syndactyly. The most common sutures to be involved are the coronal sutures, but all the sutures may be synostosed. While different authors have proposed systems of classification, the most commonly used is that of Cohen, which divides the syndrome into three subtypes based on clinical findings. He suggested diagnostic and prognostic implications of his system [98, 99].

History

Rudolf A. Pfeiffer, a German physician, is credited for first describing the syndrome in 1964. As cited by Greig, he noted a pattern of cranial anomalies with broad digits and partial syndactyly of the hands and feet across three generations within a family [99].

Epidemiology

Pfeiffer syndrome, an autosomal dominant condition, affects about 1 in 100,000 individuals [100, 101]. There is no gender predilection in this syndrome, and like Apert and Crouzon syndromes it is associated with advanced paternal age [88, 99].

Systemic Manifestations

Type 1 is the mildest and consists of craniosynostosis and midface deficiency. They may present with skeletal anomalies including vertebral fusion and elbow ankylosis [98]. Type 2 is the most severe form and consists of a trilobar or cloverleaf skull deformity, resulting from fusion of the sagittal, bilateral coronal and lambdoid sutures. Patients often have very shallow orbits and extreme exorbitism. This subtype has the highest risk of CNS involvement; patients frequently develop progressive hydrocephalus. Airway obstruction frequently manifests as progressive respiratory distress. It is similar to that seen in Apert syndrome as it is due to both upper airway anomalies, such as midface hypoplasia, and lower airway

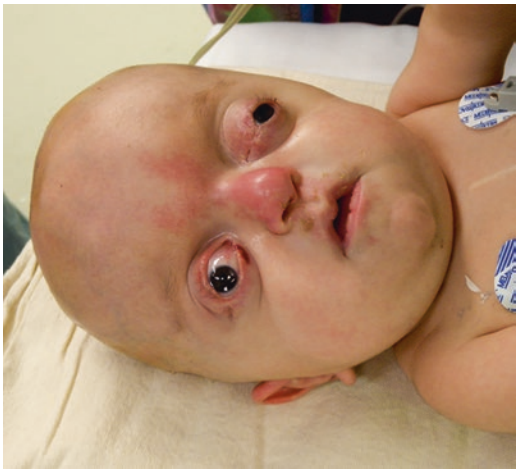

Fig. 7.12 Patient with Pfeiffer syndrome with retruded broad forehead, midface hypoplasia, exorbitism and exotropia. He has undergone a temporal tarsorrhaphy of the right eyelids and a medial and temporal tarsorrhaphy on the left eyelids because of a history of multiple episodes of spontaneous globe luxation and corneal exposure

changes, including malacia of the larynx, trachea, and bronchi [70]. Type 3 is similar to type 2 but without a cloverleaf skull (Fig. 7.12). Type 3 also carries a risk of hydrocephalus [98, 102]. Patients with types 2 and 3 may also manifest choanal atresia, external auditory canal atresia, elbow ankylosis, sacrococcygeal anomalies, and typically have a shortened lifespan [100, 102].

The spectrum of Pfeiffer syndrome is almost universally characterized by some degree of hearing loss; this deficit is primary conductive, although sensorineural and mixed types have also been described [83]. While overall the syndrome is associated with normal intelligence, this correlates with the severity of the CNS involvement, and therefore there are reports of mental deficiency associated with Pfeiffer syndrome [68, 69].

Additional abnormalities include mental retardation, hydrocephalus, Chiari malformation, external auditory canal stenosis, hydronephrosis, pelvic kidneys and hypoplasia of the gallbladder [100].

Ophthalmic Manifestations

The ophthalmic sequelae of Pfeiffer syndrome are similar to those of Apert and Crouzon syndrome, as the exorbitism will put these patients at risk of exposure keratitis and conjunctivitis, as well as corneal scarring. The optic nerve may be compromised in cases of progressive hydrocephalus seen in types 2 and 3 [77]. Patients with Pfeiffer syndrome most commonly present with a V-pattern exotropia, and frequently have higher degrees of astigmatism which is theorized to be a result of the combined factors of exposure keratopathy, ptosis, and orbital shape [75].

Diagnosis

Many times the diagnosis is made clinically based on the pattern of craniosynostosis and characteristic thumbs and large toes. Genetic testing for mutations of the FGFR genes, as described earlier, can be performed if the diagnosis is in question.

Management

The management of patients with Pfeiffer syndrome is similar to that of Apert and Crouzon syndrome and consists of staged craniofacial surgery to release the synostotic sutures. Patients should be monitored for the development of hydrocephalus and may require ventriculo-peritoneal shunt [103]. Exorbitism is managed initially with tarsorrhaphies and lubrication, later with midface advancement if needed. Patients should have ongoing ophthalmologic evaluations, with particular attention to the presence of astigmatic or other refractive errors with appropriate correction as necessary, and vigilance for the development of papilledema or optic atrophy. Evaluation and treatment of strabismus is also important to reduce the risk of amblyopia. Similar to Crouzon syndrome, conservative management of the airway is often insufficient, and these patients frequently require more aggressive surgical intervention with tracheostomies or uvulopalatopharyngeoplasty [94].

Muenke Syndrome

Definition

Muenke syndrome is characterized by uni- or bicoronal craniosynostosis with a broad spectrum of clinical manifestations including macrocephaly, midface hypoplasia, limb defects, and hearing loss [104].

History

Muenke syndrome was first described in 1996 by Dr. Maximilian Muenke, a medical geneticist at the University of Pennsylvania. Muenke and colleagues reported a case series of ten unrelated families with coronal craniosynostosis that had a distinct mutation in the *FGFR3* gene. While phenotypically there is much overlap among syndromic craniosynostosis, the identification of the *FGFR3* mutation allowed Muenke's group to genotypically distinguish this condition from mutations in *FGFR1*- and *FGFR2*-associated with Pfeiffer and Apert syndromes, respectively [104].

Epidemiology

Muenke syndrome accounts for 5 % of all craniosynostosis, with an estimated incidence of 1 in 30,000 births [15]. Among coronal craniosynostosis, there is an estimated

incidence of this condition in 1 of 20 patients with unicoronal craniosynostosis, and upwards of three of ten patients with bicoronal craniosynostosis [105]. While there is an equal distribution among sexes, Lajenie et al. noted that females with bicoronal Muenke syndrome were more likely to present with the more severe brachycephalic phenotype (68 %) than males (35 %). A minority (10–15 %) of individuals with the *FGFR3* mutation does not express any phenotypic characteristic of Muenke syndrome [106, 107].

Systemic Manifestations

The extreme variable phenotypic expression of Muenke Syndrome may clinically resemble patients with Crouzon or Saethre-Chotzen syndrome. Milder cases of Muenke syndrome may mimic nonsyndromic craniosynostosis and therefore go undiagnosed. Premature synostosis of one or both coronal sutures are the most common sutures to be involved (Fig. 7.13a, b). Additional clinical findings are mild midface hypoplasia, highly arched palate, and cleft lip and palate [108]. Mild limb maldevelopment may also occur including brachydactyly, syndactyly of digits 2 and 3, phalangeal hypoplasia, coned epiphyses, hallux valgus, and carpal, tarsal, calcaneal, and navicular fusions [109–111]. Hearing loss is common feature, and is primarily sensorineural in nature (79 %) although conductive and mixed etiologies have also been described [83, 112]. Intellectual functioning in patients with Muenke ranges from normal to slightly below normal, with 39 % of patients falling within the range of intellectual disability. Interestingly, children with Muenke syndrome have been found to have more social and inattention problems than those with other forms of craniosynostosis [69].

Ophthalmic Manifestations

The ophthalmic sequelae of Muenke syndrome mainly stem from the orbital abnormalities due to the unilateral or bilateral coronal suture synostosis. They may present with ptosis and downward-slanting palpebral fissures [107]. The incidence of elevated intracranial pressure in this syndrome is low, estimated to occur in 5 % of patients [74]. These patients manifest strabismus in 39 % of cases, typically a constant or intermittent exotropia, sometimes with a V-pattern., They are also at risk for high, occasionally asymmetric, refractive errors putting them at risk for amblyopia [113].

Diagnosis

Diagnosis of Muenke syndrome is suspected based on the above clinical findings and a positive family history, and definitively diagnosed by genetic testing, which shows the presence of the *FGFR3* pathogetnic variant c.749C>G (p. Pro250Arg.) [107].

Management

Depending on the severity, treatment of the craniofacial abnormalities can span from observation to staged procedures, including fronto-orbital advancement and subsequent posterior cranial vault remodeling, typically within the first 12 months of life. In cases of more severe phenotypes and ominous clinical findings, collaboration between craniofacial and neurosurgery services may be necessitated to perform endoscopic strip craniectomy in the first 3 months of life [55]. While strabismus is less common in Muenke syndrome than some of the other craniosynostoses, ophthalmologic evaluation is warranted to assess optic nerve status and refractive error, with treatment of strabismus and amblyopia as indicated.

Saethre-Chotzen Syndrome

Definition

Saethre-Chotzen syndrome is characterized by unilateral or bilateral coronal synostosis, low frontal hairline, facial asymmetry, depressed nasal bridge, and prominent crus helicis [114].

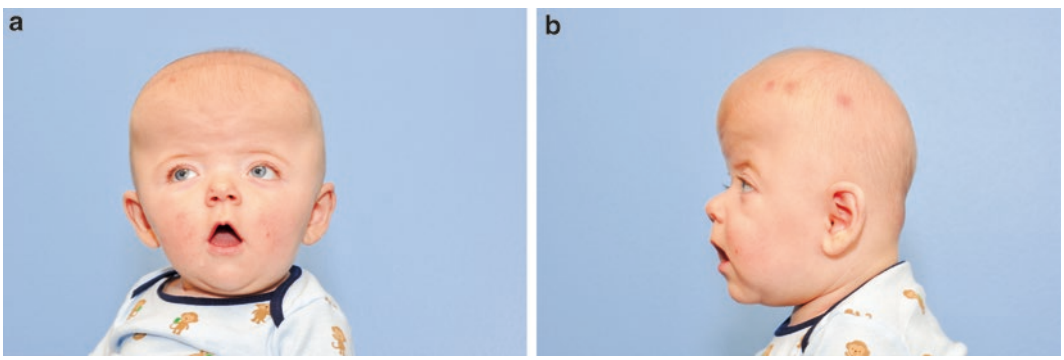

Fig. 7.13 (**a**), (**b**) Patient with Muenke syndrome and bicoronal suture synostosis with secondary broad retruded forehead, hypertelorism, and turri- and brachycephaly

History

The clinical features of Saethre-Chotzen syndrome were first described by Haakon Saethre, a Norwegian psychiatrist in 1931 [115]. In a case report, he noted a mother and her two daughters having similar dysmorphic facial features, low-set hairlines, short fingers, and webbing between digits in the hand and foot. In the subsequent year, a German psychiatrist F. Chotzen described a syndrome in which the father of two sons that had similar dysmorphic facial features and syndactyly, but in addition noted short stature, hearing loss, and mild retardation [116]. Since both physicians unknowingly described this condition separately, both their names are accredited to identifying the syndrome. Finally in 1997, separate teams led by Howard and El Ghouzzi concurrently demonstrated that Saethre-Chotzen syndrome is the result of a mutation on the TWIST1 gene on human chromosome 12 [117, 118].

Epidemiology

Saethre-Chotzen syndrome is a rare autosomal dominant genetic condition with variable penetrance and expressivity that has a global prevalence of 1 in 25,000–50,000 people (Heutink 1995). While no gender predilection has been reported, small case series show a slight male predominance [111, 114, 119, 120].

Systemic Manifestations

The variable degree and timing of suture closure between the right and left coronal sutures lead to the development of facial asymmetry and diverse cranial morphology. As mentioned earlier, the coronal sutures are most frequently involved, but there have also been reports of sagittal, metopic, lambdoid, and multisuture involvement [114]. Craniofacial findings include cleft palate, low set frontal hairline, deviated nose with depressed nasal bridge, prominent chin, and ear abnormalities. The ears tend to be small, posteriorly rotated, and have prominent horizontal crus (Fig. 7.14a, b), with an increased frequency of conductive hearing loss associated with recurrent middle ear infections [114, 121]. Variable limb involvement may include subtle brachydactyly, syndactyly of digits 2 and 3, clinodactyly, carpal and tarsal fusion, cone-shaped epiphyses, and bifid or duplicated large toes which are often laterally deviated [111, 114, 121]. Fusion may also be seen of the vertebral bodies, most commonly of the cervical spine [111]. Intelligence is commonly normal, but there are reports showing mild to moderate developmental delay, including that by Elia et al. which showed 8 of 11 patients with Saethre-Chotzen had mental retardation [68, 69, 120]. Elia and colleagues also reported a higher frequency of epilepsy than had previously been described in this patient population, which correlated to findings of abnormal cortical gyri structure.

Ophthalmic Manifestations

Ophthalmic manifestations include ptosis (81.8 %), refractive error (36–52 %) and strabismus (27–37 %). These patients frequently have downward-slanting eyes and hypertelorism as well [119]. Patients with Saethre-Chotzen are at risk for elevated intracranial pressure that has been shown to cause papilledema in 19 % of patients prior to any surgical intervention. This, in turn, can lead to optic nerve atrophy, but this complication is infrequent [74, 114]. Ongoing ophthalmic exams to evaluate for the possible development of papilledema are indicated until teenage years. Ptosis surgery may also be needed.

Diagnosis

Due to its mild clinical manifestations, Saethre-Chotzen syndrome is assumed to occur more frequently because of under-diagnosis. Syndactyly of fingers 2, 3 and duplicated large toes are pathognomonic Saethre-Chotzen syndrome. Without the presence of such findings, clinical manifestations including facial asymmetry, low frontal hairline, and ptosis may help in the diagnosis. Definitive diagnosis can be confirmed with genetic testing for *TWIST1* gene mutations, found in 40–80 % of Saethre-Chotzen patients [122, 123].

Management

The craniosynostosis of this condition is often mild and may not require surgical intervention. Patients with marked cranial dysmorphism secondary to suture synostosis should undergo the typical procedures for suture synostosis (Fig. 7.14b). Brain imaging and electroencephalography should be performed in patients with a seizure disorder [120]. Otolaryngologic evaluation is warranted in patients with recurrent otitis media because tympanostomy tubes may improve hearing. These patients are at risk for amblyopic secondary to ptosis, high or asymmetric refractive errors, warranting regular ophthalmologic evaluations.

Other Craniosysostosis Syndromes

Other craniosynostosis syndromes occur more rarely, and exhibit variable clinical and genetic heterogeneity. However, these syndromes are often caused by mutations in the same genes as the more common craniosynostosis syndromes: *FGFR2*, *FGFR3*, and *TWIST1*. Advances in molecular genetics

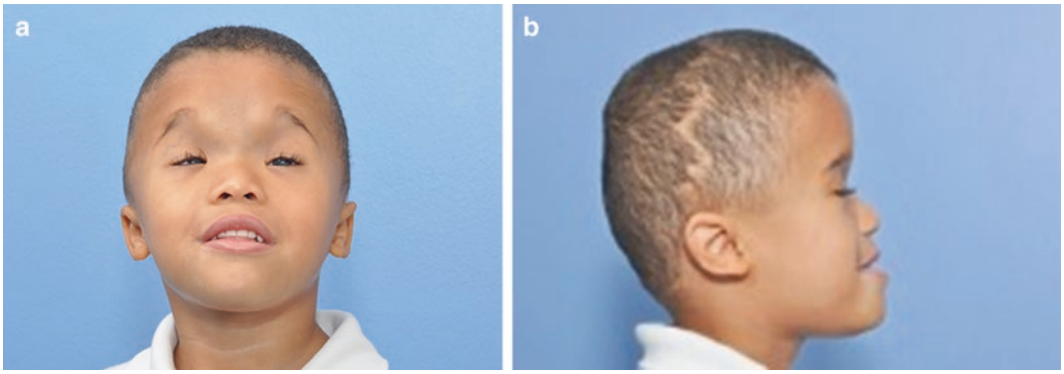

Fig. 7.14 (**a**), (**b**) Patient with Saethre-Chotzen syndrome with a classic broad retruded forehead secondary to bilateral coronal synostosis, low hairline, marked bilateral ptosis, and small, posteriorly rotated ears with abnormal crus. The patient is status post frontal orbital advancement, revealing classic zigzag-shaped incisional scar

have led to the discovery of additional genes associated with more rare craniosynostosis syndromes (Table 7.1) [124].

Conclusion

Any pediatric patient with craniosynostosis requires a multidisciplinary work-up which includes ophthalmologic evaluation. The patient should be assessed in the first year of life per the guidelines outlined by McCarthy and colleagues, with specific attention paid to the presence of proptosis, corneal exposure, globe luxation, refractive errors, strabismus, amblyopia, and optic nerve integrity [125].

Clefting Disorders

Introduction

Clefting disorders are the class of craniofacial anomalies that are associated with facial clefts. There currently is no accepted classification system that comprehensively includes the entire spectrum of craniofacial disorders. The Whitaker classification, the most commonly used and referenced system, categorizes craniofacial disorders into five morphological groups-clefts, synostoses, atrophy, neoplasia and unclassified. In this section we plan to discuss the clefting disorders [126].

Pierre Robin Sequence

Definition

Pierre Robin sequence (PRS) is classically defined as a congenital deformation consisting of micrognathia, glossoptosis, and airway obstruction [127]. Micrognathia and the retropositioned tongue can obstruct the airway causing respiratory distress and poor oral feeding. Prenatal suspicion of PRS is essential for preparing the delivery team for a possible airway emergency. Because PRS is based on clinical findings, it cannot be definitively diagnosed until delivery with demonstration of airway compromise.

History

PRS was originally described in 1923 by French physician Pierre Robin as a triad of symptoms that includes micrognathia, glossoptosis, and upper airway obstruction [36]. Robin also associated a U-shaped cleft palate with these findings.

Epidemiology

The incidence of PRS is estimated 1 in 5600–14,000 live births [128–131], with a mortality rate reported in the range of 10–30 % [132–135]. There is a slight female predilection [128, 131].

Systemic Manifestations

Micrognathia and glossoptosis cause upper airway obstruction in the majority (87.5 %) of PRS patients, which results in respiratory desaturations when these patients are in the supine position. They frequently have lower airway obstruction as well, and these findings combine to result not only in respiratory complications such as aspiration and infection, but also in feeding issues with gastroesophageal reflux disease and failure to thrive [130, 132, 134, 136–139].

Ophthalmic Manifestations

There are no ophthalmic abnormalities in patients with isolated PRS. The sequence does, however, have a strong correlation with craniofacial syndromes that do have associated ocular anomalies, including Stickler, velocardiofacial, and Treacher Collins syndromes, the latter of which is discussed in further detail below [121, 130, 138, 140].

Table 7.1 Craniosynostosis syndromes

	Diagnosis (OMIM) number	Gene	Mode of inheritance	Craniosynostosis and craniofacial abnormalities	Systemic findings	Ophthalmic findings
1	Apert syndrome 101200	*FGFR2*	Autosomal dominant	Coronal, sagittal, metopic craniosynostosis, turribrachycephalic, wide calvarial defect at level of fontanels, high prominent forehead, midface hypoplasia, beaked nose, high arched palate.	Complete syndactyly of the fngeres and toes, numerous CNS malformations, megaloencephalic, ventriculomegaly, gyral malfromations; cleft palate, hearing loss, fused cervical vertebrae, cardiovascular system and genito-urinary abnormalities.	Exorbitism, hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
2	Crouzon syndrome 123500	*FGFR2*	Autosomal dominant	Coronal craniosynostosis most common, also saggital, metopic, midface hypoplasia prominent forehead, risk of late-onset craniosynostosis.	Prominent beaked nose, cervical spine abnormalities, High arched palate, mandibular prognathism, dental malocclusion, conductive hearing loss, Chiari malformation.	Exorbitism, hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
3	Pfeiffer syndrome 101600	*FGFR1*	Autosomal dominant	Coronal craniosynostosis or pansynostosis, midface hypoplasia, mandibular prognathism, beaked nose, narrow palate.	Brachydactyly, broad and short toes and thumb, cervical or lumbar vertebrae fusion, radiohumeral and radioulnar synostosis, laryngotraceal abnormalities, choanal atresia, preauricular tags, bifid uvula, supernumerary teeth, pyloric stenosis, and anteriorly positioned anus.	Ptosis, exorbitism, hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
4	Muenke syndrome 602849	*FGFR3*	Autosomal dominant	Unicoronal or bicoronal craniosynostosis; midface hypoplasia, low set hairline, beaked nose.	Brachydactyly, phalangeal hypoplasia, coned epiphyses, hallux valgus, and tarsal, calcaneal, and navicular fusions; carpal bone fusion, sensorineural hearing loss.	Ptosis, exorbitism, hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
5	Saethre-Chotzen syndrome 101400	*TWIST*	Autosomal dominant	Unicoronal or bicoronal, sagittal or metopic craniosynostosis, low frontal hairline, abnormal ear crus.	Brachydactyly and syndactyly of digit 2 and 3, bifid halluces of the large toe.	Ptosis, exorbitism, hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
6	Antley–Bixler syndrome with genital abnormalities 207410	*POR*	Autosomal recessive	Coronal and lambdoidal craniosynostosis, trapezoidocephaly, brachycephaly with frontal bossing, severe depression of the nasal bridge, low-set ears.	Radiohumeral synostosis, medial bowing of the ulnae, bowing of the femora, slender hand and feet, contracture of the proximal phalanges, advanced bone age; congenital heart disease, genitourinary malformations, renal malformations, congenital adrenal hyperplasia.	Ocular proptosis, downslanting palpebral fissures, hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
7	Baller–Gerold syndrome 218600	*RECQL4*	Autosomal recessive	Coronal craniosynostosis most common, also metopic, lambdoidal, prominent nasal bridge.	Absent or hypoplastic radii, absent carpals, metacarpals, phalanges, shortened ulna, genitourinary malformations, capillary hemanigiomas.	Epicanthal folds, hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
8	Beare–Stevenson, cutis gyrata syndrome 123790	*FGFR2*	Autosomal dominant	Craniosynostosis commonly with cloverleaf skull or ear defects, crouzonoid facial features.	Skin manifestions: skin furrows and cutis gyrata that affect the limbs, trunk, face and scalp; acanthosis nigricans, skin tags, anogenital anomalies, pyloric stenosis.	Ocular proptosis hypertelorism, Corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
9	Carpenter syndrome 201000	*RAB23*	Autosomal recessive	Variable craniosynostosis (sagittal, lambdoid, coronal sutures).	Obesity, cardiac defects. preaxial polydactyl of the feet; syndacty, aplasia or hypoplasia of the middle phlanges of the hand, growth retardation, mental retardation, hypogenitalism, hearing loss, dental abnormalities, hydronephrosis, precocious puberty.	Hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
10	Jackson–Weiss syndrome (OMIM 123150)	*FGFR2*	Autosomal dominant	Variable features from mild prominence of the forehead to severe acrocephaly, midface hypoplasia.	Medially deviated great toes, tarsal bone fusion commonly calcaneo-cuboid fusion, cutaneous syndactyly of the second and third toes.	Exorbitism, hypertelorism, corneal exposure, amblyopia, strabismus, optic nerve edema or pallor.
11	Shprintzen-Goldberg yndrome 182212	*SKI gene*	Unknown	Variable craniosynostosis of coronal, sagittal, or lambdoid sutures.	Joint hypermobility, arachnodactyly, pes planus, hydrocephalus, chiari malformation, cardiovascular anomalies, abdominal wall defects, cryptorchidism.	Myopia

Diagnosis

The diagnosis is made clinically. Recent studies have supported the role of SOX9 and KCNJ2 mutations in the etiology of this disease, so genetic testing may be warranted if this diagnosis is unclear [141]. The mortality has dropped dramatically with introduction of modern treatment protocols [132].

Management

Clinical examination for airway obstruction should prompt the clinician to modify the patient's positioning to achieve a less labored breathing pattern. Polysomnography and monitoring for CO_2 retention are better ways to objectively evaluate for proper oxygenation and ventilation [140, 142, 143]. Initial conservative management for respiratory difficulties includes positioning, supplemental oxygen, continuous positive airway pressure, and respiratory stimulants such as caffeine or aminophylline. Nearly half of PRS patients suffering from respiratory distress will require more invasive treatments, with oro- or naso-pharyngeal airways, endotracheal intubation, or surgical intervention in the form of tracheotomy, glossopexy, or mandibular distraction osteogenesis [136].

Daily weights and oral intake should be monitored in order to see if a patient is obtaining adequate nutrition. If feeding difficulties are observed, or failure to thrive is suspected or documented, conservative interventions with feeding positioning and diet modification should be the first line of treatment. If these modifications fail to improve feeding and weight gain, more invasive treatments such as parenteral nutrition and nasogastric tubes should be pursued. If these methods are still unsuccessful, then surgical intervention with placement of a gastrostomy tube may be necessary. Patients with upper airway obstruction are more likely to need invasive feeding interventions than those without such obstruction [136].

Treacher Collins Syndrome

Definition

Treacher Collins Syndrome (TCS) is one of the craniofacial disorders characterized by bilateral zygomatic and malar hypoplasia, mandibular hypoplasia, external ear abnormalities and lower eyelid abnormalities [139, 144]. Mandibular hypoplasia often presents with micrognathia and Pierre Robin Sequence [139]. Mandibular and maxillary hypoplasia can have significant effects on the temporomandibular joint, including ankylosis.

History

The first description of the classic lid anomalies associated with Treacher Collins are credited to Barry in 1888 and were further expanded upon by Treacher-Collins in 1900 [145, 146]. In Europe, it is traditionally referred to as Franchetti-Kline syndrome named after the individuals who performed research on the condition.

Epidemiology

Affecting approximately 1 in 50,000 live births, 40 % of patients will have a hereditary form while the other 60 % result from de novo mutations. It is an autosomal dominant disorder with a gene mutation found on the *TCOF1* gene [144]. Two other genes commonly involved include the *POLR1C* and the *POLR1D* genes [147]. Van der Mulen et al. postulated that the condition is a result of failure of fusion of the facial and mandibular facial processes [144]. Others have suggested that it is manifestation of a combination of the Tessier 6, 7, and 8 facial clefts [148, 149]. No gender predilection has been described in Treacher Collins syndrome.

Systemic Manifestations

The ears are usually small, malformed, or microtic [139]. Other otologic manifestations of TCS include atretic or stenotic external auditory canals, which result in conductive hearing loss [150]. Cleft lip or palate is often noted. Clefting of the secondary palate is seen in approximately 36 % [150–152]. Ectopic growth of hair on to the cheek can be seen. They can have delayed speech or motor development, most likely related to the hearing difficulties [139].

Ophthalmic Manifestations

Adnexal anomalies in Treacher Collins syndrome include downward slanting of the palpebral fissures due to absence of the lateral orbital walls, lower-eyelid colobomas or pseudocolobomas, and absence of the eyelashes in the medial aspect of the lower eyelids [139, 152]. Other abnormalities include decreased vision, present in 37 % of patients, which is usually secondary to amblyopia and significant refractive errors, often astigmatism in the same axis as the downslanting fissures. Strabismus is present in 37 % of patients, with exotropia being more common than esotropia. Patients with significant lid dystopia may develop corneal exposure. Optic atrophy and papilledema are not associated. Dacryostenosis and ptosis have also been reported [152].

Diagnosis

TCS is a clinical diagnosis aided by radiographic findings and further supported by gene testing, as discussed earlier in this chapter. Imaging findings include hypoplasia of the malar bones, micrognathia, and absence of the lateral orbital walls [152]. These patients have a steep mandibular plane on cephalometric analysis due to a shortened posterior facial height from the hypoplastic mandible and maxilla [153].

Management

Treatment of patients with Treacher Collins involves care from birth until skeletal maturity. As with most patients with

craniofacial issues, surgical planning is age dependent. During the early years, birth until 2 years, airway and nutrition are the most important treatment considerations. If patients suffer from micrognathia and Pierre Robin sequence, treatment protocols should be implemented [154]. Poor weight gain and failure to thrive is a common occurrence in these patients. Speech and feeding specialists should become involved early to assist with care strategies. Options range from positioning, specific feeding techniques, oral/nasal gastric tubes, or gastrostomy tubes. Patients must demonstrate the ability to gain appropriate weight on a daily basis before discharge considerations. Clefts should be addressed during this age period, as is routine for non-syndromic clefts. If airway management remains an ongoing issue, consultation with the otolaryngology team regarding adequate timing of palate closure is necessary to prevent any problems post-operatively.

From age 3 to adolescence, patients with a cleft palate should be evaluated by a speech therapist. Because patients are beginning to integrate into the education system and interact with their peers it is an important time for social development. Psychological evaluation and counseling should be available to help the family and patient deal with potential problems. At 8–10 years, reconstruction of the orbito-zygomatic region should begin [155]. Because the orbits are close to fully grown by this time, full thickness cranial bone grafts are contoured to create the malar and lateral orbital deficiency. Other options for malar reconstruction have been described, including rib grafts and vascularized calvarial flaps [156, 157]. At the same time, lateral canthalplasty can be secured to the reconstructed malar complex in an attempt to correct the anti-mongoloid slant. The lower eyelid colobomas can be addressed after reconstruction of the orbital framework. This can be done with a number of techniques, the most common being a bipedicled or unipedicled upper to lower eyelid musculocutaneous flaps [158, 159]. Timing for ear reconstruction for microtic ears depends on the technique used. For advocates of the 4-staged Brent technique, this can be started at around 7 years old, or when the child is old enough to understand and participate in his or her treatment [160]. For advocates of the Nagata ear reconstruction, surgery is delayed until later, when there is enough costo-cartilage for the ear framework [161].

At skeletal maturity, 16–18 years, orthognathic surgery is considered to correct any malocclusion. These cases are some of the most complex, and require precise pre-surgical planning to achieve normal occlusion and correct the facial profile. Early mandible distraction is endorsed by some groups in an attempt to increase the vertical height of the ramus [162]. This helps treat airway difficulties caused by micrognathia, but also increases the amount of bone stock for future orthognathic procedures [163]. Mandible distraction in TCS is a controversial topic and the ideal timing is still being debated.

Ophthalmic management includes vigilance for correction of significant refractive errors, diagnosis and treatment of amblyopia, and if needed, strabismus surgery. Corneal exposure from lid dystopia can be conservatively treated with artificial tears and lubricants, but malpositions, colobomas, and pseudocolobomas often require more aggressive treatment with surgical intervention, such as lateral tarsorrhaphy or lower lid skin grafts [153]. Zygomatic and orbital reconstruction have been proposed, but no studies have looked at the application of these procedures in Treacher Collins.

Frontonasal Dysplasia

Definition

Frontonasal dysplasia (FND), also known as median cleft syndrome, frontonasal dysostosis, or Tessier 0/14 cleft, is a congenital condition resulting in malformation of the forehead and midface. Its most common features include a broad forehead with possible bony midline cleft (anterior cranium bifidum occultum), and hypertelorism. There are several subtypes of FND, which include X-linked craniofrontonasal syndrome (CFNS), acromelic frontonasal dysplasia (AFND), and oculoauriculofrontonasal syndrome (OAFNS). Each subtype has distinct phenotypic and genotypic characteristics which are discussed in further detail below.

History

Sedano and colleagues first used the term "frontonasal dysplasia" in 1970 [164]. Cohen, a coauthor on the original paper, further delineated the features of this syndrome in 1979 [165]. While multiple publications have incorporated FND into their classification schemes on craniofacial clefts, the most famous of these was introduced by Paul Tessier, He described patients with FND as having a Tessier 0/14 cleft, involving the midline structures of the facial skeleton [166]. Different classification schemes have been proposed for the subtypes of FND, but the literature is inconsistent in their usage [164, 167].

Epidemiology

While the frequency of FND is not clear, several inheritance patterns have been well characterized depending on the subtype in question. In cases of CFNS, multiple studies investigating the pedigrees of these families have shown an X-linked pattern, but it is paradoxical in that the females with this gene have a more severe phenotype than that of males. In 2004, mutations in a receptor tyrosine kinase protein encoded by the EFNB1 gene were concurrently described by labs led by Twigg and Wieland as causative of CNFS [168, 169]. This protein has been shown to be expressed in the frontonasal neural crest in murine models, with loss-of-function mutations demonstrating cleft palates, shortening of skulls, sternal abnormalities, and omphalocele in these mice. Similar to their human counterparts, female mice with this mutation also show a more severe phenotype [170, 171]. Other subtypes of FND have been associated with autosomal recessive

inheritance. The ALX, or Aristaless-like homeobox, genes are thought to be involved in craniofacial development. ALX1 mutations have been associated with microphthalmia and severe facial clefting, while ALX3 is associated with frontorhiny, and ALX4 is associated with hypertelorism, frontal alopecia, and median clefting of the nose [172–174]. Recent evidence has indicated that genetic mutations result in a disruption of ciliary proteins on neural crest cells associated with the cranium [175].

Systemic Manifestations

Systemic abnormalities vary widely between males and females affected with the CFNS subtype. Males typically only present with craniofacial involvement, including malocclusion, cleft lip, and cleft palate. Females, in contrast, frequently present with craniosynostosis, most commonly unicoronal or bicoronal, but sagittal, metopic, and multisuture synostosis have also been reported. They may have complete or partial agenesis of the corpus callosum. Females frequently develop thick and wiry hair between the ages of 18 and 36 months which is not familial in nature, with a low anterior hairline and widow's peak. Skeletal anomalies are also common in females, manifesting with abnormalities of the clavicles, thorax, and spine. They may also have mild syndactyly, camptodactyly, or ridging/splitting of the nails on their fingers [176, 177].

FND subtype OAFNS is characterized by ear tags, microtia, epibulbar dermoids, and hemifacial microsomia, which may make it difficult to distinguish from oculo-auriculovertebral syndrome (see CFM section below for further detail). These patients generally have normal intellect, and may have a lipoma of the corpus callosum [167].

AFND is characterized by terminal limb defects, most commonly aplasia or hypoplasia of the tibia. They may also have preaxial polysyndactyly, or hypoplasia of the talipes or tibia. They frequently have agenesis or lipoma of the corpus callosum, and may have delayed development or encephalocele. Males may present with cryptorchidism [167].

Other systemic associations with FND include cardiac malformations, such as tetralogy of Fallot and atrial or ventricular septal defect, and neurologic manifestations, including cortical dysplasia, encephalocele and seizures [167].

Ophthalmic Manifestations

The most common ophthalmic abnormality in the CFNS subtype is strabismus, typically V-pattern exotropia secondary to hypertelorism, although esotropia and dissociated vertical deviations have also been described. They may have ametropia, with astigmatism and hypermetropia being the most common presentations, which may result in amblyopia. Patients also frequently have nystagmus [77, 177]. The OAFNS subtype is frequently associated with epibulbar dermoids and eyelid colobomas [167].

Other ocular manifestations associated with FND include optic nerve anomalies, such as morning glory disc [178]. Patients have also been reported to have colobomas of the iris, choroid or retina, and ptosis. Less commonly reported associations are cataract, nystagmus, anophthalmia, and microphthalmia [167].

Diagnosis

The diagnosis of FND is made clinically, but genetic testing can be confirmatory if the clinical presentation and inheritance pattern are consistent with a particular subtype. Genetic counseling is always encouraged for families with a history of FND.

Management

Facial bipartition allows medialization of the orbits. Any bony operation on the orbits is delayed until 8–10 years of age to prevent relapse and revisionary surgery. Nasal reconstruction with onlay bone grafts is commonly preformed to reconstruct the bony nasal vault and provide for proper nasal tip projection. Refer to the earlier section on craniosynostosis for further details on the management of the CFNS subtype. Given the diverse systemic involvement of the different subtypes of FND, thorough history and physical should be performed with additional neurologic and cardiac workups as indicated.

Ophthalmic management includes vigilance for amblyopia, correction of refractive errors, and strabismus surgery if needed. Orbital repositioning often leads to an eso-shift of the eyes, and it may be prudent to wait to perform any strabismus surgery until after the orbital procedures.

Craniofacial Microsomia

Definition

Craniofacial microsomia (CFM), also called oculoauriculovertebral (OAV) spectrum, is a distinct subgroup of unilateral or bilateral craniofacial syndromes, arising from anomaly of the first and second branchial arches. The neural crest cells migrate into the arches during week 4 of gestation. Disturbance of this migration result in defects of the face, ears and maxilla [151]. Facial asymmetry is frequently the presenting symptom, affecting both facial skeleton and soft tissue. Skeletal deformities include mandibular and maxillary hypoplasia, which results in hemifacial microsomia, as well as cervical bone abnormalities and microtia [156, 179]. Goldenhar syndrome is part of the spectrum of CFM, and is characterized by mandibular hypoplasia, cervical anomalies and an ipsilateral dermoid of the globe.

Epidemiology

Genetically, CFM is typically sporadic, although there have been reports of families with autosomal dominant and auto-

somal recessive inheritance patterns [157, 158, 179]. The incidence is approximately 1 in 3500 to 26,000 live births [156, 179]. Males are more frequently affected than females with a birth prevalence of 3:1. The right side of the face seems more severely affected than the left. Risk factors for CFM include maternal diabetes and twin pregnancy [179].

Systemic Manifestations

In addition to the craniofacial manifestations described earlier, these patients may present with cleft lip, cleft palate, transverse facial clefts, and bilateral micrognathia. Otic findings include microtia, anotia, atresia of the external auditory canal, and preauricular skin tags [179]. Extracranial manifestations include cervical spine fusions, commonly at the C2–C3 level, and scoliosis or kyphoscoliosis [162, 179]. Spina bifida has also been described, as has developmental delay or intellectual disability. CFM is frequently seen in association with facial nerve palsy, affecting the upper, lower, or both branches of the facial nerve [180]. Patients may present with congenital heart defects, including atrial and ventral septal defects, patent ductus arteriosus, patent foramen ovale, and pulmonary valve stenosis. Pulmonary defects and urogenital defects are uncommon [163, 179, 181].

Ophthalmic Manifestations

Epibulbar dermoid and/or limbal dermoids may be found in patients with CFM spectrum, namely Goldenhar syndrome. Other ocular abnormalities include ipsilateral upper and lower lid colobomas, epicanthal folds, dystopia canthorum, orbital dystopia, Duane syndrome, and microphthalmia [179].

Diagnosis

The diagnosis of patients with craniofacial microsomia is clinical, but should follow one of the commonly accepted classification systems due to the wide range of phenotypic variability. This variability can range from simple preauricular skin tags to severe hemifacial microsomia with microtia or anotia [159]. Patients frequently present with extracraniofacial manifestations. The most commonly used classification system is the OMENS+ classification [160]. This system takes into account major anomalies, including (O)rbital, (M)andible, (E)ar, (N)erve, (S)oft tissue, and +/− any extracranial manifestations. Orbital manifestations include dystopia due to ipsilateral maxillary hypoplasia, shortened palpebral fissures and coloboma of the upper eyelid. Mandibular defects typically present as micrognathia (associated with Pierre Robin sequence), and asymmetry of ramus and condyle. The degree of manifestation ranges from general hypoplasia to poorly formed or missing temporal mandibular joints. Pruzansky et al. provide a clear classification of the spectrum [161]. Ear anomalies encompass pre-auricular facial tags or pits and microtia/anotia, with conductive or neurosensory hearing loss. Nerve involvement frequently includes anomalies of facial nerve with absent parotid gland [180].

Management

Treatment of CFM depends on the severity. In milder cases, in which only skin tags are present, simple removal at an appropriate age can be the extent of the treatment. It is important to keep in mind that skin tags may be associated with the facial nerve, particularly when there are cartilage remnants. Ear reconstruction in microtia follows the same principle as described in other associated craniofacial syndromes.

Conservative management of mandibular hypoplasia consists of surgery at the time of skeletal maturity, with additional orthognathic procedures if needed [182, 183]. This approach is universally accepted for milder forms of mandibular and maxillary hypoplasia. In more severe cases, early intervention with mandibular distraction and orthodontic techniques may be indicated [184].

Ophthalmic evaluation of limbal dermoids with particular attention to induced astigmatism and the presence of anisometropia is indicated. Management may include excision of the limbal dermoid via lamellar keratoplasty, though this runs the risk of increasing astigmatism postoperatively [185]. Therefore, careful follow-up with refraction and monitoring for the development of amblyopia is required. Epibulbar dermolipomas are typically lateral and hidden by the eyelids, and rarely require excision. Strabismus surgery may be indicated in patients with Duane syndrome. Patients with facial paralysis are at risk for corneal exposure, and management may include use of artificial tears and ointments, tarsorrhaphy, and gold weights implanted in the upper eyelid.

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Ocular Manifestations of Dermatologic Diseases

8

Jennifer L. Jung, Lance M. Siegel, Lawrence F. Eichenfield, and Gregg Lueder

Genetic Syndromes

Albinism

Definition

Albinism refers to a group of disorders with mutations in the melanin synthesis pathway resulting in reduced or absent pigmentation in eyes, skin or hair [1, 2]. It is most often due to a defect in tyrosine conversion affecting pigment production. The condition with simultaneous hypopigmentation of the skin, hair and eyes is referred to as oculocutaneous albinism (OCA). If it is only involving the eyes, the disorder is called ocular albinism (OA).

OCA is a group of autosomal recessive disorders involving many different genes [Table 8.1] [2]. Most patients are compound heterozygotes, meaning they have two different mutations in earn copy one of the genes [2]. The clinical spectrum for OCA can vary from complete lack of pigmentation in OCA1A to milder forms where pigment can accumulate over time [1, 3].

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OA, which represents 10 % of all albinism, is a X-linked recessive disorder. Patients may have slightly lighter skin and hair, but it can also occur in patients with black hair [1]. It is due to a mutation in the *GPR143* gene whose protein product controls the number and size of melanosomes [1]. Due to lyonization, approximately 80 % to 90 % of carrier females have a mud-splattered fundus where patches of amelanotic retinal pigment epithelium (RPE) cells expressing the X chromosome with the mutation are adjacent to patches of melanotic RPE cells without the mutation [1]. About 75 % of carriers can also manifest iris transillumination.

Epidemiology

Albinism can affect people of all ethnic backgrounds. Approximately one in 17,000 people have albinism [Table 8.1] [2]. OCA2 is the most prevalent form worldwide and is the most common type of albinism in OCA patients of African descent. OCA3 is rare in Caucasians and Asian population. OCA4 is reported to be present in approximately 5–8 % of German patients with albinism and 18 % of Japanese patients [2].

Systemic Manifestations

Patients with OCA have generally reduced but variable degree of skin and hair hypopigmentation [2]. In OCA1A, hair, eyelashes, eyebrows and skin are white. Pigment does not develop and skin does not tan. In OCA1B, previously known as yellow albinism, hair and skin may develop some pigment with time, usually after 1 to 3 years. Temperature-sensitive variants may have depigmented body hairs but pigmented hairs on hands and feet due to lower temperatures. In OCA2, the amount of cutaneous pigment varies. Newborns may have pigmented hair and may also have nevi and ephelids. Patients with OCA3, also called Rufous or red OCA in African patients, have red hair and reddish brown skin. OCA4 cannot be distinguished from OCA2 clinically [2]. Incidence of skin cancer is increased in patients with OCA [2].

Two types of albinism with special importance are Chediak-Higashi syndrome (CHS) and Hermansky–Pudlak

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Table 8.1 Some types of oculocutaneous albinism

Type	Gene	Gene product	Prevalence
OCA 1 (A and B)	*TYR*	Tyrosinase	1/40,000
OCA 2	*OCA2*	P Protein	1/36,000 (Caucasians)
			1/3900–10,000 (Africans)
OCA 3	*TYRP1*	Tyrosinase-related protein I	1/8500 (Africans)
OCA 4	*MATP*	Membrane-associated transporter protein	Rare (Caucasians)
			1/85,000 (Japanese)

Syndrome (HPS). Chediak-Higashi syndrome is a rare autosomal recessive disorder of intracellular vesicle formation that leads to accumulation of lysosomal granular inclusions in different cell types including melanocytes, white blood cells, platelets and neurons [1, 3]. Accumulation of melanosomes in melanocytes leads to hypopigmentation and ocular findings similar to OCA. Cutaneous manifestations include metallic silver sheen to the hair and gray patches on this skin. These patients are also prone to severe bacterial infections resulting from decreased neutrophil chemotaxis and have an increased propensity for bruising, peripheral neuropathy, and lymphoreticular malignancy. Diagnosis can be made microscopically by the presence of macromelanosomes on skin biopsy and giant peroxidase-positive granules in leukocytes [3]. Bone marrow transplant is the only curative treatment for CHS.

Hermansky-Pudlak syndrome is an autosomal recessive disorder that is rare, except in Puerto Rico where prevalence is 1 in 1800 individuals [2, 3]. There are eight identified gene mutations to date that affect the formation of intracellular vesicles, including melanosomes in melanocytes and dense bodies in platelets. Cutaneous and ocular findings range from mild to severe forms of OCA. These patients may also suffer from bleeding disorders, which usually manifest as cutaneous bleeding but may also lead to more severe forms of intracranial hemorrhage. About 50 % of individuals also have accumulations of ceroid lipofuscin, which leads to interstitial lung fibrosis, cardiomyopathy, granulomatous colitis and renal failure [1, 3]. HPS can be diagnosed by bleeding time, platelet aggregation studies, electron microscopy of platelet morphology, and biopsy of affected tissue demonstrating ceroid deposition [1, 3]. Patients with HPS should receive preprocedural platelets and should have regular ophthalmologic examination.

Ocular Manifestations

Ocular manifestations of albinism include iris translucency, hypopigmentation of the fundus, foveal hypoplasia, nystagmus, refractive error, strabismus and abnormal decussation of optic nerve fibers [1, 2]. The most common finding is varying degrees of iris transillumination. While most have light colored irises, some have such severe absence of pigment in the iris that the fungus reflex gives the iris a red or pink color. Nystagmus is commonly present and can vary in type from triangular wave form in infancy to later pendular or jerk nystagmus [2]. Because pigmentation in RPE is required for normal development of macula, patients with albinism often have foveal hypoplasia, which contributes to a significant impairment in vision. Thinning of the retina and absence of the foveal pit can be demonstrated in an optical coherence tomography. Foveal hypoplasia is not specific for albinism as it can occur in other disorders such as aniridia, or as an isolated finding. Patients with albinism often have photophobia and reduced visual acuity in the range of 20/60 to 20/400. Reduced vision may be due to refractive error, nystagmus, amblyopia and/or foveal hypoplasia [1].

A characteristic feature of albinism is the abnormal decussation of the optic nerves [1–3]. In normal individuals, 55 % of the optic nerve fibers decussate to the contralateral side at the optic chiasm [1]. In albinism, there is excessive crossing of the fibers, where up to 75–85 % of the optic nerve fibers decussate [1, 2]. This abnormal decussation is illustrative of the importance of developmental genetics. Due to the hypopigmentation of RPE and resulting macula hypoplasia, there is a delay in the development of retinal ganglion cells and their growth to the chiasm, leading to the misrouting of the optic nerves. This abnormal decussation of fibers may be a risk factor for developing strabismus as well as reduced stereoscopic vision [2]. The asymmetric decussation can be detected by 3-lead visual-evoked potential.

Management

For photophobia, dark glasses or photochromic lenses that darken with light exposure may be helpful [1, 2]. Visual acuity should be optimized with correction of refractive error with spectacles or contact lenses. Low vision consultation and individualized plans for low vision support is warranted for patients with severe vision impairment. Special attention should be given at school, such as high contrast written material, large type books, as well as optic devices that will help maximize their vision potential [1, 2].

Sunscreens are recommended with the minimum sun protective factor of 15.

Blau Syndrome

Definition

Blau syndrome (BS) (OMIM # 186580), also known as familial juvenile systemic granulomatosis, is a rare autosomal dominant systemic granulomatous disorder caused by a

mutation in the *NOD2* gene. Blau syndrome usually presents before age 4 [4]. The classic triad of Blau syndrome was uveitis, arthritis, and exanthema.

History and Epidemiology

Blau syndrome was initially described in 1985 by Dr. Blau and Dr. Jabs, who both reported families with granulomatous disease of the eyes and joints and were HLA B27 negative. Since then, many further reports were published that expanded the phenotypic variations to include fever, cranial neuropathies, cardiovascular abnormalities and visceral granulomas, including the liver and kidneys [4]. In 2009, an international registry was merged, and contains more than 100 cases of BS. There have been fewer than 200 persons belonging to 63 families with BS reported in the literature.

Systemic Manifestations

Skin inflammation usually presents as a granulomatous dermatitis as early as 1 month of age with tiny red/tan dots that start on the face and spread to the trunk. This rash consists of discrete erythematous plaques with multiple papules. The rash can be scaly or have hard nodules under the skin. Arthritis is usually a polyarticular synovitis and tenosynovitis and is commonly present (95%). Camptodactyly with synovial cysts are also be present. Other systemic findings, such as cardiovascular, visceral and cranial nerve abnormalities, are present in approximately one-third of patients with BS [4].

Diagnosis can be made by clinical findings, family history, genetic analysis, and biopsy of skin lesions or joint fluid revealing noncaseating granulomas. Clinically, BS may be indistinguishable with early-onset sarcoidosis (EOS) as both entities involve inflammation of skin, joints, and eyes. Both disorders are also caused by mutations in the *NOD2* gene, but the main difference is in the inheritance pattern where BS has an autosomal dominant inheritance pattern and EOS usually arises from de-novo mutations [4].

Ocular Manifestations

The most common ocular finding is granulomatous uveitis, which usually occurs in the first decade [5]. It is never the presenting symptom of BS but carries the greatest morbidity for patients with BS. It is what often drives the need for treatment [4]. Uveitis is can be in the form of bilateral anterior uveitis, vitritis, panuveitis, and/or multifocal choroiditis. Macular edema, optic nerve edema, and retinal detachments are also known to occur as well as other complications including band keratopathy, cataracts, and glaucoma. Significant visual loss has been reported in up to 46% of patients [4].

Management

Children with uveitis due to BS are treated similiarly to those with juvenile idiopathic arthritis [4]. Systemic treatment includes low to moderate steroids or methotrexate, with variable success. TNF-α (tumor necrosis factor-alpha) inhibition has also shown some efficacy in recent years [6]. There have been some reports of success with thalidomide and IL-1 receptor antagonists in small case series.

Blue Rubber Bleb Nevus Syndrome (Bean Syndrome)

Definition and History

Blue rubber bleb nevus syndrome (BRBNS) (OMIM #112200) is a venous vascular malformation syndrome primarily involving the skin and the gastrointestinal tract [7, 8]. BRBNS was initially described by Gascoyen in 1860, who reported the association of vascular hamartomas of the skin with intestinal lesions and gastrointestinal bleeding. Bean coined the term "blue rubber bleb nevus syndrome" in 1958 and since then, the disorder has been also termed Bean's syndrome. To date, fewer than 150 cases of BRBNS have been reported in the literature. Cases of autosomal dominant inheritance have been described, but most are sporadic [7].

Systemic Manifestations

Bluish venous malformations in BRBNS have a range of clinical appearance from small blue-black punctate papules to large disfiguring tumors. The most characteristic cutaneous lesion is raised, nipple like and refills slowly after compression. They can be numerous, numbering up to several hundred and most often occur on trunk or extremities. While many lesions are present at or shortly after birth, some have been diagnosed prenatally as early as in the fifth month of gestation. Lesions can increase in size and number with age [8]. In the past, these lesions have been incorrectly categorized as hemangiomas but now recognized as venous malformations. They have been occasionally reported on the face and eye [9]. Although many can by asymptomatic, pain and hyperhidrosis may be present. Skin lesions do not bleed spontaneously or undergo malignant change [8].

Gastrointestinal venous malformations are most often in the small intestines but can be present anywhere from the mouth to the anus. These lesions can result in frequent bleeding, potentially leading to occult blood loss and iron-deficiency anemia. Abdominal pain and other complications including intussusception, volvulus and infarction have been described. Venous malformations have been described in other organs including adrenal glands, kidneys, heart, lungs, bladder, penis, thyroid, spleen, central nervous system and muscle [8].

BRBNS is diagnosed clinically based on classic cutaneous findings. Basic evaluation should consist of complete history, physical exam, blood count and stool guaiac test. Histologically, vascular lesions are characterized by clusters of dilated irregular capillary spaces lined by a thin layer of endothelial cells in the dermis or subcutaneous fat [8]. Early diagnosis is important as gastrointestinal tract lesions can cause life-threatening hemorrhage, consumptive coagulopathy and iron-deficiency anemia [7].

Ocular Manifestations

Ocular findings included vascular lesions in the conjunctiva, iris, and macula. Orbital lesions have been reported as well, which have presented with sudden proptosis or intermittent proptosis with increase in intrathoracic pressure [7]. They are often tender with localized hyperhydrosis. Orbital lesions can be complicated by occurrence of thrombosis [7].

Management

Treatment for cutaneous lesions is required only when lesions are cosmetically disfiguring or functionally bothersome. Treatment modalities include Ruby, argon, and carbon-dioxide laser treatments, electrodessication, surgical excision and injection sclerotherapy. Pulsed dye laser is the most successful treatment for removing hundreds of lesions without recurrences [8].

Symptomatic gastrointestinal lesions can be treated with endoscopic photocoagulation, laser, sclerotherapy, or surgical excision. Oral iron supplementation is crucial in treating associated anemia with occult blood loss [8, 10].

Cowden Syndrome-Multiple Hamartoma Syndrome

Definition

Cowden syndrome (OMIM #158350) is an autosomal dominant cancer syndrome with increased risk for benign and malignant neoplasias [11]. It was initially described in 1962 as a mainly dermatologic disease; however, over time, the phenotypic spectrum has expanded to include cancer risks and neurodevelopmental disorders. The defect is associated with mutations in the tumor suppressor gene protein tyrosine phosphatase and tensin homologue (*PTEN*). It is now recognized that Cowden syndrome is part of a larger syndrome called PTEN hamartomatous syndrome, which includes Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome, and Proteus-like syndrome. These conditions all have risks of developing specific cancers. These syndromes are still considered to be heterogeneous as PTEN mutation may not be detected in all cases. Prevalence of PTEN mutation in Cowden syndrome is 80 % and 60 % in Bannayan-Riley-Ruvalcaba [12].

Systemic Manifestations

Cowden syndrome usually presents in the second or third decade of life. Mucocutaneous features include numerous flesh colored benign hamartomas coalescing in the skin to give a cobblestone appearance. Other dermatologic findings include lipomas, fibromas, and freckling of the glans penis. Tumors occur throughout the body in all three germ cell layers, with predilection for the breast, thyroid, endometrium, skin, and gastrointestinal tract [12]. In addition, high-flow vascular malformations accompanied by increased adipose tissue are frequently found in PTEN hamartomatous tumor syndromes. Among the first 100 cases of Cowden syndrome, the most common manifestations were thyroid goiter (68 %), fibrocystic breast disease (52 %), GI polyps (35 %), lipomas (31 %), and macrocephaly (21 %). Estimated breast cancer risk of 25–50 % is reported. A slight increase in risk for melanoma (6 % compared to 2 % in general population) is reported in patients with PTEN mutations. Annual dermatologic examination is recommended. Lhermitte-Duclos disease, or dysplastic gangliocytoma of the cerebellum, is a phenotypic variant of Cowden syndrome. Severe forms can be life-threatening with increased intracranial pressure, ataxia, and seizures.

Bannayan-Riley-Ruvalcaba syndrome (BRRS, OMIM # 153480) is the name used to denote the combination of three conditions formerly recognized as separate disorders which are Bannayan-Zonana, Riley-Smith, or Ruvalcaba-Myhre-Smith syndromes. It is an autosomal dominant syndrome of pediatric onset characterized by macrocephaly, hamartomas, hemangiomas, penile lentigines, and developmental delay [12]. Ophthalmic findings include downward slanting palpebral fissures, hypertelorism, strabismus, and pseudopapilledema [12].

Several characteristics as listed below should raise strong clinical suspicion for PTEN hamartomatous syndrome [11]:

- Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma)
- Extreme macrocephaly (children, +5 standard deviations above the mean adult women >60 cm, adult men >63 cm)
- Oral mucosal papillomatosis
- Penile freckling
- Hamatomatous/ganglioneuromatosis gastrointestinal polyps
- Glycogenic acanthosis
- Pediatric non-medullary thyroid carcinoma
- Endometrial cancer diagnosed prior to age 30

Ocular Manifestations

Trichilemmomas are tumors of the outer root sheath follicular epithelium that occur in isolation or in association with Cowden syndrome. Individual lesions measure between 3 and 8 mm in diameter and are generally smooth surfaced but a pileup of keratin can simulate a cutaneous horn [13]. Papillomatous papules also occur around the eyes and face. Retinal hamartomas can also be present, potentially leading to vision loss [14]. Retinal neovascularization in patients with Cowden syndrome has been described and is thought to be due to PTEN's role in regulating VEGF-regulated angiogenesis [15].

Management

Most critical aspect of management of patients with Cowden syndrome is heightened cancer surveillance according to the screening guideline advocated by National Comprehensive Cancer Network (NCCN) [12].

Local excision of trichilemmomas are often adequate with careful scrutiny of surgical margins to prevent benign recurrence [13].

Dyskeratosis Congenita

Definition and Epidemiology

Dyskeratosis congenita (DC) is a rare inherited bone marrow failure syndrome with increased risk for squamous cell carcinoma and hematolymphoid neoplasms [16]. First described by Zinsser in 1906, it is a disease of telomere maintenance dysfunction and can be inherited in autosomal dominant, autosomal recessive and X-linked recessive patterns [16]. Telomere maintenance has a significant role in aging and cancer predisposition. DC patient have premature telomere shortening, ultimately leading to premature stem cell exhaustion and tissue failure. Estimated annual incidence is <1 in one million. DC occurs more commonly in males, and clinical signs manifest around ages five to twelve [16].

Systemic Manifestations

The classic triad of dyskeratosis congenita is nail dystrophy, mucosal leukoplakia, and lacy reticular hyperpigmentation and atrophy of the upper body. It may be commonly accompanied by alopecia and premature graying as well. Skin and nail changes first appear. Nail dystrophy (present in 90 %) begins with ridging and longitudinal splitting and progresses to result in rudimentary or absent nails. Mucosal leukoplakia (80 %) can occur in the buccal mucosa, oropharynx, and tongue, and about 30 % of these leukoplakic areas can develop into squamous cell carcinoma, requiring frequent monitoring [16]. Other manifestations include dental, gastrointestinal, skeletal, neurological, immunological, ophthalmic, genitourinary and pulmonary tissue involvement. Additional minor features of dyskeratosis congenital are as follows: microcephaly, developmental delay, excessive sweating, short stature, hypogonadism, liver disease, and osteoporosis [16]. The most common complication of dyskeratosis congenita is bone marrow failure in childhood and pulmonary fibrosis in adults [16]. Bone marrow failure occurs in 80–90 % of cases by age 30 years and is the leading cause of death in patients with DC.

Ocular Manifestations

Eye problems develop in approximately 40–50 %. Most common findings are nasal lacrimal duct obstruction, trichiaisis, and cicatricial entropion, likely secondary to epithelial abnormalities in ocular skin and mucous membranes. Complications can lead to recurrent blepharitis, conjunctivitis, keratitis and permanent corneal changes. Retinal abnormalities can also occur and include hemorrhages, granular retinal pigment epithelium changes, peripheral retinal nonperfusion and retinal neovascularization [16, 17]. Exudative retinopathy has been reported to be specific to Revesz syndrome, a severe variant of DC. In addition to the syndrome specific ophthalmic findings, patients who receive radiation and steroids as treatment can develop cataracts, glaucoma and radiation retinopathy and optic atrophy [17]. Ophthalmologic evaluation should be performed on every patient with DC on diagnosis, and subsequent examinations should be part of their routine care.

Management

The only curative treatment is allogenic hematopoietic stem cell transplant. Bone marrow failure with DC does not respond will to immunosuppressive therapy. About 50–70 % of DC patients respond to androgens. These patients should be monitored closely for abnormalities in lipid profile and liver function [16].

Epidermolysis Bullosa

Definition

Epidermolysis bullosa (EB) is a group of disorders characterized by fragile epithelial tissue that is prone to blistering even with minor trauma [18]. EB is inherited as either autosomal dominant or autosomal recessive disease, depending on the type and subtype. Mutations in at least 18 genes have been identified to cause EB. These genes express various signaling and structural proteins within the epidermis and at the epidermal-dermal junction [19]. EB is classified under four major types: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler syndrome. Each of these forms has many different subtypes.

Systemic Manifestations

Epidermolysis Bullosa Simplex

EBS is the term for EB with blistering confined to the epidermis. It can be subdivided based on whether the blisters occur in the suprabasal or basal layer [19, 20]. Intraepithelial blisters come from cytolysis of the basal cells. Onset of disease usually occurs at or shortly after birth. Patients with milder forms of localized EBS may not develop symptoms until late childhood or early adulthood [19]. Depending on the subtype, patients can have varying severity of milia, scarring and nail dystrophy, especially when compared to the other forms of EB [19].

Junctional Epidermolysis Bullosa

In JEB, blisters develop in the junction, also called the lamina lucida, of the skin basement membrane zone. One characteristic clinical finding of JEB is the presence of enamel hypoplasia, which presents as localized or generalized pitting of tooth surfaces [19]. JEB-Herlitz is the more severe

subtype that comprises about 20 % of the American JEB population. Extensive granulation tissue formation that arises in within the first few months to 2 years of life is pathognomonic finding of JEB-Herlitz [19]. Hands and feet are relatively spared, but mucosal membrane involvement can be severe, leading to complications such as tracheolaryngeal obstruction and esophageal strictures [19]. Growth retardation and multifactorial anemia is almost always present [19]. Severe ocular problems can occur including corneal erosions, scarring and ectropion formation [19]. Bacteremia, septicemia and death usually occurs before 3 years of age. Non-Herlitz, JEB is more common but has less severe symptoms and complications. Prominent features include hypopigmentation of skin, atrophic scarring and alopecia [19].

Dystrophic Epidermolysis Bullosa

DEB can be subcategorized into autosomal dominant and autosomal recessive types. In both forms, blisters are located within the uppermost dermis, also known as the sub-lamina densa layer of the basement membrane zone [19, 20]. In general, all have some degree of blistering that in severe cases can cause of fusion of skin around digits, and scarring of the skin. Dystrophic or absent nails are common. Recurrent esophageal blistering leading to stricture is also common in both dominant dystrophic EB (DDEB) and recessive dystrophic EB (RDEB). DDEB tends to present with a mild phenotype. Blisering in the newborn period is common, but this tendency may decrease with age [21]. Patients with RDEB tend to have extensive blistering and erosions that develop from birth. The extensive and recurrent blistering and scarring often leads to pseudosyndactyly, or loss of interdigital space and contractures [21]. RDEB patients are at a higher risk for developing metastatic squamous cell carcinoma [19].

Kindler Syndrome

Kindler syndrome is a rare, autosomal recessive form of EB, which was added to the EB classification in 2008. It represents EB with blistering that occurs in multiple levels of the skin, rather than in a specific plane as in the other types of EB [20]. Clinical manifestation occurs at birth as generalized blistering and later as characteristic poikilodermatous pigmentation, skin atrophy, and photosensitivity [19]. Teeth are not involved although gingival fragility can be seen.

Diagnosis of EB can be made by the collective findings acquired from personal and family history and with laboratory data including immunofluorescence antigenic mapping and transmission electron microscopy [19]. Genetic testing for the specific mutations causing EB in a patient is often preferred because it can be helpful to distinguish cases in which clinical findings alone are unclear and help guide genetic counseling and future management and treatment.

Ocular Manifestations

Eye involvement can occur in all types of inherited EB as ocular surface is derived from ectoderm like the skin (Figs. 8.1, 8.2, 8.3). Common ocular signs of EB include

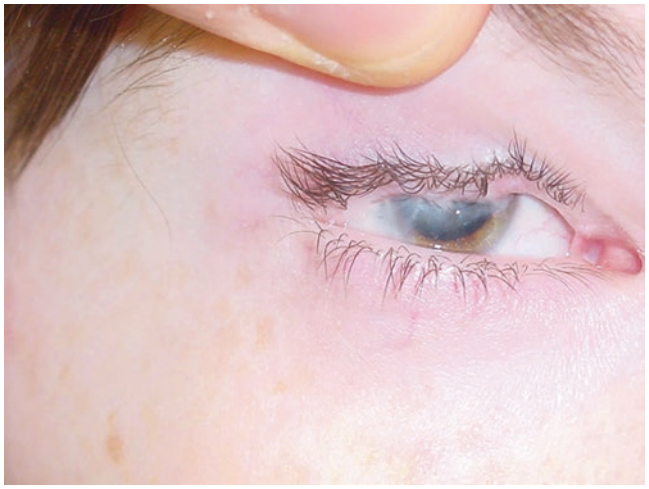

Fig. 8.1 EB Symblepharon, lid to cornea

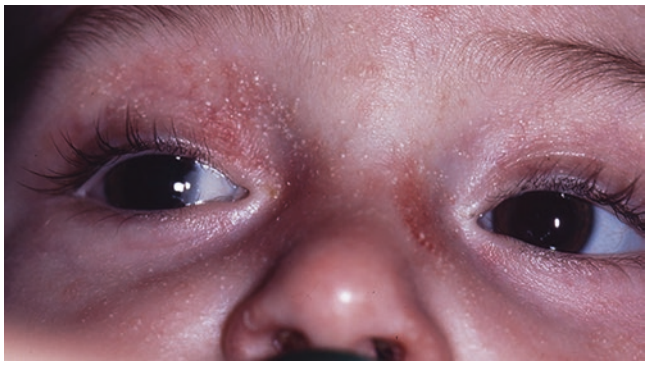

Fig. 8.2 EB Eyelids <<permission requested from McGraw Hill>>

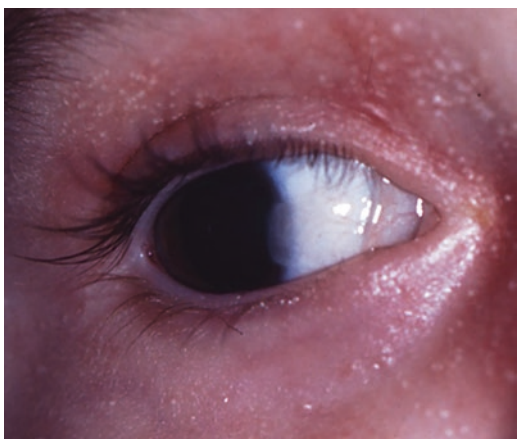

Fig. 8.3 EB Cornea <<permission requested from McGraw Hill>>

conjunctival irritation, corneal erosions, exposure keratopathy, and cicatrisation of eyelids and conjunctiva [22]. Corneal blister formation, either as intact vesicles or corneal erosions is one of the most common findings in EB [18]. Corneal findings have been reported in about 50–60 % of patients with JEB and RDEB as opposed to 1–6 % in EBS patients [18]. Repeated episodes can lead to pannus formation and corneal scarring. Symblepharon formation is confined to JEB and RDEB. Lacrimal duct obstruction has been reported in all EB types but in highest frequency in RDEB (12 %). Ectropion formation most often occurs in JEB patients (14 %). Patients with minimal symptoms, especially those with EBS, do not need regular eye exams as long as the patient and parents are cognizant of the symptoms and importance for evaluation when symptoms arise [22, 23]. For patients with JEB and RDEB, at least a biannual ophthalmic exam is recommended given the morbidity associated with the increased risk for ocular complications [22].

Management

The main therapy for ocular involvement is maintaining moisture and lubrication for irritated ocular surfaces from dryness and poor eyelid function [22]. In case of corneal erosions, soft contact lenses and topical antibiotic may be helpful under close monitoring. Ocular surface reconstruction and eyelid surgeries may be required for severe ocular involvement.

There is no effective cure for EB at present although active research promoted in the areas of gene therapy and cell therapy [24]. Prognosis is highly dependent on the type or subtype of EB. Patients with EBS and DDEB have normal life expectancy although with significant morbidity due to complications that can occur. Supportive care to prevent scarring, strictures and infection is crucial. Some forms of EB require daily wound dressing changes, which may take several hours to perform. Surgical intervention may be useful to prevent permanent deformities, and laser, skin grafts, tissue-engineered skin grafts, amniotic membranes, have been tried with variable success. GI strictures of oropharynx can often be problematic and endoscopic dilation has been employed. Bone-marrow transplant and gene-based therapies are in evolution.

Goltz Syndrome (Focal Dermal Hypoplasia)

Definition

Goltz Syndrome or focal dermal hypoplasia (FDH) (OMIM#305600) is a rare, X-linked dominant disorder of congenital mesodermal and ectodermal abnormality [25]. About 250 patients have been reported, mostly in females although there are few (usually mosaic) males affected with FDH. About 95 % of cases occur sporadically and 5 % are familial [25, 26]. It is due a mutation in *PORCN* gene, which is involved in the secretion and signaling of Wnt proteins that play a role in embryonic tissue development [25].

Systemic Manifestations

FDH is a multisystem disorder primarily involving the skin, skeletal system, eyes, and face. Classic features are patchy, hypoplastic skin, split hand/foot deformities, and ocular abnormalities [25]. In FDH, cutaneous findings are variable and can be present at birth or develop with age. Most characteristic feature is the blistering and widespread hypoplasia or aplasia of the skin that frequently follows Blashko's lines, which are the cell migration pathways that are linear on the limbs and circumferential on the trunk [27]. Hypoplastic areas are usually evident at birth although the severity and distribution may change with time. Unilateral involvement has also been reported [28]. Numerous soft tan papillomas may develop with age. Verrucoid papillomas commonly occur around the mouth and nose but also can be present in the esophagus, larynx and in genitoanal region [27]. Dystrophic or hypoplastic nails are less common. Sparse and brittle hair, and localized areas of alopecia are present. There can also be absent or supernumerary nipples [27].

Most patients with FDH have limb malformations evident at birth, including, syndactyly, oligodactyly, and split-hand/foot malformation [25, 27]. Less common malformations include camptodactyly and reduction defects of long bones. Osteopathia striata, which is a striated appearance of bones on X-rays, is commonly seen. Costovertebral segmentation abnormalities, such as fused ribs and hemivertebrae, are present at birth. These malformations may cause scoliosis as the child grows. Fibrous dysplasia of bone may affect any bone at any time. They are often asymptomatic but becomes evident when it is the site of a pathologic fracture. Giant cell-like tumors of long bones have been reported in associated with FDH and may develop in childhood or adulthood [27].

Craniofacial abnormalities include facial asymmetry, notched alae nasi, pointed chin, and small underfolded pinnae. These characteristics usually develop with time. Oral manifestations, including enamel hypoplasia, hypodontia, sypernumerary teeth, microdontia, taurondontia (prism-shaped molars), and fused teeth, are seen in more than half of affected individuals. Abnormalities of gastrointestinal and urogenital systems also occur such as diaphragmatic or fat herniations and structural abnormalities of kidneys [25, 27]. Development is usually normal for individuals with FDH. Some may have cognitive impairment [27].

Following evaluations are recommended to establish of extent of disease in individuals diagnosed with FDH: Chest X-ray, eye exam, consideration of abdominal MRI, renal ultrasound, hearing evaluation, and medical genetics consultation [27].

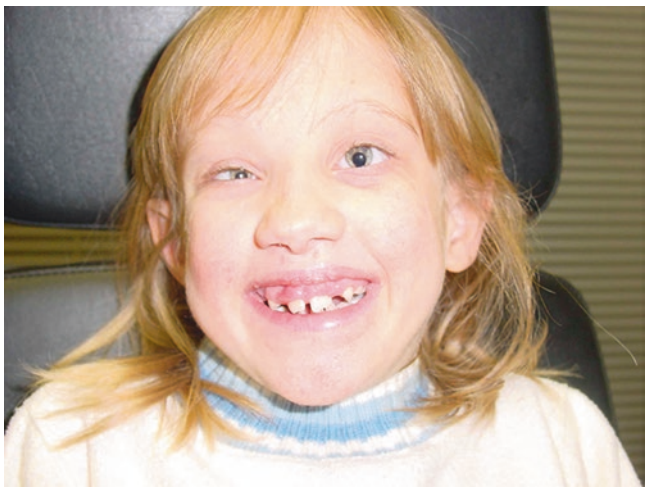

Fig. 8.4 GOLTZ patient

Ocular Manifestations

Ocular abnormalities occur in 40 % of FDH cases [29] (Fig. 8.4). The most frequent manifestations are ocular colobomas, strabismus, and microphthalmia [28]. Anophthalmia, hypertelorism, nasolacrimal duct obstruction, and lid abnormalities such as ectropion and ptosis may occur in patients with FDH. Anterior segment problems include aniridia, heterochromia, subepithelial corneal opacities, corneal clouding and blue sclera. In addition to retinal colobomas, other posterior abnormalities such as optic nerve atrophy, retinal neovascularization and vitreous hemorrhages have been reported as well [30, 31].

Management

Patients with significant dermal aplasia require regular care with a dermatologist with use of occlusive dressings and antibiotics creams to prevent secondary infections [27]. Pulsed dye laser may be helpful in some cases. Verrucoid papillomas may require surgical or laser therapy if they are present in the GI tract and causes obstruction or dysphagia [27]. Management of ocular abnormalities depends on the extent and severity of the symptoms.

Ectodermal Dysplasia

Ectodermal dysplasias are a heterogeneous group of disorders that results from abnormal development in at least two of the four major ectodermal derivatives. Ectoderm forms the skin, teeth, hair, nails, sweat glands, and part of the eyes. There are at least 150 syndromes with primary alterations in structures that derive from the embryonic ectoderm. The most frequently encountered syndromes are hypohidrotic ectodermal dysplasia (HED), hidrotic ectodermal dysplasia, ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC), and ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC). EEC and AEC are *TP63*-related disorders with autosomal dominant inheritance [32].

HED manifests with hypohidrosis (partial or complete absence of sweat glands), hypodontia (absence or abnormalities or teeth), hypotrichosis (sparseness of scalp or body hair), and cranial abnormalities [33]. The condition is most predominantly due to an x-linked recessive inheritance pattern, due to an *ED1* gene mutation in Xq12-13.1 region. However, a clinically identical autosomal recessive and milder autosomal dominant form have been identified. Patients may often present with a collodion membrane or marked scaling at birth [21]. Neonates with HED often have peeling skin or periorbital hyperpigmentation. Infants with HED may show signs of irritability due to heat intolerance due to reduced sweat function. Often, diagnosis is delayed until the teeth fail to erupt at the expected age of 6 to 9 months. Teeth are also conical in shape when they eventually erupt. Scalp hair is sparse, fine, and lightly pigmented and slow-growing, which may be a result from excessive fragility of shafts that break easily. Skin also has a fragile appearance in addition to chronic eczematous changes. Periorbital hyperpigmentation can persist and also result in periorbital wrinkling of skin. Dry eyes are common and thought to be due altered lipid layer of the tear film and meibomian gland and goblet cell dysfunction. Patients have hyperthermia due to inadequate sweating, which can be life threatening, and requires close environmental modifications to control temperature. Other findings include asymmetric development of the alveolar ridge, depressed nasal bridge, raspy voice, and retruded appearance of the midface. Diagnosis may be aided by scalp biopsy [33].

A second classic type is hidrotic ectodermal dysplasia, also known as Clouston Syndrome (CS). It is an autosomal dominant disorder of skin, hair, and nails. Dentition and sweat glands are not involved in CS [33]. There is dystrophic, hypoplastic or absent nails. Hyperkeratosis is noted on the palms and soles as well as hyperpigmentation of the skin, especially over the joints. Scalp hair is wiry, brittle, patchy and pale with progressive hair loss that may lead to total alopecia by puberty [33]. Absence of eyelashes and eyebrows are also seen. Development and cognition is normal. Mutations in the *GJB6* gene encoding the gap junction protein connexin 30 cause this disorder [33].

EEC is a rare autosomal dominant disorder with 95 % penetrance and variable expression. It is characterized by lobster claw-like clefting deformity of hands and feet (ectrodactyly) (70 %), cleft lip and palate (40 %), and ectodermal dysplasia. EEC patients often may complain of dry eyes and photophobia. These symptoms can be due to both lid and ocular surface abnormalities. Lid abnormalities include ankyloblepharon, entropion, trichiasis, madarosis, and agenesis of lacrimal puncta [34, 35]. Lacrimal anomalities are fre-

quently seen and EEC should be on the differential in a child with congenital lacrimal anomalies [36]. Ocular surface manifestations can range from dry eyes due to deficient lacrimal and meibomian gland secretion, to recurrent erosions, severe corneal pannus and limbal cell deficiency [35, 37]. The etiology of corneal pathology may be multifactorial. Di Iorio reported 23 patients with EEC of which 61 % had limbal stem cell deficiency that likely led to progressive keratopathy and dense vascularized corneal pannus [38]. Corneal changes may also be due to tear film instability or be a manifestation of ectodermal dysplasia itself as cornea is partially derived from the ectoderm [35]. Multiple cases of spontaneous corneal perforations have been reported [35, 39]. Although it is derived from the ectoderm, lens does not seem to be affected in EEC. As soon as dry eye symptoms are noticed, conservative management should be initiated. Limited but successful reports of living related conjunctival allografts have been reported for limbal stem cell deficiencies [40]. For various congenital lacrimal anomalies, various techniques including canalicular probing with or without intubation, dacryocystorhinostomy, and conjunctivodacryocystorhinostomy can be successful in epiphora resolution [36].

AEC is a *TP63*-related disorder characterized by ankyloblepharon (70 %), ectodermal defects (100 %), cleft lip/palate (100 %), and craniofacial findings [32]. Ankyloblepharon can vary in severity from partial to significant adhesion of the upper and lower eyelids. Mild adhesions can spontaneously lyse in infancy. Lacrimal puncta are often absent, leading to epiphora and chronic conjunctivitis [32]. Erosive skin lesions and congenital erythroderma can be recurrent or intermittent with frequent involvement of the head, neck, palms, soles and skin fold. Skin can also have a shiny collodion membrane. Due to recurrent erosions, children have cutaneous depigmentation and scarring. Hair and nail changes become more obvious with age. Hypodontia and malformed teeth are present as well as subjective decreased sweat production with heat intolerance. However, hyperthermia or fevers as seen in HED are not observed [32]. More than 90 % of children have conductive hearing loss, often accompanied by secondary speech delay [32].

Ichthyoses

Definition

The ichthyoses are a group of disorders with abnormal epidermal differentiation characterized by variable presentation of scaling and hyperkeratosis [41]. The Greek root, *ichthys*, means fish, referring to the scaling that resembles scales of a fish [42]. Patients with ichthyosis have compromised barrier function of the skin and therefore, have increased susceptibility to infection, dehydration, and chemical or mechanical assault [42]. Ocular manifestations are present with variable

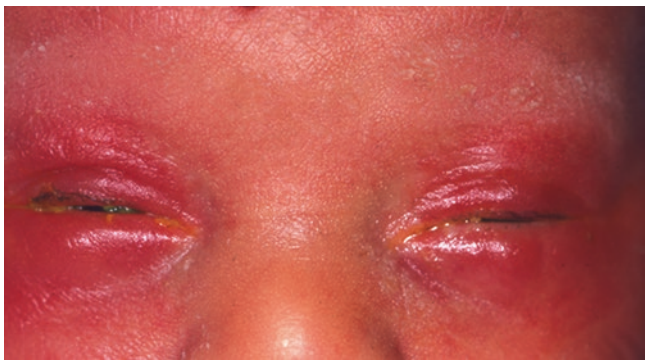

Fig. 8.5 Ichthyosis infant, eyelids<<permission requested from McGraw Hill>>

severity in ichthyosis and includes blepharitis, lagophthalmos, madarosis, ectropion, and risk of corneal damage [43] (Fig. 8.5). Peripheral fundus pigmentation and corneal opacities have also been reported in the literature [44]. Reversible conduction deafness can also occur in all types due to desquamation within the external auditory canal [43]. Ichthyoses can be divided into several categories as follows: Ichythyosis vulgaris, autosomal recessive congenital ichthyosis, X-linked ichthyosis, keratinopathic ichthyosis. Ichthyosis is considered nonsyndromic when only skin findings are present and syndromic when other organs are involved [43, 45].

Nonsyndromic Ichthyosis

Ichthyosis vulgaris (OMIM 146700), also known as ichthyosis simplex, is a nonsyndromic ichthyosis caused by homozygous or heterozygous loss-of-function mutations in the filaggrin (*FLG*) gene on chromosome 1q21 [46]. It is the most common type with prevalence of 1:100 [41]. Clinical onset occurs within the first year of life. It is characterized by scaling, xerosis, keratosis pilaris, palmar and plantar hyperlinearity (deeper furrows), and a strong association with atopic disorders [46]. Scales can be fine (powdery) or coarse (polygonal) and involve the extensor surfaces of limb, trunk and face [46]. Ocular manifestation is limited to mild scaling of the eyelids. There is spontaneous improvement of symptoms during summer [41].

Autosomal recessive congenital ichthyosis (ARCI) is a group of nonsyndromic ichthyosis without a tendency toward blistering. ARCI includes lamellar ichthyosis (LI), congenital ichthyosis erythroderma (CIE), harlequin ichthyosis (HI) and less commonly, self-healing collodion baby, acral self-healing collodion baby, and bathing suit ichthyosis [41, 42, 45]. Patients with ARCI are usually born prematurely, enveloped in a shiny, taut, cellophane-like collodion membrane [42]. The tight skin around the eyes and mouth can cause ectropion and eclabium, eversion of lips. Collodion babies look very similar at birth, but as the membrane dissolves in the first weeks of life, they take different clinical courses.

In about 10 %, the skin findings resolve spontaneously as the membrane disappears [41]. This benign course is referred to as self-healing collodion baby. The most severe and often fatal type of ARCI is harlequin ichthyosis (OMIM 242500), which is caused by mutations in the *ABCA12* gene (2q35) [42]. The membrane that encase neonates with HI are thick and armor-like, resembling harlequins and hence the name. When patients with HI survive the neonatal period, they have the phenotype of severe CIE. LI and CIE are very similar except that LI lack the presence of erythroderma. LI (OMIM 242300) is most commonly due to mutations in the keratinocyte transglutaminase (*TGM1*) (14q11.2). CIE is due to mutations in several genes, including *TGM1* and *ALOX12B* [45]. The most common ocular abnormality seen in ARCI is cicatrical ectropion of the upper and lower lids [47]. This occurs from progressive subepithelial cicatrization and abnormal cornification of eyelid skin that leads to lagophthalmos, corneal exposure and keratopathy [48, 49]. Severe ectropion requires full-thickness skin grafts. Penile skin graft has been used successfully as it does not seem to be affected by the disease. When autograft is not possible, options include allograft overlay, mucous membrane, human engineered skin, and maternal skin allograft [48, 49]. Ophthalmologic evaluation upon diagnosis and close follow up to assess corneal integrity is recommended.

X-linked ichthyosis (OMIM 308100), also known as steroid sulfatase deficiency, is an X-linked recessive disorder due to a complete deletion or an inactivating mutation of the *STS* gene [42]. Its prevalence is 1:4000 [41]. Because steroid sulfatase is also deficient in the placenta, there is low maternal urinary estrogen secretion and low amniotic fluid estrogen, leading to difficult labor [42]. Affected males have pink or red skin with large translucent scales at birth. X-linked ichthyosis is associated with cryptorchidism (~20 %), attention deficit hyperactivity syndrome (40 %), and autism (25 %) [41]. White, comma-shaped corneal opacities in descemet membrane are present in 10–50 % of patients. These opacities do not affect vision but can cause recurrent corneal erosions and scars. Up to 25 % of female carriers also have these corneal opacities.

Keratinopathic ichthyosis refers to ichthyosis due to mutations in keratin genes (KRT) where blistering of skin is a prominent feature. It includes epidermolytic ichthyosis, superficial epidermolytic ichthyosis and congenital reticular ichthyosiform erythroderma. Inheritance is usually autosomal dominant although autosomal recessive forms can occur [41].

Syndromic Ichthyosis

Few of the important syndromic ichthyoses are Refsum disease, Sjogren-Larsson syndrome (SLS), keratitis-ichthyosis-deafness syndrome (KID), ichthyosis follicularis alopecia and photophobia (IFAP), and X-linked chondrodysplasia punctate 2 [3]. Individuals with Refsum disease and Sjogren-Larsson syndrome often have retinopathy. In SLS, macular crystalline inclusions, "glistening dots," appear in infancy and increase with age [50]. Symptoms are variable in severity and seem to stabilize in late childhood. In addition to maculopathy, SJS patients have spastic paraplegia, intellectual disability, and ichthyosis. Individuals with KID have vascularizing keratitis (95 %). Although the word keratitis suggests a primary inflammatory disease, corneal abnormalities in KID results from generalized ectodermal disturbance with lid disease and limbal stem cell deficiency. Surgical treatment for corneal disease including limbal allografts, corneal grafts, lamellar keratoplasty, and amniotic membrane transplantation have been reported to be unsuccessful in patients with KID [51]. IFAP is characterized by the triad of ichthyosis follicularis, alopecia and photophobia. Photophobia is an essential feature for diagnosis and can present early in life or later in childhood. Corneal ulceration and vascularization often progress to scarring and vision loss [52]. Individuals with X-linked chondrodysplasia punctate 2 have growth deficiency, distinctive craniofacial appearance, ichthyosis and ocular changes. Congenital cataracts are present in 67 % of patients and can be asymmetric or sectoral. Microphthalmia and microcornea have also been reported.

Management

Treatment for ichthyoses is mostly symptomatic and supportive. The goal is to reduce scaling and providing a humidified, temperature-controlled environment. Urea-based ointments, glycerin-based ointments, and lactic acid-based ointments are available [41]. Vitamin A ointments may be used for problem areas. When necessary, systemic retinoids can be administered with caution, being mindful of the potential teratogenicity and risk for increased intracranial pressure. In certain types such as KID, it may worsen ocular surface disease [53]. Daily baths with only water or mild soap is crucial as well. Lubrication for eyes and eyelids is warranted for those at risk of exposure keratopathy. As mentioned previously, severe ectropion may require surgical correction. For *TGM1*-associated ichthyosis, a causal topical enzyme replacement therapy is on the horizon [41].

Kinky Hair Disease (Menkes Disease)

Definition and Epidemiology

Kinky hair disease, also known as Menkes disease, is a X-linked recessive disorder of copper transport and metabolism [54, 55]. It is cause by mutations in the copper-transporting ATPase gene (*ATP7A*). Impaired intestinal copper absorption leads to reduced the activities of copper-dependent enzymes are decreased, ultimately resulting in inhibited formation of collagen, elastin, keratin, ceruloplasmin, and melanin. The clinical spectrum of *ATP7A*-related copper transport disorders ranges from the most severe form in classic Menkes disease to the less severe

forms in occipital horn syndrome and distal motor neuropathy [55]. Incidence of Menkes disease is 1 in 100,000 to 250,000 live birth [54, 55].

Clinical Manifestations

Infants with classic Menkes disease appear healthy until age 2–3 months when they develop hypotonia, failure to thrive, seizures and neurodegeneration [55]. Then, hair changes become manifest. Scalp and eyebrow hair are short, sparse, twisted, and often lightly pigmented. They can be reminiscent of steel wool cleaning pads. Light microscopy reveals pili torti (hair shafts twisting 180°), trichoclasis (transverse fracture of the hair shaft), and trichoptilosis (longitudinal splitting of the hair shaft). Other clinical features of Menkes disease include distinctive facial features (jowly appearance with sagging cheeks), pectus excavatum, skin laxity especially on the nape of the neck and trunk, umbilical or inguinal herniae, vascular tortuosity, and bladder diverticulae [55]. Subdural hematomas and cerebrovascular accidents are common. Electroencephalograms are moderately to severely abnormal including high rates of status epilepticus and infantile spasms. Diagnosis is usually made around 8 months of age. Biochemical testing reveals low levels of copper in plasma, liver and brain due to impaired intestinal absorption, reduced activities of copper-dependent enzymes, and paradoxical accumulation of copper in certain tissues (duodenum, kidney, spleen, pancreas, skeletal muscle, placenta) . Early treatment with parenteral copper is crucial. Sometimes, even with early treatment, infants with classic Menkes disease progress to severe neurodegeneration and death between ages 7 month to 3 years. The most common cause of death is respiratory failure, often due to pneumonia [55].

Infants with mild Menkes disease have better motor and cognitive development compared to those with classic Menkes disease. They may talk and walk independently but have characteristic neurologic features of weakness, ataxia, head bobbing. Seizures, if present, manifest in mid-late childhood. Pili torti are present. Connective tissue and skin problems may be more prominent than in classic Menkes disease [55].

Ocular Manifestations

There is high prevalence of very poor visual acuity in patients with Menkes disease [54, 56]. Poor vision is attributed, in part, to acquired, progressive ganglion cell atrophy that leads to macular and optic nerve atrophy. Optic discs pallor is commonly seen in younger patients and become paler as they age [54]. Vision changes also occur due to retinopathy, which is caused by overall systemic copper deficiency and the loss of retinal Menkes protein that regulates copper levels in photoreceptors [57]. Retinal vascular tortuosity with mild retinal hemorrhages may rarely occur abnormal electroretinographic findings have been reported in patients with Menkes disease [56].

Myopia and strabismus also occur at a high rate. Patients may also have rotary nystagmus and gaze-evoked nystagmus, especially with anticonvulsant therapy. Other findings include blue irides, iris stromal hypoplasia, aberrant lashes, and peripheral retinal hypopigmentation [54, 56]. These features can also be present in mild variants of Menkes disease. The high prevalence of poor vision, refractive error, and strabismus warrants early eye exam for individuals diagnosed with Menkes disease.

Management

To date, there is no curative treatment for Menkes disease. Early copper replacement therapy has been shown to improve neurologic outcomes [58]. Benefit increase when treatment begins prior to appearance of signs of symptoms. Early diagnosis based on positive family history and high index of suspicion is crucial in order for early treatment initiation [55, 58]. After diagnosis, patients with Menkes disease should undergo developmental assessment, evaluation of feeding and nutrition and assessment of bladder function in order to establish the extent of disease. Some patients may need gastrotomy tube placement to manage caloric intake or surgery for bladder diverticulae, if present [55].

Cardiofaciocutaneous Syndrome

Definition

Cardiofaciocutaneous (CFC) syndrome is an autosomal dominant multiple congenital anomaly disorder. It is one of the RASopathies, which are disorders caused by mutations in the Ras/MAPK pathway [59, 60]. Other syndromes in this group include Noonan syndrome and Costello syndrome. CFC was first reported in 1986 with major features of craniofacial dysmorphology, congenital heart disease, dermatologic abnormalities, growth delay, and intellectual disability.

Systemic Manifestations

Virtually all CFC patients develop cutaneous findings. These dermatologic manifestations help differentiate CFC from other RASopathies [60]. Numerous acquired melanocytic nevi and keratosis pilaris (follicular hyperkeratosis of extremities and/or face) is seen in majority of patients with CFC. Abnormalities in hair are common and includes curly scalp hair, sparse hair at the temples, poor hair growth, sparse arm and leg hair. Ulerythema ophryogenes, which is brow erythema with loss of follicles, leads to sparse or absent eyebrows in 90 % of individuals with CFC [60]. Abnormal sweating often leads to heat intolerance and axillary body odor. Other dermatologic findings include eczema, dystrophic nails with rapid nail growth, acanthosis nigricans, and generalized hyperpigmentation. Infantile hemangiomas are more commonly seen in CFC individuals (25 %) compared to other RASopathies and general population. In adolescence and adulthood, individuals may develop palmo-plantar calluses and peripheral lymphedema, often in the lower limbs [60].

Neurologic abnormalities are also universally present and can range in severity. Hypotonia, motor delay and learning

disabilities are common. Examination may reveal macrocephaly, corticospinal tract findings, touch sensitivity, and tactile defensiveness. These findings are often accompanied by structual malformations on brain imaging. Seizures are present in 40–50 % of children with CFC [61, 62].

Failure to thrive and poor growth in infancy due to severe feeding problems are seen is almost all individuals with CFC. Swallowing difficulties can be detected early by prenatal polyhydramnios that is followed by difficult maintaining adequate oral intake after birth. Oral aversion and sensory integration difficulties with solid foods can continue through adulthood. Short stature is common in all RASopathies, including CFC [59, 60].

Nearly 75 % of individuals with CFC have cardiovascular involvement, ranging from congenital pulmonic stenosis (most common) and heart valve anomalies to progressive hypertrophic cardiomyopathy (40 %). Other systemic findings include scoliosis (33 %), pes planus (66 %), hyperextensibility of joints, renal/urogenital abnormalities (33 %), laryngotracheal abnormalities, and abnormal ear canals necessitating ear tube placements [59, 60].

Ocular Manifestations

Most individuals with CFC have ocular manifestations. Most commonly seen are strabismus, refractive errors, nystagmus, ptosis, and optic nerve hypoplasia. Exotropia is the most common type of strabismus encountered, and most require surgical correction in early infancy/childhood. Amblyopia is a common finding and must be treated early. Optic nerve changes ranges in severity. Craniofacial features include ocular hypertelorism, epicanthal folds, and hypoplastic supraorbital ridges. Most ocular problems in CFC are amenable to treatment. Thus, early detection, intervention, and regular follow up examinations are recommended [59, 60].

Management

Multidisciplinary approach to management of various systemic manifestations is essential for individuals with CFC. Consultations with following specialties are recommended after diagnosis: genetics, cardiology, dermatology, ophthalmology, otolaryngology/audiology, orthopedist, and neurologist. Following testing should be performed upon diagnosis: echocardiogram, electrocardiogram, renal ultrasound, thyroid and insulin-growth-factor levels, complete blood count, and audiologic evaluation [59, 60].

Pseudoxanthoma Elasticum

Definition

Pseudoxanthoma elasticum (PXE), is a rare inherited multisystem disorder of aberrant mineralization of soft connective tissue. It is caused by mutations in the *ABCC6* gene in chromosome 16, resulting in fragmentation of elastic fibers in the skin, eyes, and cardiovascular system [63–62].

History and Epidemiology

PXE was originally described by the French dermatologist Rigal in 1881 although the name was coined by Darier in 1896. It is a rare disease with estimated prevalence of 1:50,000. Females are more commonly affected in 2:1 ratio [61].

Systemic Manifestations

Clinical features of PXE are rarely present at birth and usually manifest during the second or third decade of life [62–63]. Cutaneous findings are usually the first sign of PXE and present during childhood or adolescence. They consist of small (1–5 mm), yellowish or skin-colored papules that are initially in a reticular pattern but progressively coalesce into larger papules. Affected skin often becomes lax, wrinkled, and redundant. Initially, the lateral and posterior regions of the neck are first to be involved followed by flexural areas and periumbilical skin. Amount of skin changes often increase during pregnancy. Mucosal lesions of oral cavity, especially in the inner lower lip, and genital area can be present, resembling cutaneous changes. Cutaneous findings are not pathognomonic for PXE as similar lesions are present in other disorders including Paget's disease, focal cutaneous elastosis, and beta-thalassemia [61]. Absence of skin findings does not exclude the diagnosis of PXE. Diagnosis can be confirmed by skin biopsy showing fragmented and clustered calcified elastic tissue in the middle and lower dermis. Although cutaneous lesions generally pose cosmetic problems, severity can predict the risk for development of ocular and cardiovascular complications with considerable morbidity and mortality.

Cardiovascular manifestations can vary and include reduced peripheral pulse (25 %), hypertension (22.5 %), angina pectoris (19 %), restrictive cardiomyopathy, mitral valve prolapse (70 %), and intermittent claudication [61]. Cardiovascular changes are caused by mineralization and fragmentation of elastic fibers of the internal elastic lamina, medial and adventitial layers of medium-sized arteries and aorta as well as myocardial tissue. Premature atherosclerosis with acute myocardial infarction and cerebrovascular accidents can also occur in PXE patients. Most patients with PXE do not experience cardiovascular problems before their third or fourth decade of life although onset as early as age 9 years have been reported. Abnormal lipoprotein composition with hypertriglyceridemia and low HDL cholesterol may occur [62–63].

Another important complication holding significant morbidity is the increased risk of gastro-intestinal (GI) hemorrhage (13–15 %). After retinal hemorrhage, GI bleeding is the second most common bleeding. The exact cause of this risk is unclear although it is postulated that spontaneous rupture of vessels may occur as in Ehlers-Danlos syndrome.

Ocular Manifestations

The first visible changes on fundoscopy in PXE patients are fine, yellow drusen-like appearance of the retinal pigment epithelium called peau d'orange that is most prominent temporal

to the fovea. Retinal function does not appear to be affected in these areas. Peau d'orange precedes angioid streaks by 1–8 years [63].

PXE is the most common systemic disorder associated with angioid streaks. Review of large case series of angioid streaks found the association with PXE in 59–87 % of cases. Angioid streaks were first described by the English ophthalmologist Doyne in 1889 as "irregular jagged lines" that were thought to "rupture to the pigment layer of the retina" in a patient who presented after blunt trauma [62]. The term angioid streak was first coined by Knapp in 1892. In 1929, two Swedish physicians Gröenblad and Strandberg made the association between PXE and angioid streaks [63]. Angioid streaks are brownish-gray irregular lines that originate from the optic disc, may radiate outwards or be concentric around the nerve [63]. They can vary in diameter from 50 μm to several times the diameter of retinal vessels. Angioid streaks are breaks of calcified and thickened Bruch's membrane that can progress to become full-thickness defects with atrophy of choriocapillaris, RPE, and photoreceptors. Indocyanine green angiography (ICGA) is superior to fluorescein angiography (FA) in visualizing angioid streaks. Fundus autofluorescence of angioid streaks also show areas of increased and decreased autofluorescence [62–63].

Fibrovascular tissue can grow through the defect leading to choroidal neovascularization (CNV)[63]. CNV can results in the development of subretinal fibrosis and disciform scar. Only a few cases of angioid streaks under the age of 10 have been reported, but most develop angioid streaks within 20 years after first diagnosis [63, 64]. Calcification in bruch's membrane predisposes to breaks even with minor trauma. These breaks can lead to retinal hemorrhages independent from the presence of angioid streaks or CNV [62]. Therefore, activities with potential eye trauma should be avoided and adequate eye protection is recommended.

Other ocular features of PXE include comettial lesions, pattern-dystrophy-like changes, and optic disc drusen. Comettial lesions are halos of pigment hypertrophy with localized RPE atrophy pointing towards the posterior pole of the retina like a comet's tail. These atrophies are small with the average diameter of 125 μm and located in the midperiphery [63]. They do not affect visual function. In contrast to angioid streaks, comettial lesions are pathognomonic for PXE [61]. Pattern dystrophy-like changes are observed in 10–70 % of PXE patients [62]. The prevalence of optic disc drusen is reported to range from 6 to 20 % compared to 0.3 % in the general population [62]. Its presence can be confirmed with ultrasound or fundus autofluorescence.

Management

Visual prognosis of patients with PXE depends on the management of CNV. The only stage where intervention is possible is when CNV has developed. Therapeutic options include intravitreal injections of VEGF inhibitors or steroids, laser photocoagulation, and photodynamic therapy [62–63].

To date, there is no established therapy for PXE. Lifestyle factors including tobacco abstinence and healthy diet may help delay cardiovascular involvement. Anticoagulants should be prescribed with caution due to the increased risk of GI bleeding. Common sense suggests avoidance of high-risk sports such as boxing that can lead to ocular and physical trauma with devastating effects [63, 65].

Waardenburg Syndrome

Definition

Waardenburg syndrome (WS) is a heteregenous genetic syndrome cause by physical absence of melanocytes in the skin, hair, eyes and the stria vascularis of the cochlea [66]. It affects 1 in 40,000 according to population studies. There are four types. Types I, II, and III are autosomal dominant whereas Type IV is autosomal recessive. Dystopia canthorum is a feature that distinguishes Type I WS from Type II WS. Type III WS, also known as Klein-Waardenburg syndrome, is an extreme representation of Type I WS but is also characterized by musculoskeletal anomalies. Type IV WS (Shah-Waardenburg) is associated with congenital aganglionic megacolon (Hirschsprung disease). Fulfillment of two major criteria or one major and two minor criteria is required for diagnosis. Major criteria include characteristic white forelock (hair depigmentation), pigmentary anomalies of iris, congenital sensorineural deafness, dystopia canthorum, or an affected first degree relative. Minor criteria are depigmented maculars or patches, synophrys, broad nasal root, nose hypoplasia, and early graying of hair by age 35. Genes involved include *PAX3, MITF, SOX10, EDN3*, and *EDNRB* genes [66–68].

Systemic Manifestations

White forelock, which is usually midline, is found in 30–40 % of patients. It can be present at birth or may develop or fade with age and also be variable in severity ranging from few strands to clump of ha**ir** being affected. Premature graying can occur in approximately 10 % of individuals. Pigmentation defects can affect eyebrows and eyelashes as well [66].

Hypopigmentation of skin is congenital and can be found on the face, trunk, or extremities. It may be associated with adjacent white forelock. Hyperpigmentation can develop in previously hypopigmented area, especially along the borders. If depigmented patches are extensive, piebaldism due to *KIT* gene mutation should be suspected, especially in a patient with normal hearing [66].

Sensorineural hearing loss, which is dues to malformations of organ of Corti, is most commonly seen in type II WS. It is congenital and usually nonprogressive. It can be unilateral or bilateral and vary in severity from mild to profound loss.

Musculoskeletal abnormalities seen in Type III WS are usually abnormalities of upper extremities, flexion contractures, and syndactyly. Hirschsprung disease seen in Type IV WS and is due to mutations in *EDN3* and *EDNRB* genes [66].

Ocular Manifestations

Dystopia canthorum is the most distinguishing feature of Type I WS, being present in 99 % of affected individuals. There is appearance of blepharophimosis with fusion of inner eyelids medially, resulting in reduced medial scleral show. The inferior lacrimal puncta are laterally displaced. Inner canthal, interpupillary and outer canthal distances are greater than normal, indicative of hypertelorism in addition to telecanthus. The W index is a formula based on measurements of these distances. W index value of greater 2.07 is indicative of dystopia canthorum [66].

Iris heterochromia can be partial or complete, which the hypochromic iris being the affected eye due to absence of melanocytes and deficient iris stroma. If partially affected, differently colored areas are sharply demarcated and usually in radial segments (Fig. 8.6). Anterior segment optical coherence tomography revealed that hypopigmented iris were thinner and had shallower crypts compared to normal iris [66, 69].

Hypopigmentation of the choroid can also be seen in a sectoral or diffuse pattern. Posterior segment optical coherence tomography showed the retina to be normal in structure although the subfoveal choroid in hypopigmented region was slightly thinner compared with the opposite normal choroid. Fundus autofluorescence demonstrated mild hyperautofluorescence (scleral unmasking) in hypopigmented choroid with no lipofuscin abnormality. Visual acuity is known to be preserved unless with presence of foveal hypoplasia or amblyopia. Strabismus is more common in WS1 compared to the general population [66, 69].

Xeroderma Pigmentosa

Definition

Xeroderma pigmentosa (XP) is a heterogeneous group of autosomal recessive disorders caused by defective UV-radiation induced damage repair. When DNA is exposed to UV radiation, multiple nucleic acid based photobyproducts form and serve as substrates for DNA repair in the nucleotide excision repair (NER) process. Damaged DNA is recognized via the transcription-coupled repair (TCR) pathway and the global genome repair (GGR) pathway. Mutations in any of the proteins involved in the NER, TCR, and GGR pathways lead to abnormalities in DNA repair and manifest as clinical syndromes with overlapping features including XP, Cockayne syndrome (CS), and trichothidystrophy (TTD) [70].

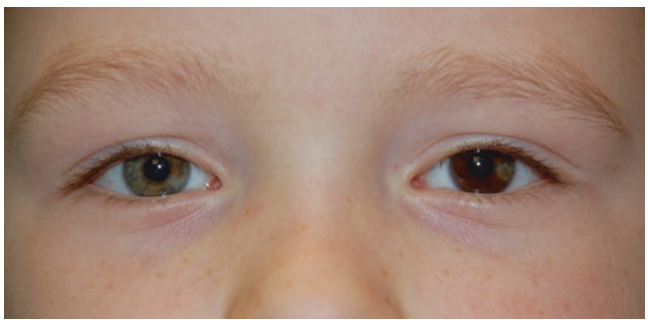

Fig. 8.6 Waardenburg patient, iris heterochromia

Different complementation groups (A–G) have been described for XP, each with distinct DNA excision repair defects. XP variant (XPV) is clinically similar to other subtypes but does not involve a mutation of the NER system. XPV patients may have increased long-term survival compared to the other subtypes of XP. Prevalence varies depending on geography with XPC being the most common complement type in the United States, Europe and North Africa whereas XPA is the most common type in Japan [70].

Systemic Manifestations

Classic phenotype of XP presents in the early childhood as freckling by the age of two, severe burning with minimal sun exposure, and skin cancer manifesting at an early age [70]. Skin often undergoes premature aging with progressive atrophy, telangiectasias, and abnormal lentiginous pigmentation with intermixed hypopigmented and hyperpigmented areas. All complement types of XP have photosensitivity and increased cancer risk although some types are less severe than others. Individuals with XPC, XPE, and XPV subtypes may tan and acquire abnormal pigmentation but experience less severe sun burning after minimal sun exposure [70].

XP patients have a >10,000 fold risk over their lifetime of developing nonmelanocytic skin cancer and >2000 fold risk for melanoma compared to the general population. The median age for the first diagnosis of skin cancer is 9 years (age range 1–32 years) for non-melanocytic skin cancer and 22 years for melanoma (age range 2–47 years) [70]. Skin cancer accounts for the highest number of disease-related deaths in XP patients. XP patients also have a 50-fold increased risk of developing brain tumors such as medulloblastoma, glioblastoma, spinal cord astrocytoma, and schwannoma. XP patients who smoke have a higher risk of lung cancer compared to the general population [70].

The nervous system is affected in a significant subset of XP patients. Although the nervous system does not receive direct UV radiation exposure, unrepaired oxidative damage may be a possible cause of the neurodegeneration that is seen in 24 % of XP patients. The most commonly affected subtypes are XPD and XPA. It is rarely seen in subtypes XPC and XPE [70]. Signs include loss of intellectual functioning, impaired hearing, abnormal speech, areflexia, ataxia, and peripheral neuropathy. Neuroimaging may reveal neuronal loss, cortical atrophy and ventricular dilatation without inflammation.

Ocular Manifestations

Ocular involvement in XP is common, ranging from 40 % to 91 % in literature review [71]. Ocular tissues that are exposed to ultraviolet radiation are involved in XP, and symptoms appears early in childhood. By the age of 10 or less, most patients have some degree of ocular morbidity. The earliest report of ocular symptoms was described by Hebra and Kaposi in the late nineteenth century when they noted xerosis, ectropion, corneal ulcers and opacities in two patients with XP [72]. Ocular manifestations can be divided into the following categories: structural eyelid abnormalities, neoplasms of ocular surface and eyelids, ocular surface inflammation, and corneal abnormalities [71].

Eyelid involvement, with both benign and malignant lesions, is seen in approximately 80 % of patients [73]. In one the largest report of 87 XP patients, 11 % had a history of ocular surface and skin cancer with the median age of onset at 16 years [71]. Atrophic skin changes can lead to lagophthalmos, ectropion and less commonly, entropion [71]. Tear film and tear production is often abnormal due to keratinization of lid margins and structural lid abnormalities. Twenty percent of patients had conjunctival melanosis, but these lesions rarely developed into malignant melanoma [71]. Ocular surface problems include conjunctivitis, pterygium, band-like keratopathy, conjunctival neoplasms and xerosis [51]. Exposure keratopathy can lead to corneal opacification, pannus formation, and neovascularization. Ocular surface malignancy can be present in 10 % of patients.

Management

There is currently no cure for XP. Consistent UV radiation protection is imperative and can substantially reduce the number of skin cancers. Protection consists of layered clothing, ample sunscreen and eye protection, including fully shielded eyewear and adequate lubrication. Decreasing UV radiation exposure may not decrease neurodegenerative effects. Vitamin D supplementation should be initiated to offset sun avoidance. Systemic treatment with retinoids has been reported with some benefit. Regular examination of skin and eyes are required with early excision of suspicious lesions The most commonly affected subtypes are XPD and XPA. It is rarely seen in subtypes XPC and XPE [70].

Cockayne Syndrome

Definition

Similar to XP, Cockayne syndrome (CS) is an autosomal recessive disorder of severe photosensitivity and premature aging caused by mutations in *CSA* (25 %) or *CSB* (75 %), which are involved in the NER pathway. Individuals with CS have photosensitivity but do not develop abnormal pigmentation and also do not have increased risk of cutaneous malignancy [74].

Systemic Manifestations

The phenotypic spectrum of CS can be described into four types: CS type I (classic), CS type II (severe form), CS type III (mild), and Xeroderma pigmentosum-Cockayne syndrome (XP-CS).

CS type I has moderate phenotype with normal development until age two after which there is neurodegeneration leading to death in the first or second decade of life. By the time the disease has become manifest, height, weight, and head circumference are below the fifth percentile. There is progressive impairment of vision, hearing, and decline in central and peripheral nervous system function leading to severe disability. Severe dental caries occur in up to 86 % of patients. Neurologic symptoms and signs include spasticity, abnormal gait or inability to walk, incontinence, tremor, abnormal speech, seizures, poor feeding, and muscle atrophy. Many CS patients exhibit sociable and outgoing behavior. Neurodegeneration seen in CS is due to demyelination, and patients often have increased deep tendon reflexes unlike patients with XP. Neuroimaging shows cerebral atrophy, ventricular dilation, calcification of the basal ganglia and cerebral cortex. Neuropathology shows characteristic "tigroid" pattern of demyelination in the subcortical white matter of the brain and multifocal calcium deposition with relative preservation of neurons. Skin manifestations consist of anhidrosis and butterfly malar rash after sun exposure. Facial dysmorphism with "bird-like" appearances have been described. Abnormal renal function and elevated liver function tests can be present in 10 % of patients. Undescended testes and absent sexual maturation. No individuals with CS type I or type II have been known to reproduce [74]. Diagnosis of CS I is made clinically [Table 8.2] [74]. In an older child, CS I is suggested when both major criteria are present and three minor criteria are present. In an infant, it can be diagnosed when both major criteria are present, especially with increased cutaneous photosensitivity.

Table 8.2 Diagnostic criteria of Cockayne syndrome

Major criteria	Minor criteria
• Postnatal growth failure (height and weight <5th percentile by age 2 years)	• Cutaneous photosensitivity with or without thin or dry skin/hair
• Progressive microcephaly and neurologic dysfunction or leukodystrophy on brain MRI	• Demyelinating periphery neuropathy
	• Pigmentary retinopathy
	• Cataracts
	• Sensorineural hearing loss
	• Dental anomalies
	• Characteristic physical appearance of "cachectic dwarfism"
	• Characteristic radiographic findings of thickening of the calvarium, sclerotic epiphyses, vertebral and pelvic abnormalities

Type II is more severe and manifests with growth failure at birth with little to no postnatal neurologic development. Arthrogryposis or early postnatal contractures of the spine and joints are commonly seen. Congenital cataracts and other structural anomalies of the eye may be present in 30 %. Death occurs in the first decade of life. CS type II overlaps clinically with cerebrooculofacioskeletal syndrome (COFS) [74].

Type III has milder symptoms and later onset of disease. A difficult but successful pregnancy has been reported in a young woman with CS type III.

XP-CS has features of XP including facial freckling and early skin cancers in addition to features of CS with intellectual disability, spasticity, short stature, and hypogonadism.

Ocular Manifesations

The classic ocular finding in Cockayne syndrome is pigmentary retinopathy, which was initially described by Cockayne in 1936 [73]. It is reported in 60–100 % of patients in the literature and is most commonly seen as a "salt and pepper" fundus [73]. Bony spicules and optic atrophy have been reported as well. Electroretinograms may show diminished scotopic and photopic responses, depending on the severity of fundus changes and the age of patients [73]. Cataracts of various types, including nuclear, cortical, and posterior subcapsular, are seen in 15 % to 36 % of patient, often with CS type II [73, 74]. Pupils can be miotic and do not respond well to mydriatics, which can complicate intraocular surgery. Enophthalmos is common and is due to the lack of subcutaneous orbital fat [73, 74]. Other ocular findings include dryness, strabismus, nystagmus, and refractive error [74]. Predictors of poor prognosis include cataracts noted at birth or within the first 3 years of life, microphthalmia or iris hypoplasia [73].

Management

Treatment of manifestations is the mainstay of management for patients with CS and includes individualized educational programs for developmental delay, physical therapy to maintain ambulation, medications for spasticity and tremor, gastrotomy tube placement as needed, treatment of hearing loss, and use of sunscreens and sunglasses for photosensitivity. Surgery for cataracts and ophthalmologic complications are performed as in the general population. Annual surveillance for complications such as hyptenstion, renal and hepatic dysfunction, vision and hearing is recommended [74].

Trichothiodystrophy

Definition

Trichothiodystrophy (TTD) is a rare autosomal recessive disease of defective transcription in DNA repair, in which patients have brittle sulphur deficient hair [75]. Patients with TTD typically display a wide variety of clinical features, including abnormal hair, intellectual impairment, decreased fertility, short stature, and ichthyosis. Several acronyms have been created to describe the cutaneous findings of trichothiodystrophy. PIBIDS stands for photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature [21]. Other acronyms include IBIDS and BIDs. To date, four genes have been identified as causing TTD: *XPD*, *XPB*, *TTDA*, and *TTDN1* [75].

Systemic Manifestations

Patients commonly have sparse, brittle, and friable sulfur-deficient hair (96 %). The hair shows tiger tail banding (striped light and dark pattern) under a polarizing microscope [75]. The majoritiy of patients with TTD have skin findings, most commonly being ichthyosis (65 %). Second most frequently seen skin manifestation is photosensitivity (42 %), but similar to Cockayne syndrome, TTD is not associated with increased risk for malignancy or abnormal pigmentation. Premature aging can frequently be seen. Nail abnormalities including onychodystrophy, brittle nails, and kolionychia are commonly present [75].

Developmental delay and intellectual impairment has been reported in 86 % of patients [75]. Other neurologic findings described include microcephaly, abnormal gait, and spasticity. Neurodegeneration is thought to be due to abnormal myelin development. Neuroimaging shows demyelination and may also show cortical heterotopias, partial agenesis of the corpus callosum, perimedullary fibrosis of the spinal cord, and intracranial calcifications.

Facial dysmorphism was reported in two-third of patients with TTD. Microcephaly, large or protruding ears, and micrognathia can be seen. Growth abnormalities leading to short stature and poor weight gain can be seen in up to 80 % of patients with TTD. Reproductive abnormalities include hypogonadism, cryptorchidism, delayed pubertal development and partial panhypopituitaris [75].

Ocular Manifestations

Eye findings are found in approximately 51–94 % in studies of TTD patients [75, 76]. Ocular manifestations include refractive error (12–66 %), nystagmus (14–38 %), cataracts (29–62 %), strabismus (10–19 %), dry eyes (31 %), ectropion, and pigmentary retinopathy [75, 76]. Microcornea and microphthalmias can be seen as well. Cataracts are usually bilateral and can vary in severity and may not necessarily require removal [76]. Brittle eyelashes can lead to keratitis due to their abnormal orientation [73]. Retinal degeneration, although not commonly seen, may be a late-occurring phenotype and should be monitored [76].

Management

Effective management of multisystem abnormalities of TTD requires a multidisciplinary approach [75].

Rothmund-Thomson Syndrome (RTS)

Definition

Rothmund-Thomson syndrome (RTS), also known as poikiloderma congenitale, is a rare autosomal recessive disorder of abnormal skin, hair, bone and increased risk for cancer.

History

The initial description of RTS was in 1868 by the German ophthalmologist Rothmund who reported ten children with poikiloderma, growth retardation, and rapidly progressive bilateral cataracts [77]. Subsequently, the English dermatologist Thomson described three children with similar symptoms of poikiloderma and skeletal abnormalities [78]. The name Rothmund-Thomson syndrome was first coined by Taylor in 1957 who also reported a group of patients with similar symptoms [79].

Two forms of RTS have been described: type I RTS, characterized by poikiloderma, ectodermal dysplasia, juvenile cataracts, and negative for the *RECQL4*-mutation (DNA helicase gene); and type II RTS, characterized by poikiloderma, skeletal abnormalities and increased risk of osteosarcoma due to *RECQL4* mutations [77].

Systemic Manifestations

Skin is typically normal at birth. Rash of RTS develops between age 3 and 6 months as erythema and blistering of cheeks and face that spreads to the extensor surfaces of extremities and buttocks. Rash typically spare the trunk and abdomen. This evolves over months to years into a chronic pattern of poikiloderma which consist of reticulated hypo- and hyperpigmentation, telangiectasias, and areas of punctate atrophy [80]. This chronic phase usually persists throughout life If the rash is atypical in appearance or distribution, a diagnosis of probably RTS can be made with presence of two other following features: sparse scalp hair, eyelashes or brows, short stature, gastrointestinal disturbances (chronic vomiting or diarrhea), skeletal abnormalities, dental abnormalities, nail abnormalities, hyperkeratosis, juvenile bilateral cataracts, and skin (basal cell or squamous cell carcinoma) or bone cancers (osteosarcoma). Benign and malignant hematologic abnormalities have been reported and includes: isolated anemia, neutropenia, myelodysplasia, aplastic anemia, and leukemia. Prevalence of osteosarcoma is as high as 30 % in patients with RTS with median age at diagnosis of 11 years [80].

Ocular Manifestations

The most common ocular sign of RTS is bilateral juvenile cataracts that are present in up to 70 % of cases [81]. Cataracts are usually subcapsular and may present between ages 3 and 7 years although cases as early as few months of life to early adulthood have been reported [77]. Most reports of bilateral cataracts are from Europe. A more recent international cohort of 41 patients had only two patients with cataracts [82]. Madarosis or sparseness of eyelashes and eyebrows are frequently seen . Other less common ocular features include exophthalmos, corneal scleralization, blue sclera, and bilateral congenital glaucoma [73, 81].

Management

Surveillance for complications and cancer screening is key to management of patients with RTS. Avoidance of excessive sun exposure and liberal use of sunscreen are recommended to prevent skin cancer. Calcium and vitamin D supplements are warranted in patients with osteopenia or history of fractures [80].

Incontinentia Pigmenti (Block-Sulzberger Syndrome)

Incontinentia pigmenti (IP) is a rare, X-linked dominant genodermatosis of ectodermal tissues including skin, ocular, dental and central nervous system abnormalities. It is lethal in males [83]. Mutation in the *NEMO* gene (Xq28), result in defective NEMO protein, which is a crucial subunit of a complex multi-protein kinase that is responsible for activating transcription factor NF-kappa B in the regulation of immune and apoptotic pathways [83].

Systemic Manifestations

Classic cutaneous findings of IP occur in four stages within the first 2 years of life: vesicular, verrucous, hyperpigmented, and atrophic [84] (Fig. 8.7). The first vesicular stage is characterized by small, scattered blisters on an erythematous base that develop along the lines of Blashko. This stage is most prominent in the first 6 months of life. The verrucous phase is characterized by verrucous, hyperkeratotic, linear lesions, mainly on the limbs. The hyperpigmented stage usually occurs after resolution of the verrucous phase.

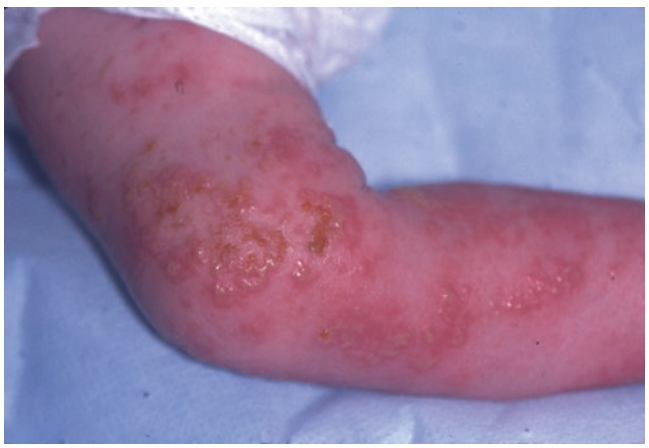

Fig. 8.7 Incontinentia pigmenti, leg lesions

Hyperpigmented streaks and whorls that respect Blaschko's lines occur mainly on the trunk and fades in adolescence. Finally, the hypopigmented/atrophic phase occurs last where patches and streaks of pale, hairless, and atrophic skin are present. IP is also commonly associated with alopecia, nail dystrophy, and loss of sweat glands. Hypodontia or anodontia (partial or complete absence of teeth), microdontia and abnormally shaped teeth may be seen [84].

Central nervous system (CNS) abnormalities can also be present in patients with IP as CNS is also of ectodermal origin. In an analyzed literature data of 1393 IP patients from the period of 1993 to 2012, CNS anomalies were diagnosed in 30 % of patients [85]. Most common CNS manifestations were seizures, motor impairment, microcephaly, and developmental delay [85]. The most frequently seen CNS lesions on brain imaging were brain infarcts, atrophy, and corpus callosum lesions [85].

Ocular Manifestations

Ocular involvement occurs in 35–77 % of studied populations [86]. In contrast to cutaneous findings that usually attenuate with time, ocular involvement persists throughout the lifetime of patients with the prevalence of blindness reported to be between 7 and 23 % [83]. The most problematic ocular manifestation is in the retina, affecting the peripheral vascularization of the retina and retinal pigment epithelium [83]. Vaso-occlusions that predominantly affect the arteries lead to peripheral nonperfusion and irreversible ischemia, which results in a cascade of events: proliferation of new blood vessels, exudation, hemorrhage, tractional retinal detachment, and even to a retrolental mass at its late stage if left untreated [83, 87]. Vasculopathies may also occur in the macula where fundus appearance may be normal but fluorescein angiography shows nonperfusion and capillary remodeling [88]. Other ophthalmologic findings in IP are secondary and include cataract, strabismus, nystagmus, and anterior segment abnormalities [89]. Strabismus is most often due to retinal pathology or poor vision [90].

Patients with IP are recommended to undergo examination by a pediatric ophthalmologist or retinal specialist at birth, at least monthly for the first 3–4 months, at 3-month intervals for 1 year, and twice yearly up to 3 years [84, 90]. Fluorescein angiography is crucial in evaluating for areas of nonperfusion and vascular abnormalities.

Management

Laser photocoagulation when performed in the early stages before neovascularization ensues can arrest the development of proliferative vitreoretinopathy and retinal detachment [91].

Treatment depends on the manifestations of disease. Patients may need treatment of blisters and skin infections, neurologic assessment and management of seizures, dental care which may include implants at an early age, and developmental programs and special education as needed for developmental delay.

Linear Nevus Sebaceous (Nevus Sebaceous of Jadassohn)

Nevus sebaceous is a hamartoma of epidermal, sebaceous and apocrine elements associated with mosaic activating Ras mutations (*HRAS* or *KRAS* most commonly).

History

Linear nevus sebaceous lesions were initially described by Jadassohn in 1895 as congenital cutaneous lesions in linear distribution. He described the lesions as organoid nevus because they may contain any or all components of the skin. Subsequently Robinson introduced the term nevus sebaceous of Jadassohn and suggested that malignant tumors, particularly basal cell carcinoma, can arise in the area of sebaceous nevus. In 1957, Schimmelpenning noted the association of these skin lesions with abnormalities of the CNS, skeletal system and eyes. In 1962, Feuerstein and Mims reported cutaneous lesions and seizures suggesting that the condition is a neurocutaneous syndrome [92, 93].

Systemic Manifestations

These lesions are usually present as solitary, well-demarcated smooth, hairless plaques that favor the face and scalp. They may extend to the eyelids (or rarely the eye as well). When located in the scalp, alopecia is often present. Classically, they present as hairless, yellowish plaques. On palpation, they may seem verrucous or velvety. They are often quiescent from birth until puberty, when they may become more verrucous or greasy in appearance. Histologically, nevus sebaceous display epithelial hyperplasia with abnormal sebaceous glands, sweat glands, and poorly formed hair follicles, which lack terminally differentiated hair follicles. Three stages of sebaceous nevus have been described, depending on the age of the patient. First presents in infancy with papillomatous hyperplasia with underdevelopment of hairs, sebaceous glands, and other adnexal tissue. Second stage occurs in puberty characterized by massive overdevelopment of these adnexal structures due to hormonally driven development and maturation of sebaceous and apocrine glands. It is at this stage where smooth lesions transform into verrucous plaques. Third stage in adulthood has pronounced development of benign and malignant tumors in the area of the cutaneous lesion [92, 93]. There are multiple reports of tumor growth including localized malignancy within the lesions, usually after puberty. Up to 20 % of patients with sebaceous nevus may develop basal cell carcinoma in affected areas [92, 93].

Linear nevus sebaceous syndrome (LNSS) is the term used when cutaneous lesions are seen with a broad spectrum of abnormalities that can affect every organ system. Most commonly involved are central nervous system, cardiovascular, skeletal, ophthalmologic, and urogenital systems, among others. The most common neurologic manifestations are seizures and developmental delay [92–95].

Ocular Manifestations

Ocular abnormalities have been described in up to 50 % of individuals with nevus sebaceous. The most common findings are ocular choristomas and colobomas of the uvea, optic disc and lids [92, 93]. Choristomas include epibulbar dermoids, lipodermoids, simple and complex choristomas. The pathogenesis of choristomas in association with LNSS may be related to an early developmental anomaly. The CNS, skull and ocular abnormalities are thought to be a result of abnormal development of the neuroectoderm before the fourth week of gestation, while sebaceous nevus lesions are proposed to be caused by the failure of separation of skin appendages from adjacent epithelium at a later stage during the third month of gestation. Epibulbar choristomas are usually stationary and usually do not progress. Fundus exam of LNSS patients may reveal abnormal optic nerves including pseudopapillema, optic nerve hypoplasia or optic nerve coloboma. Consistent fundus finding in the literature is poorly defined light-colored area usually in the posterior fundus, which can sometimes be mistaken as retinal/choroidal coloboma or choroidal osteoma. This discoloration is reported to be deep to retina, possibly in the outer choroidal or scleral level. Compared to colobomatous lesions, this finding is flat, not excavated, and vision is usually better than expected in patients with colobomas [93].

Management

Excision of epibulbar choristoma can be considered for cosmetic or visual reasons. Caution should be taken as surgery carries the risk of perforation.

Immunologic Disorders

Eczema (Atopic Dermatitis)

Definition

Atopic dermatitis (AD) typically begins in infancy, with most cases present by 5 years of age. Acute lesions are intensely pruritic with erythematous papules [96]. Younger children and infants tend to have prominent facial involvement, while older children have lichenification of the skin, with more involvement of the flexural folds and extremities. Infants and children with AD are more prone to allergic rhinitis and asthma. AD can be exacerbated by environmental triggers, which can include inhaled, skin or food irritants. The etiology of AD is associated with IgE mediated sensitization in approx. 75 % of affected individuals. Memory T cells express cutaneous lymphocyte-associated antigens, which produce increased levels of Th2 cytokines. Proinflammatory cytokines and chemokines are involved with cascades that affect the surrounding tissue, leading to clinical manifestations and chronicity. Other conditions can mimic AD and must be excluded and can include congenital/syndrome (e.g., ichthyoisis), psoriasis, infectious (e.g., Scabies), malignancies (e.g., histiocytosis, T cell lymphoma), autoimmune disorders (e.g., graft versus host, dermatomyositis), immunodeficiencies (e.g., Wiskott-Aldrich), and metabolic disorders (e.g., zinc deficiency).

Ocular Manifestations

Atopic dermatitis (AD) has significant ocular morbidity with eye or eyelid involvement in 20 % to 42 % of patients [97, 98]. AD is associated with ocular disorders including atopic keratoconjunctivitis (AKC), keratoconus, cataract, glaucoma and ocular infections [97]. Hogan first described AKC as a severe complication of AD in 1953 [97]. AKC is defined by Guglielmetti as a chronic ocular surface noninfectious inflammatory condition which is always associated with atopic conditions, occurring at any time in the course of the atopic disease and with evidence of corneal involvement during the course of disease [98]. Patients with AKC have an increased susceptibility to infection that results from the compromised innate immunity [98]. Thus, they are more prone to bacterial and viral infections of skin and eye compared to the general population. AKC presents in the late teens and early twenties and only occasionally presents in early childhood [99]. The peak incidence of ocular complications of AKC occurs during the third to fifth decades [99].

Symptoms of AKC are itching, watering, redness, photophobia, blurred vision and presence of stringy mucoid discharge [98]. Symptoms are present in both eyes symmetrically. Exacerbations can be seasonal that can be worse either in summer or winter. Skin and eyelids as well as periorbital skin may have severe eczema, and patients with pigmented skin can have increased pigmentation around the eyes [98]. Dennie-Morgan lines are single or double infraorbital creases of eyelid skin caused by edema and thickening [99]. Increased tearing and rubbing due to itching can result in macerated eyelid skin. Both tarsal and palpebral conjunctiva can be chronically inflamed and thickened. Later in the disease, papillae can be replaced by scarred tissue and shortening of fornix can even develop in some patients [98]. Trantas dots can also be seen although not as commonly as in vernal keratoconjunctivitis [98]. Cornea involvement includes punctate erosions and filamentary keratitis to severe corneal ulcers and corneal thinning [98]. As mentioned previously, these areas can be secondarily infected with bacteria or virus, further complicating the clinical picture. Most commonly, they can be infected with *Staphylococcus aureus* and *Herpes simplex* virus [97].

Cataracts, both anterior and posterior subcapsular, are associated with AD and AKC. Cataracts tend to occur about 10 years after the onset of disease [97]. A unique feature of AKC cataracts is the predominantly anterior location and the tendency for rapid progression that can lead to complete opacification in 6 months [99]. Posterior subcapsular cataracts can occur and may be associated with prolonged use of

oral and topical steroids. Keratoconus is reported to occur in 1.5 % to 16 % of patients with AD, and conversely, AD was associated with 16 % of patients with keratoconus [99]. Keratoconus is associated with positive skin prick test to environmental allergens [99]. Keratoconus can be further exacerbated by chronic eye rubbing [97]. Although AD patients with keratoconus did not significantly differ in terms of gender, age of onset or rate of keratoplasty with those without atopy, atopic patients, especially those with high IgE levels, have higher incidence of corneal graft rejection [97, 99].

Management

Treatment is directed at avoiding the inciting agent, skin hydration, topical anti-inflammatory agents (steroids), and if necessary systemic treatment. Initial treatment is removing any irritating or offending agents. This may include avoiding soaps or creams, certain types of blankets or bedding. Hydration of the skin and avoiding drying soaps is helpful, as is putting on petroleum ointment while the skin is still moist and the infant/child is getting out of the bath. Pimecrolimus cream 1 % or Tacrolimus 0.03 % or 0.1 % ointment are alternatives as well that avoid risk of cutaneous atrophy that can result from chronic topical steroid use [100].

The goal of AKC treatment is to control the symptoms, decrease recurrence and exacerbations, reduce treatment side effect, and to avoid potential vision loss from complications [97]. First line treatment for AKC is topical mast cell stabilizer ophthalmic drops or ointment, which is helpful in decreasing symptoms as well as minimizing the use of steroids [97]. It is also useful for maintenance treatment in chronic disease. Topical antihistamine drops can be used in conjunction as well as dual-acting agents that have both mast cell stabilizing effects with H1 receptor blocking effects. Severe AKC often requires a short course of topical steroids. Calcineurin inhibitors cyclosporine A and FK506 (tacrolimus) are also steroid-sparing agents that can be effective in treatment of AKC [97].

Contact Dermatitis

Contact dermatitis is a condition that can be due to irritant or allergic contact reactions. Irritant contact dermatitis is due to exposure to a nonspecific noxious substance that induces an irritant eczematous reaction by nonspecific injury to the skin. Saliva, soap and detergents are common causes. Allergic contact dermatitis is due to a T-cell delayed hypersensitivity reaction. Once sensitization to a chemical has occurred, each new antigenic challenge will produce a reaction. The reaction is an erythematous, intensely pruritic, eczematous dermatitis, which, if severe may be edematous and vesiculobullous. The distribution often helps elucidate the cause, e.g., (A reaction around the wrist from a nickel containing bracelet). Particular patterns of findings may be associated with certain exposures, such as eyelid dermatitis being commonly associated with contact allergy to nail polish. Removing the offending agent, and topical corticosteroid therapy of the dermatitis will usually resolve the problem. When the eyes are involved, artificial tears and topical antihistamines may help.

Graft-Versus-Host Disease

Definition and Epidemiology

Graft versus host disease (GVHD) is a major complication of allogenic stem cell transplantation (allo-SCT) that occurs in 25–70 % of patients undergoing allo-SCT [101–103]. It is an immune-mediated disease that leads to complex interactions between donor and recipient adaptive and innate immunity. According to the National Institutes of Health (NIH), GVHD is categorized into two broad classifications: acute GVHD and chronic GVHD [103].

Systemic Manifestations

Acute GVHD

Acute GVHD is an immediate multi-organ inflammatory syndrome that mainly affects skin, liver and gastrointestinal (GI) tract with occasional manifestations in the eyes and oral mucosa [101, 103]. Approximately 81 % have skin involvement seen as pruritic, and sometimes painful, maculopapular rash with associated blistering and ulceration in severe cases [104]. Rash is classically distributed in the palms, soles and later spreads to the cheeks, ears, neck, trunk, chest, and upper back but spares the scalp [101, 103]. Gastrointestinal involvement is present in about 54 % of patients in the form of secretory diarrhea with or without upper GI symptoms such as vomiting and anorexia [104]. Liver dysfunction is seen in 51 % resulting in elevated conjugated bilirubin and alkaline phosphatase and to a lesser degree, transaminases [104]. Risk factors that predispose patients to acute GVHD include female donor to male recipient, female donor with prior pregnancies or transfusions, old recipient age, no acute GVHD prophylaxis and cyclosporine-based prophylaxis. Risk is less in patients with matched sibling transplantation and those receiving tacrolimus-based prophylaxis [101].

Chronic GVHD

Chronic GVHD, previously described as occurring 100 days after transplant, now has no time limit according to the new NIH classification [101, 103]. Diagnosis requires the following [103]:

1. Distinction from acute GVHD
2. Presence of at least 1 diagnostic clinical sign or presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests

Table 8.3 Signs and symptoms of chronic GVHD

Organ or Site	Diagnostic signs[a]	Distinctive signs[b]
Skin	Poikiloderma	Depigmentation
	Lichen planus-like features	
	Sclerotic features	
	Morphea-like features	
	Lichen sclerosus-like features	
Nails		Dystrophy
		Longitudinal ridging, splitting, or brittle features
		Onycholysis
		Pterygium unguis
		Nail loss
Scalp and hair		New onset alopecia (after recovery from chemotherapy)
		Scaling, papulosquamous lesions
Mouth	Lichen-type features	Xerostomia
	Hyperkeratotic plaques	Mucocele
	Restriction of mouth opening from sclerosis	Mucosal atrophy
		Pseudomembranes
		Ulcers
Eyes		New onset dry, gritty, painful eyes
		Cicatricial conjunctivitis
		Keratoconjunctivitis sicca
		Confluent areas of punctate keratopathy
Genitalia	Lichen planus-like features	Erosions
	Vaginal scarring or stenosis	Fissures
		Ulcers
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology
Muscles, fascia, joints	Fasciitis	
	Joint stiffness or contractures secondary to sclerosis	

GVHD indicates graft-versus-host disease; PFTs, pulmonary function tests
[a]Diagnostic signs: sufficient to establish the diagnosis of chronic GVHD
[b]Distinctive signs: Seen in GVHD, but insufficient alone to establish a diagnosis of chronic GVHD

3. Exclusion of other possible diagnosis

Manifestations of chronic GVHD resemble autoimmune disorders with prominent features of Sjogren-like syndrome. It affects multiple systems including musculoskeletal and hematologic systems as well as skin, gut, lungs and eyes. Table 8.3 summarizes the diagnostic and distinctive signs of chronic GVHD [103]. Factor predisposing patients to develop chronic GVHD include occurrence of acute GVHD, risk factors for acute GVHD, and the use of peripheral blood stem cells. Lower rate is seen in patients receiving cord blood transplantation [103].

Ocular Manifestations

Ocular complications develop in 40–60 % of patients after allo-SCT and in 60–90 % of patients with systemic GVHD [101, 102]. Although it may be seen as part of acute GVHD, ocular GVHD is mainly associated with and more severe in chronic GVHD. Ocular symptoms may be the first manifestation of systemic GVHD. Ocular GVHD usually does not lead to permanent vision loss but typically follows a stable clinical course with good visual acuity. However, it is known to significantly impair the quality of life and activities of daily living [101]. Presence of skin or mouth findings increases the risk of ocular involvement in GVHD patients.

Ocular tissues involved in GVHD are eyelid, periorbital skin, conjunctiva, cornea, lacrimal system, sclera, and less commonly, lens, uvea and retina. Ocular surface and lacrimal glands are most commonly affected and abnormalities are due to inflammation, cicatricial scarring and meibomian gland dysfunction. The grading systems for conjunctivitis in acute and chronic GVHD is shown in Table 8.4 [101, 105].

In acute GVHD, severity of ocular signs correlates with the severity of systemic disease. Conjunctival involvement in acute GVHD is a poor prognostic factor associated with a higher rate of mortality [101]. Cornea and conjunctiva are immunological targets in GVHD and show histological changes similar to that seen in cutaneous GHVD.

In chronic GVHD, ocular symptoms resemble those seen in dry eye disease/keratoconjunctivitis sicca (KCS). KCS is present in 69–77 % of patients with chronic GVHD and is often an early sign of systemic involvement [101]. Primary etiology of KCS in chronic GVHD has been attributed to

Table 8.4 Conjunctival grading in acute and chronic GVHD

Classification of Conjunctivitis in Acute GVHD
• 0. None
• 1. Hyperemia
• 2. Hyperemia/chemosis with serosanguinous discharge
• 3. Pseudomembranous conjunctivitis
• 4. Pseudomembranous conjunctivitis with corneal epithelial sloughing
Classification of Conjunctivitis in Chronic GVHD
• 0. None
• 1. Hyperemia
• 2. Palpebral conjunctival fibrovascular changes with or without epithelial sloughing
• 3. Palpebral conjunctival fibrovascular changes involving 25–75 % of total surface area
• 4. Involvement of >75 % of total surface area with or without cicatricial entropion

Table 8.5 National Institute of Health Eye Score

Score	Symptoms
0	No symptoms
1	Mild dry eye symptoms not affecting ADL (requiring eye drops less than 3 per day)
	OR
	Asymptomatic signs of keratoconjunctivitis sicca
2	Moderate dry eye symptoms partially affecting ADL (requiring eye drops more than 3 times per day or punctual plugs) WITHOUT vision impairment
3	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain)
	OR
	Unable to work because of ocular symptoms
	OR loss of vision caused by keratoconjunctivitis sicca

ADL activity of daily living

Table 8.6 Treatment Recommendation for Dry Eyes Based on Severity

Level	Recommended measure
1	Education and counseling
	Environmental management
	Elimination of offending systemic medications
	Preserved tear substitutes, allergy eye drops
2	Unpreserved tears, gel, ointments
	Steroids
	Cyclosporine A
	Secretagogues
	Nutritional supplements
3	Tetracyclines
	Autologous serum tears
	Punctal plugs (after control of inflammation)
4	Topical vitamin A
	Contact lenses including Prosthetic Replacement of Ocular Surface Ecosystem (PROSE)
	Acetylcysteine
	Moisture goggles
	Surgery

fibrotic destruction of tubuloalveolar glands. Aqueous deficiency with KCS usually does not recover.

According to the NIH consensus diagnostic criteria, new onset KCS with a Schirmer test score of 6–10 mm at 5 min, or symptoms accompanied by a Schirmer score of ≤5 mm at 5 min in the presence of distinctive features in at least 1 other organ is diagnostic of chronic GVHD [103]. This criterion was developed for the use of transplant physicians and not by ophthalmologists. Various authors have since questioned the use of Schirmer's test as an effective tool for diagnosis due to high false positive and negative rates [106–108]. In addition, the accepted wetting of 5 mm is applicable only when test is performed without anesthesia and comparable diagnostic values for Schirmer's test with anesthesia is not clear. The NIH eye score (Table 8.5) as well as the Ocular Surface Disease Index (OSDI), has been shown to be a sensitive measure of eye symptom changes [107, 108]. Dry eye disease and KCS is currently considered a distinctive sign and not as diagnostic criteria for chronic GVHD [103]. Recently, the International chronic GVHD Consensus Group, in addition to various other authors, have proposed a change in the NIH consensus diagnostic criteria to include ocular GVHD as a diagnostic criteria sufficient alone to establish a diagnosis of GVHD [107].

Other ocular manifestations of GVHD include eyelid dermatitis, lagophthalmos, lid margin abnormalities, poliosis, madarosis, and vitilgo [102]. Uveitis has been reported in 8 % of cases with chronic GVHD, and it is crucial to distinguish such cases with infectious or inflammatory etiologies as well as masquerade syndrome [102, 109]. Patients may also have retinal microvasculopathy, likely related to irradiation. Cataract formation is also a late complication of all-SCT, which is mainly attributed to irradiation and steroid therapy [102]. Ocular complications due to other predisposing factors such as infections, medications, and conditioning therapies must be ruled out before consideration of ocular GVHD. Assessment of ocular symptoms, comprehensive eye exam, and consideration of other systemic symptoms and signs are important in determining the presence and severity of ocular GVHD.

Management

Treatment of systemic GVHD constitutes immunosuppressive therapy with close monitoring and treatment of organ specific symptoms and complications. In ocular GVHD, the main aim of treatment is to relieve dry eye symptoms by controlling inflammation, supporting tear film, and maintain mucosal integrity. These include topical and systemic medications, surgical approaches as well as eyewear and environmental modifications depending on the severity of the

symptoms. A proposed recommendation for treatment is provided in Table 8.6 [102].

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Definition

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, life-threatening acute mucocutaneous syndromes that affect both adults and children. Due to considerable overlap of clinical and histopathological features, these syndromes are considered to be in a wider spectrum known as SJS/TEN [110]. The percentage of body surface area (BSA) of skin detachment determines the entity where SJS involves epidermal detachment of less than 10 % BSA, SJS/TEN overlap involves detachment of 10–30 %, and TEN is when more than 30 % of BSA is involved [110].

Epidemiology and Etiology

The annual incidence of SJS/TEN is reported to be approximately 1 to 7 cases per million inhabitants [110]. Case fatality rate for SJS is approximately 10 % in adults but may be less in children [111]. SJS/TEN is considered to be a delayed-type hypersensitivity reaction (type IV reaction), but the immune-pathophysiology is not fully understood [110]. There are also genetic predispositions. Most cases are triggered by a medication. Infectious etiologies are also increasingly recognized. SJS/TEN is more commonly associated with a drug if an offending agent was used within 8 weeks prior to the onset of the rash [110]. More than 200 drugs have been identified to trigger SJS/TEN. Most common drugs associated with SJS/TEN are sulfonamides, anticonvulsants, penicillins/cephalosporins, nonsteroidal anti-inflammatory drugs (NSAID), and allopurinol [110, 112]. An infectious cause is considered if signs of infection started 1 week prior to the onset of the rash and a titer or cold agglutinins (IgM) of the infectious agent are positive. Most common infectious etiologies include *Mycoplasma pneumoniae* and viruses such as human herpes virus, influenza, Epstein-Barr, and hepatitis A virus [110, 112]. Recently, there have been reports of an outbreak of SJS in children which was predominantly associated with *Mycoplasma* infection, suggesting that it may be a distinct clinical entity [111, 113].

Systemic Manifestations

SJS/TEN presents with prodromal symptoms of fever, malaise and ocular pruritis lasting 1 to 7 days, followed by onset of cutaneous and mucosal lesions. Inflammation and pain of mouth and genitalia are frequent and often precede the skin rash by a few days [110]. Skin lesions present as red macules and papules that can coalesce to atypical targetoid lesions and generalized rash. They become vesicular and bullous, leading to skin necrosis that detaches in large sheets. Large amounts of skin can ulcerate causing severe pain, and is prone to superinfection and insensible fluid loss. Nikolsky sign, which is defined as epidermal detachment that appears with gentle, tangential pressure on non-blistering skin, can be helpful where generalized erythema is prominent [110, 112]. Mucous membrane involvement affecting eyes, nasal and oral mucosa, respiratory and digestive tracts, varies in severity and is often painful and hemorrhagic.

Mycoplasma-associated SJS may present with a distinct clinical presentation. It is associated with extensive mucositis (especially ocular surface disease) and less extensive skin disease. There is evidence of preceding respiratory infection, usually atypical "psittacosis-like" pneumonia [111, 113]. Erythrocyte sedimentation rate is often falsely elevated due to presence of cold agglutinins, suggesting its use as a potential biomarker for Mycoplasma associated diseases. Mycoplasma infections can now be more accurately diagnosed through the use of PCR testing compared to serology alone. Based on these findings, some have proposed distinct diagnostic criteria for Mycoplasma-associated SJS and different nomenclature (Mycoplasma-induced rash and mucositis) [113].

Ocular Manifestations

Ocular involvement of SJS/TEN is common, and long-term sequelae due to scarring of ocular surface and eyelids can be debilitating and even blinding [114, 115]. All patients with SJS/TEN require prompt evaluation by an ophthalmologist, regardless of the extent of skin involvement as severity of eye involvement may not always correspond with systemic disease. Eye involvement can vary in severity from self-limited mild conjunctivitis to sloughing of the entire mucosal surface. In the acute phase, there is rapid keratinocyte apoptosis with secondary inflammation and loss of ocular surface epithelium [116]. Intense inflammation can lead to formation of pseudomembrane, frank membrane, and corneal ulceration.

Conjunctival ulceration can result in fusion of bulbar and forniceal surfaces leading to permanent symblepharon, ankyloblepharon, and lid malposition (Fig. 8.8). Meibomian gland atrophy and inpissation, cicatricial punctual occlusion, and keratinization of the eyelid margins with eyelash malposition may also occur. Late corneal blindness can occur with development of chronic limbal stem cell dysfunction [116].

Ophthalmologists play a critical role in early evaluation and treatment of SJS/TEN. Within 1 day of admission, a detailed eye examination should be performed. Careful inspection of eyelid skin, lid margin, and entire ocular surface is warranted and always should include fluorescein staining to detect epithelial defects, presence of membranes and denuded epithelium. Rapid progression of ocular

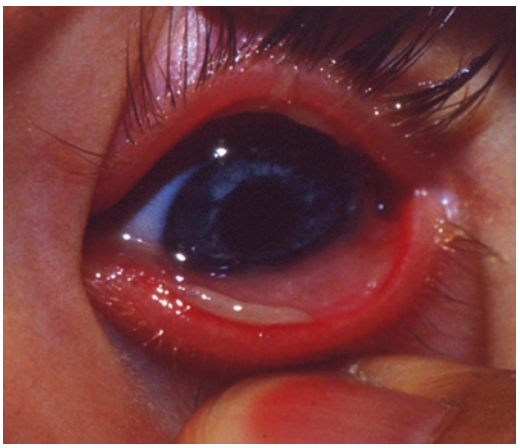

Fig. 8.8 Stevens Johnson, conjunctival lesion<<permission requested from McGraw Hill>>

involvement is possible, and daily evaluations should be performed until symptoms and signs are stable. During daily evaluations, saline solution should be used to rinse away any debris that may obscure the underlying epithelial defects. The extent of epithelial defect and sloughing should be re-evaluated daily using fluorescein and handheld ophthalmoscope with blue light. Inspection of fornices and tarsal conjunctiva with eyelid eversion should also be performed.

Management

The modern approach to acute management of ocular SJS involves controlling the intense inflammation that occurs as a result of extensive keratinocyte apoptosis [117]. Aggressive ophthalmic treatment is indicated even before diagnosis is confirmed by skin biopsy to reduce the risk of disease progression and reduce the risk of long-term complications. Intensive topical corticosteroid therapy is beneficial, but it alone may not be sufficient. Systemic pulsed steroids within 4 days of onset in addition to topical treatment have also been reported to be effective without systemic complications. Limited areas of epithelial sloughing can be medically managed with close daily monitoring for progression. For more extensive areas of sloughing, urgent AMT to the lid margins and palpebral conjunctiva is recommended. If there is limited sloughing of the ocular surface, a Prokera may be applied to the ocular surface. A Prokera (Biotissue, Miami, Florida, USA) is a sheet of amniotic membrane stretched across a polycarbonate ring that provides anti-inflammatory effects and helps to prevent symblepharon formation. For more extensive or rapidly progressing eye involvement, sutured AMT is performed to the lids, palpebral conjunctiva and entire ocular surface to prevent chronic scarring and sequelae. It is important to treat the lid margins and palpebral conjunctiva in all cases requiring AMT. A Prokera alone is not sufficient treatment. The window of opportunity for AMT to be effective is within the first week of illness [115, 117, 118]. Indications for AMT include enlarging areas of sloughing and epithelial defects of cornea, tarsal conjunctiva or lid margins [115, 118]. Once scarring has occurred, the process cannot be effectively reversed by AMT. Suggested management of acute ocular SJS/TEN based on clinical assessment is provided in Table 8.7 [119].

Table 8.7 Suggested management of acute ocular SJS/TEN

Grade	Exam findings	Management
0	No ocular involvement	PFAT 4×/day
1	Conjunctival hyperemia	Dexamethasone 0.1 % QID
		Cyclosporine 0.05 % BID
		PFAT every 1–2 h if feasible
2	Epithelial defects in:	Above plus Moxifloxacin 0.5 % QID
	• Bulbar or palpebral conjunctiva (<1 cm in greatest diameter) or	
	• Eyelid margin (<1/3 of lid margin length) or	
	Pseudomembrane formation	
3	Epithelial defects in:	Above and consider AMT
	• Bulbar or palpebral conjunctiva (>1 cm) or	
	• Eyelid margin (>1/3 of lid margin length on at least 1 lid) or	
	• Cornea (an epithelial defect more than punctate staining)	

SJS/TEN Stevens-Johnson syndrome/ toxic epidermal necrolysis, *PFAT* Preservative free artificial tears, *AMT* Amniotic membrane transplantation

Chronic ocular complications of SJS/TEN are difficult to manage, and despite recent advances, most treatments have limited success rates. The most common sequelae is marked ocular surface dryness resulting from changes in all the layers of the tear film [117]. Cicatricial ocular surface changes include corneal ulceration, corneal and conjunctival scarring, symblepharon, and limbal stem cell deficiency. Changes in the eyelid such as trichiasis and entropion can also be debilitating. Frequent lubrication with preservative-free artificial tears is often the first-line treatment. Autologous serum tears can be beneficial due to its epitheliotrophic properties and components that are similar to natural tears. Scleral lenses and prosthesis like PROSE (prosthetic replacement of the ocular surface ecosystem) devices can provide symptom relief and visual rehabilitation [117]. For severe ocular surface and eyelid changes, ocular surface reconstruction and lid surgeries may be required.

Systemic treatments during the acute episode include supportive therapy, immunosuppressive drugs, intravenous immunoglobulins (IVIG), plasmapheresis, corticosteroids, cyclosporine, and appropriate antibiotic therapy for suspected infections [112, 114].

Vogt-Koyanagi-Harada Syndrome-VKH

Vogt-Koyanagi-Harada (VKH) disease is a T-cell mediated autoimmune multi-organ disorder where the main targets are melanin-containing cells present in the eye, meninges, ear and skin [120–123]. It is an inflammatory condition occurring in genetically susceptible individuals. VKH is most commonly in patients of Hispanic, Asian, Middle-Eastern, or Native American descent. Increased prevalence of VKH in certain ethnicities originates from genetic risk factors rather than the degree of skin pigmentation. Individuals of African heritage rarely develop VKH. There is genetic association with human leukocyte antigen DR4 (HLADR4) with particular strong association with HLA-DRB1*0405 [120–123]. The inciting event that activates the immune system is not well known although viral causes have been suggested.

Systemic Manifestations

Clinical features of VKH are related to the tissues with melanocytes. Melanocytes are present in the uveal trace, meninges, and inner ear, in addition to skin. Clinical course follows four stages or phases: prodromic, uveitic, convalescent and recurrent/chronic [120–123]. In the prodromic stage, patients present with viral illness-like symptoms, neurologic symptoms, headache, and meningismus. During this stage, cerebrospinal fluid shows pleocytosis in 80 % of cases within 1 week of disease onset. Uveitic stage follows in a few days characterized by acute, bilateral, diffuse uveitis. Auditory symptoms such as vertigo, tinnitus, dysacusis, and sensorineural hearing loss can develop in the prodromic and uveitic stages. After several weeks, convalescent stage ensues with depigmentation of the skin and choroid. The most notable skin findings are vitiligo, alopecia, and poliosis. Erythema may precede development of vitiligo. Approximately two-third of patients eventually develop recurrent/chronic phase of disease, which is mainly characterized by recurrent anterior uveitis [120–123].

Diagnosis of VKH is made by clinical examination. There are five diagnostic criteria based on the international committee in 2001 [124]:

1. No history of penetrating ocular trauma or surgery
2. No evidence of other ocular disease that can explain presenting clinical features
3. Bilateral ocular involvement
4. History or presence of neurologic or auditory findings such as meningismus, tinnitus, or CSF pleocytosis
5. Presence of alopecia, poliosis, or vitiligo, which have not preceded CNS findings

Complete VKH requires all five diagnostic criteria. Incomplete VKH requires 1 to 3 and either 4 or 5. Probable VKH requires criteria 1–3 only.

Ocular Manifestations

Acute ocular findings in the uveitic stage are bilateral, granulomatous panuveitis and exudative retinal detachment [120–123]. Optic disc swelling are often seen as well. Choroidal thickening can be seen on ultrasonography and enhanced depth imaging optical coherence tomography. Dalen-Fuchs nodules are mounds of retinal pigment epithelium (RPE) cells with lymphocytes and macrophages between RPE and Bruch membrane that have been reported in patients with VKH.

Chronic ocular findings include diffuse depigmentation of the fundus due to loss of melanocytes, resulting in "sunset glow" appearance. Focal areas of loss of RPE can be seen as well. Loss of pigment can also occur in the anterior segment. Perilimbal vitiligo, known is Sugiura sign, is pathognomonic. Recurrent anterior uveitis is a prominent feature of chronic/recurrent phase of VKH. Recurrent posterior uveitis is uncommon. Other ocular complications include cataract (10–42 %), glaucoma (6–45 %), subretinal fibrosis (8–40 %) and neovascular membrane (9–14 %) [120].

Complementary ophthalmic testing and imaging, such as fluorescein angiography (FA), ICGA, OCT, and ocular ultrasound, are valuable in substantiating the diagnosis. FA in the acute phase characteristically shows numerous punctate leakage and subsequently pool in the subretinal space. In the chronic phase, FA shows window defects from RPE loss. Nearly 70 % of patients will have disk leakage in the acute phase of disease. Differential diagnosis includes sympathetic ophthalmia, posterior scleritis, benign reactive lymphoid hyperplasia of uvea, neoplasia, infectious choroiditis, inflammatory diseases such as sarcoidosis, and choroidopathy due to malignant systemic hypertension. Overall, visual prognosis is favorable with final visual acuity better than 20/40 in about 60 % of patients [120–123].

Management

In the acute uveitic stage, early and aggressive treatment with systemic corticosteroids is the mainstay of VKH therapy. Prompt diagnosis and treatment in this initial phase can reduce subsequent recurrences and alter the course of depigmentation of choroid, skin, and hair. High does steroids of oral prednisone (1–2 mg/kg/day) or intravenous methylprednisolone (1 g/day) are given for 3 days, followed by slow taper over 6 or more months. Inadequate treatment (later than 15 days from disease onset, suboptimal dose, interruption before 6 months) are associated with increased risk of inflammatory recurrences and worse visual prognosis. Nonsteroid systemic immunosuppressive therapy may be necessary in refractory cases or those with recurrences. Some believe that nonsteroidal immune-modulating therapy should be initiated as first-line therapy for VKH. Cyclosporine A is a good choice drug that has been extensively studied. Renal function must be monitored carefully, especially in elderly patients. Other medications including azathioprine, myco-

phenolate, and biologic agents may also be beneficial. Anterior segment inflammation is treated with topical steroids and mydriatic agents [120–123].

Skin and Hair Lesions

In children, many skin and hair lesion can involve the eye or adnexa. The following conditions will discuss associations and management.

Acne

Acne vulgaris is the most common cutaneous disorder worldwide. Its pathogenesis is multifactorial and includes increased production of sebum, increased androgen production, follicular hyperkeratinization, and P. acnes proliferation. It usually occurs around puberty and present as open and closed comedones with possible inflammatory papules, pustules and nodules. Ocular problems are related to the lesions of the periocular area, as well as the increased oil production may exacerbate meibomian gland dysfunction and blepharitis [125]. Medications used in the treatment of acne vulgaris has been associated with idiopathic intracranial hypertension [126]. Strong association has been shown with tetracycline derivatives. Few reports of association with minocycline and doxycycline have been published. Retinoids, including vitamin A and isotretinoin, may also increase the risk of idiopathic intracranial hypertension.

Rosacea

Definition

Rosacea is a chronic cutaneous disorder that primarily affects blood vessels and pilosebaceous units of the central facial skin. The disease is categorized in four subtypes: erythematotelangiectatic, papulopustular, phymatous, or ocular rosacea [127]. A variant form, granulomatous rosacea, was also described.

Epidemiology

Rosacea affects over 16 million Americans [128]. A large observational study in the United Kingdom revealed an incidence rate of 1.65/1000 person-years as diagnosed by general practitioners [129]. Rosacea is most frequently observed in fair-skinned patients of European descent but can arise in other ethnicities [128, 130]. Rosacea can be diagnosed in early childhood and in the elderly but is most commonly seen in the middle-aged population [128, 130, 131].

Pathogenesis and Etiology

Pathogenesis of rosacea remains unclear. Various hypothesized possible causes include altered innate immune response, neurogenic inflammation, neurovascular dysregulation, dermal matrix degeneration, sun damage, and microorganisms [128, 130, 132]. *Demodex* species (*Demodex folliculorum, D. brevis*) may play a role in the pathogenesis and/or exacerbation of the disease. They are microscopic parasitic mites that are commonly found in hair, eyelash follicles and sebaceous glands. Studies have reported strong correlation of *demodex* infestation with eyelid inflammation and particularly papulopustular rosacea. These may also act as vectors for other organisms such as *Bacillus olenorium*, which may be responsible for the inflammatory response in rosacea through stimulation of Toll-like receptor 2 [128, 132].

Systemic Manifestations

Rosacea is characterized by transient or persistent facial erythema, edema, papules, pustules, and telangiectasia that are usually confined to the central face. Classic manifestation is the phymatous changes of the nose, as known as rhinophyma [127, 128, 130]. Four subtypes of rosacea have been identified and includes erythematotelangiectatic, papulopustular, phymatous, and ocular [133].

Ocular Manifestations

More than 50 % of patients with rosacea may have ocular involvement, and ophthalmic complications may not correlate with the severity of facial rosacea [130, 131, 134, 135]. About 20 % of patients may develop ocular symptoms prior to emergence of skin findings [135]. Ocular rosacea affects both males and females equally, in contrast to facial rosacea that has a slight female predilection [129].

Ocular rosacea can manifest with varying degrees of eyelid and ocular surface inflammation. Symptoms include redness, tearing, burning, foreign body sensation, itching, photophobia and blurred vision depending on the amount of corneal involvement [128]. Ocular involvement is often bilateral and can be nonspecific.

Lid disease is most commonly observed and can manifest as blepharitis, meibomian gland dysfunction, recurrent chalazion, and periorbital edema [128]. Slitlamp examination of the lid margins may reveal telangiectases, blockage of meibomian orifices, dilated meibomian glands, and collarettes around the lashes. Abnormal Schirmer testing and diminished tear break-up time have been reported in a large majority of patients with ocular rosacea [128].

Conjunctiva can be chronically inflamed in ocular rosacea. Interpalpebral bulbar hyperemia as well as papillary reaction may be observed [128]. Starr and Macdonald described an “arcade” of dilated vessels in the superficial limbal plexus that are isolated to the conjunctiva and are most commonly seen in the inferior aspects of the bulbar conjunctiva [131]. Cicatricial conjunctivitis have been reported in ocular rosacea and may involve the lower lids and upper lids, mimicking trachoma [128, 136, 137]. Patients with ocular rosacea may develop symblepharon following conjunctival surgery [128].

About a third of patients may have corneal involvement, which if not treated promptly can lead to sight-threatening complications [128, 131, 137]. Corneal involvement may begin with superficial punctate keratitis, more commonly in the inferior aspect of the cornea. Peripheral neovascularization and pannus formation may then ensue with associated subepithelial marginal triangular, "spade-shaped" infiltrates along the advancing vascular border of the vessels [128, 132]. These changes may lead to peripheral thinning and asymmetric astigmatism. Infiltrates may progress circumferentially or centrally and lead to stromal ulcerations and even perforation [132, 137]. Less commonly, patients may have recurrent corneal epithelial erosions, secondary infectious keratitis, and pseudodendritic ulcers [128]. Other ocular manifestations such as episcleritis, scleritis and phlyctenules have also been reported [132].

Although rosacea predominantly affects adults, ocular rosacea can occur in the pediatric population and is called pediatric ocular acne rosacea [132, 134]. It is thought that pediatric ocular acne rosacea is frequently under-diagnosed or misdiagnosed, leading to ocular complications. Clinical manifestations in the pediatric population resembles adult disease, with the exception of chronic changes, such as rhynophyma, that occur later in the disease process [132, 134].

Management

A collaborative approach involving the ophthalmologist and dermatologist is necessary for effective management of ocular rosacea. Trigger factors for ocular rosacea must be identified and avoided to reduce symptomatic episodes. Regular use of broad-spectrum sunscreen is recommended for rosacea patients.

A step wise regimen can be effective in the treatment of rosacea, using more conservative approach with lid hygiene, warm compresses and artificial tears first, followed by antibiotic and anti-inflammatory medications and late surgical intervention, if necessary [132]. Lid hygiene is imperative for prevention of ocular surface inflammation. Warm compresses can liquefy thick meibomian gland secretions and help remove clogged debris. Topical cyclosporine 0.05 % (Restasis, Allergan Inc, Irvine, CA) used twice daily have been shown to be more effective than artificial tears for the treatment of rosacea-associated ocular disease [138]. Topical metronidazole gel may also be effective in treating moderate rosacea blepharitis [139]. Topical Azithromycin eye drops, Azasite (azithromycin 1 %, Inspire Pharmaceuticals) is FDA approved to treat bacterial conjunctivitis but is commonly used off label in the treatment of meibomian gland dysfunction, which is a common finding in ocular rosacea [132]. Persistent ocular inflammation may require the use of topical corticosteroids. It is important to use it judiciously due to the risks of secondary bacterial infections and long-term side effects, including glaucoma and cataracts [128]. Long-term oral supplementation of omega-3 fatty acids may improve the quality of meibomain gland secretion [128].

The only oral agent for rosacea approved by the US Food and Drug Administration (FDA) is a modified-release doxycycline 40-mg capsule, which is a combincation of 30 mg of immediate-release and 10 mg of delayed-release doxycycline [140]. It works by decreasing lid bacterial flora, decreasing production of lipases by *Staphyloccoci*, altering meibomian secretion, and inhibiting several matrix metalloproteinases and protease expression and activity [132]. Due to the relapsing nature of rosacea, doxycycline should be used chronically at a low, suppressive dose or discontinued and restarted with episodic flare-ups. Tetracyclines should not be used in pregnancy, during lactation, or in children younger than 7 years of age due to bone growth retardation and permanent discoloration of teeth [132]. Instead, Erythromycin and Azithromycin may be used.

Surgical treatment may be necessary for severe case of ocular rosacea. Punctal occlusion may be helpful in management of dry eye disease. Persistent chalazia may require incision and drainage. For recurrent chalazia, specimens should be sent to pathology to rule out sebaceous gland carcinoma. Corneal perforation can be managed with adhesives, conjunctival flaps, corneal sutures, amniotic membrane grafts, lamellar or full-thickness patch grafts, or corneal transplantations [128, 137].

Trichotillomania (Trichitillosis)

Trichotillomania, also known as trichotillosis, is self-induced compulsive pulling, twisting and breaking of hair. Trichotillomania, skin picking, and other body-focused repetitive behaviors have a combined prevalence of approximately 5 % of the general population [141]. They are largely considered to be among the most difficult behavioral symptoms to treat. Trichotillomania often presents with irregular

Fig. 8.9 Trichillomania, missing eyelashes<<permission requested from McGraw Hill>>

patches of hair loss with areas of broken hairs of different lengths. It can lead to scarring alopecia. These patches frequently appear on the contralateral side of their dominant hand. This may also be present in the eyelashes and eyebrows (Fig. 8.9). Results of various cross-sectional studies have reported the increased risk of depression and anxiety with age in pediatric trichotillomania. Poorer long-term prognosis has been associated with increased focused pulling and older age among children with trichotillomania [142, 143].

Salmon Patch (Nevus Simplex)

Nevus simplex is the most common vascular lesion of infancy and presents as a flat salmon to pinkish faint colored patch that occurs frequently on the posterior neck, around the face and eyelids and glabellar region. They can be present in up to 40 % of newborn infants. These "stork bite" lesions usually fade on the face, but can persists around the orbit or back of the neck. They consist of localized vascular ectasia, which can get more pronounced with valsalva, change in temperature or crying. No treatment is indicated, as it is a benign condition, but one must be sure to differentiate the lesions from Sturge–Weber syndrome or flat appearing hemangioma.

Infectious Conditions

Demodex

Demodex mites are parasites that are considered to play a role in the pathogenesis of chronic ocular surface inflammation [144–146]. They were first identified by Jacob Henle in 1841, and 1 year later by Simon who isolated *Demodex* in hair follicles. Subsequently, Demodex has been found in eyelid margins, eyelash follicles, and tarsal cyst material. The term demodecosis was first used by Ayres in 1961, when it was linked to one of the pathogenesis of acne rosacea. The prevalence of *Demodex* infestation increases with age, being present in 84 % of population at age 60 and close to 100 % for those older than 70 years [146]. The life cycle of *Demodex* mite is approximately 14–18 days from egg to larva to adult stage [144].

Two species of *Demodex*, *Demodex follicularum* and *Demodex brevis*, have been identified in humans and can commonly appear in seborrheic areas of the facial skin (forehead, chin, around eyes and mouth) [144–146]. It has recently been thought to be a contributor to chronic diseases such as rosacea, and marginal blephritis of the lashes, while it may be asymptomatic and still recovered in skin specimens. *D. folliculorum* is implicated in causing anterior blepharitis whereas *D. brevis* has been associated with posterior blepharitis, meibomian gland dysfunction, recurrent chalazia, and refractory keratoconjunctivitis. Pathogenesis is multifold. Mites consume the lining of the hair follicles and lay eggs within the follicles, leading to follicular distention and misdirection of lashes [144]. Debris and waste generated by mites can accumulate forming cylindrical dandruff, which is pathognomonic for *Demodex* infestation [144–146]. They can also block the sebaceous ducts and induce epithelial hyperplasia and hyperkeratinization. The cytoskeleton of the mites may also incite granulomatous reaction resulting in chalazia. In addition, *Demodex* mites may act as a vector carrying bacteria such as *staphylococci* and *streptococci*, which are common causes of blepharitis [144]. They can also carry symbiotic bacteria, such as *Bacillus oleronius*, in their intestines. *B. oleronius* has been associated with triggering host immune reaction in patients with rosacea [144].

It is important to suspect *Demodex* infestation in patients with chronic blepharitis, especially when refractory to conventional treatment. Slit-lamp examination can reveal cylindrical dandruff at the root of the eyelashes. Lash sampling and microscopic examination can provide definitive diagnosis by identifying the mite species as well as the life stage. Recently, in-vivo confocal microscopy has been used as a non-invasive method to evaluate the follicle and also identify *D. brevis*, which burrows deep into sebaceous glands and can be otherwise missed [144–146].

Daily lid scrubs with tea tree oil have been shown to be effective in eradicating ocular *Demodex* infestation [144–146]. Fifty percent tea tree oil can be prepared by mixing 100 % tea tree oil with mineral oil. Terpinen-4-ol (T4O) is the active ingredient in tea tree oil and has been shown possess anti-inflammatory, antimicrobial, and antifungal properties. Cliradex (Bio-Tissue, Inc., Minami, FL, USA) is a lid hygiene wipe that contains (T4) and can be used for treatment of demodicosis by applying twice a day for 6 weeks to cover two *Demodex* life cycles [144].

Molluscum

Molluscum contagiosum (MC) is a common, self-limiting cutaneous infection with a prevalence of 5.1 % to 11.5 % in children aged 0 to 16 [147]. It is caused by a large double stranded DNA poxvirus with four genetically distinct but clinically indistinguishable types [148]. Type 1 is most prevalent and the most common cause of MC in children. Type 2 occurs in the anogenital area of sexually active individuals. Transmission can be from direct contact including contact sports, swimming pools, day care, sexual activity, and shared baths and equipments [148]. It usually presents as asymptomatic lesions in the trunk, face, and limbs. Lesions are discrete pearly, skin-colored dome shaped lesions with central white cores, which may have a central umbilication. They can be single or grouped and usually range in size from 1 to 5 mm. MC can be associated with chronic follicular conjunc-

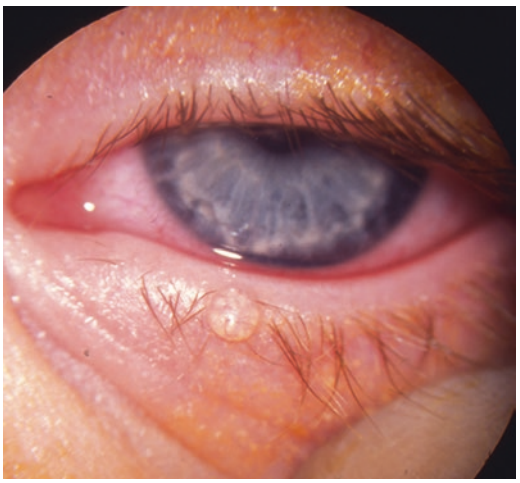

Fig. 8.10 Molluscum contagiosum, lesion lid margin

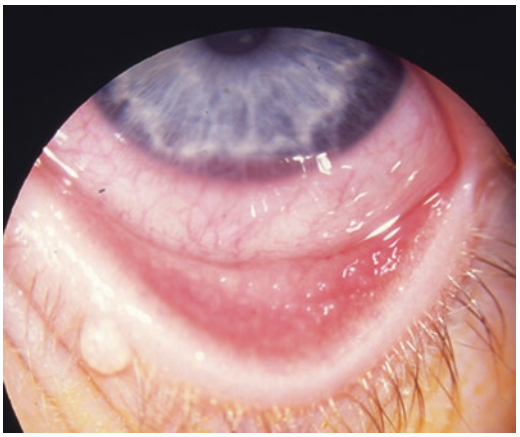

Fig. 8.11 Molluscum contagiosum, follicular conjunctivitis

tivitis so a thorough examination of the eyelids is crucial (Figs. 8.10 and 8.11). Ocular molluscum contagiosum has an increased incidence in patients with HIV (5–10%) and in children with atopic dermatitis (18%) and can present with conjunctival nodules [149].

Occasionally, MC can be symptomatic in children with eczema and manifest as hypersensitivity reaction known as molluscum dermatitis [148]. Patients with eczema may also have more MC lesions compared to those without eczema, but the time to resolution was similar to children without eczema. Severe cases and diffuse spread can be present in immunocompromised individuals. However, much of the time, MC is considered to be a benign and self-limited disease although treatment can be pursued for cosmetic purposes and to prevent the spread of the virus. In large reviews, most MC lesions resolve within 12–18 months regardless of whether lesions were treated [147, 148].

There are many approaches to treatment of cutaneous lesions, including pharmacologic and nonpharmacologic treatments. Cantharidin is an extract from blister beetles and acts as a protein phosphatase inhibitor. It is directly applied to the lesions, covered for 2 to 6 h, then washed off with soap and water [150]. It can be repeated every 2–4 weeks. Potassium hydroxide 10% is another form of destructive therapy for MC. Imiquimod has been a longstanding, common treatment for MC, but it has recently been shown to be neither efficacious or safe [150]. Other modes include cryotherapy and curettage. Care should be taken if the lesion is to be treated around the eye. Lesions that rupture into the eye can induce a pruritic conjunctivitis, which responds to topical steroids.

Verruca

Verruca, also known as (cutaneous) warts, develop in 5–10% of all children [151]. The human papilloma virus (HPV) is a highly contagious cause of verruca and is transmitted by direct contact. To date, there are more than 100 types identified in the human population [151]. Cutaneous warts are usually caused by HPV strains with low malignant potential and included 1, 2, 3, 4, 27, and 57 [150]. Some studies have found that high risk strain, HPV 16, has been detected in cutaneous warts too. Incubation period varies from 3 weeks to 8 months. More than 50% will spontaneously resolve within 2 years. A very small subset will predispose the infected site to cellular atypia and cancer.

Verruca vulgaris, also known as common warts, can appear anywhere in the body. They typically present as flesh-colored, painless, raised, rough and dome-shaped papules or plaques. Filiform warts appear mainly near eyelids and lips as narrow, long, finger-like projections of skin-colored lesions that may be single or be in clusters [150]. Verruca plana, or flat warts, appear as smooth, pink or flesh-colored flat topped papules or plaques, located mainly on the face. Verruca plantaris, or plantar warts, are lesions that present on the feet and may frequently be confused with callouses. They often have black punctate spots due to clotted blood vessels. Plantar warts are typically symptomatic because of the pressure from walking. Genital warts, also known as condyloma acuminatum, are the only type considered a sexually transmittable disease. They appear as raised lesions resembling a cauliflower [150, 151].

Presently, there is no cure for HPV. Even though most warts will resolve with time, various treatment options are available. Three major treatment options are chemical, physical obliteration, immunotherapy, and surgical excision. If there is no response to the initial treatment after 3 weeks or if complete resolution has not occurred in 12 weeks, a different method of treatment is recommend. Pharmacologic treatment includes salicylic acid, 5-fluorouracil or imiquimod.

Ablative therapy consists of cryotherapy and laser. For recurrence, excision or fulguration is recommended to obtain specimen for analysis and imiquimod cream can be used as adjuvant therapy for 12 weeks [150, 151].

There is emerging research in the utility of HPV vaccine in the treatment of cutaneous warts. Although the current HPV vaccine targets against high-risk HPV strains, including HPV-6, 11, 16, and 18, reports have proposed that vaccine induces cross-protective effect against various HPV strains that enables children to clear their warts [150]. More studies are needed to further evaluate its efficacy and utility.

Other Dermatologic Disorders

Juvenile Xanthogranuloma

Histiocytic disorders are broadly divided into categories of Langerhans' cell histiocytoses (LCH) and non-Langerhans' cell histiocytoses. Juvenile xanthogranuloma (JXG) is the most common form of non-LCH. It is a benign cutaneous disorder characterized by lesions that are firm dome-shaped pink, yellow or orange papule or nodule, ranging between 4 and 30 mm in size, with a predilection for the face and upper trunk. They appear during the first years of life and spontaneously resolve with time. They may appear singular or in groups. Ulceration or crusting may occur as well. Similar lesions presenting at an age younger than 2 years of age or multiple lesions may be associated with neurofibromatosis and childhood leukemia, especially chronic myelogenous leukemia. JXG lesions can involve the eye, brain, lungs, liver, spleen, and other organs.

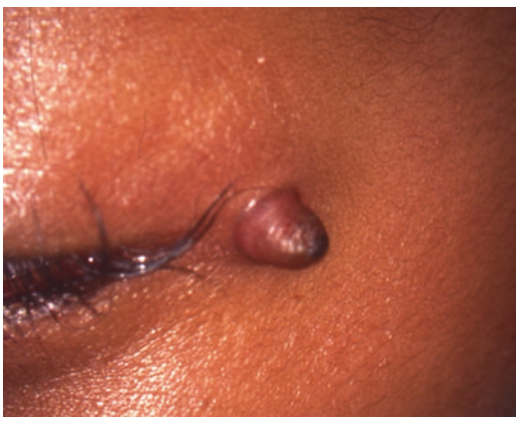

Fig. 8.12 JXG, eyelid lesion

Ocular Manifestations

The most common extracutaneous involvement of JXG is in the eye. The literature incidence of eye involvement in cutaneous JXG is 0.3 to 10 % [152, 153]. The age of onset of eye disease is usually during the first 2 years of life [152, 153]. In up to 45 % of patients, ocular involvement precedes cutaneous manifestation [153]. The most common ocular presentation is spontaneous hyphema as iris is the most frequently involved ocular tissue. Other presentations include asymptomatic iris lesions, unilateral glaucoma, signs of uveitis or heterochromoia iridis [152]. Sight-threatening eyelid lesions, and epibulbar lesions have been reported. Orbital involvement is unusual but can occur usually during the perinatal period and must be considered in the differential for unilateral exophthalmos in an infant [152]. Posterior involvement is rare. Glaucoma can be a problematic complication in ocular JXG. Trabecular meshwork can be compromised due the histiocytes from the lesion and red blood cells from the recurrent hyphema [154]. In JXG patients with both skin and eye findings, all of them had multiple skin lesions [152, 153] (Fig. 8.12). The need for routine ocular screening is controversial due to the low incidence of eye disease. Chang and colleagues concluded that routine screening for possible ocular JXG in asymptomatic children with skin disease does not lead to early diagnosis, treatment or decreased morbidity [153]. Hernandez-Martin suggested that it may be reasonable to screen those with multiple skin lesions every 6 months up to the second year of life [152].

Management

Treatment depends on the ocular manifestation. The first line treatment for inflammation associated with ocular JXG is topical, local or systemic corticosteroids. Localized radiotherapy has been reported but is associated with a risk of cataract formation. More recently, cases of off-label intraocular anti-VEGF have been reported to be successful with potentially fewer side effects than radiation and steroid treatment [155].

Infantile Hemangiomas/PHACES

Infantile hemangiomas (IH) are benign tumors of the vascular endothelium that arise after birth during infancy [156]. IH are the most common tumors of the head and neck [156]. Historically, the incidence of IH has been reported to range.

IH are recognized by characteristic clinical course divided into six proposed phases: nascent, early proliferative, later proliferative, plateau, involution, and abortive [156]. Nascent stage typically lasts 0–3 months, followed by proliferative stages in the next 6–10 months [156]. About 80 % of IH reach

Table 8.8 Major and minor criteria for ocular findings for diagnosis of PHACES syndrome

Major criteria	Minor criteria
Posterior segment abnormality	Anterior segment abnormalities
Persistent fetal vasculature (persistent hyperplastic, primary vitreous)	Sclerocornea
Retinal vascular anomalies	Cataract
Morning Glory disc anomaly	Coloboma
Optic nerve hypoplasia	Microphthalmia
Peripapillary staphyloma	

their maximum size by 5 months, although deeper lesions may continue to grow beyond 6 months [157, 158]. Hemangiomas with deep component tend to have a later onset and prolonged proliferative phase compared to superficial hemangiomas [159]. Although most IH are benign, IH can cause serious problems depending on the size and location. Eyelid IH can lead to amblyopia, subglottic IH can compromise airway, and very large IH can even result in high-output congestive heart failure [158]. Even after involution, 40% to 80% of IH leave permanent residual skin findings [158].

PHACES is the condition associated with hemangiomas. The condition is much more common in females, and is associated with hemangiomas on the face and neck that are 5 cm or greater in size. PHACES is a mnemonic for posterior fossa defects (including cerebellar hypoplasia and Dandy walker), hemangioma of the face, Arterial abnormalities, coarctation of the aorta or heart abnormalities, **e**ye abnormalities, and sternal raphe defects such as pits or scars. Large face or scalp hemangiomas warrant evaluation of related organ systems including the eye, cardiac system including great vessels, and brain for structural and cerebrovascular anomalies. The Consensus Statement on Diagnostic Criteria for PHACE Syndrome (the Statement) was published in 2009 and is beyond the scope of this text [160]. The major and minor criteria for ophthalmologic findings are presented in Table 8.8 [160]. MRI and MRA brain imaging, cardiovascular imaging, and an ophthalmologic examination must be completed in any patient suspected to have PHACES syndrome. The incidence of periocular hemangiomas and ocular abnormalities in patients with PHACES syndrome range from 33 to 75% [161]. These underlying conditions often require treatment. PHACES hemangiomas appear to be responsive to the propranolol, but cardiac effects and systemic conditions must be monitored very closely.

Ocular Manifestations

The most common ophthalmic complication is amblyopia, which can be deprivational, refractive (inducing astigmatism), anisometropic or be a combination of all three. The rate of amblyopia range from 19 to 76% in the literature [162]. Periocular hemangiomas have a predilection for the superior lid and orbit. Lesions that are greater than 1 cm in greatest dimension is an important predictor for developing amblyopia [163]. Diffuse hemangiomas and patients with PHACES syndrome are at a higher risk as majority of cases are associated with amblyopia. In addition, hemangiomas associated with PHACES syndrome are more prone to ulceration and are typically larger in size, necessitating prompt treatment [164]. Increased rate of strabismus and other ocular abnormalities is seen in patients with PHACES syndrome [161]. Although less common, orbital hemangiomas can lead to complications associated with their mass effect, such as proptosis, exposure keratopathy, strabismus, or compressive optic neuropathy [156].

Management

Traditional treatments for hemangiomas include observation, systemic and intralesional corticosteroids, interferon alfa-2a, vascular lasers, sclerotherapy, embolization, immunomodulators and surgery. In 2008, Léauté-Labrèze reported a serendipitous case of a 9 week old who developed steroid-induced cardiac myopathy after receiving systemic corticosteroids for a large, complicated hemangioma [165]. Treatment with propranolol for the cardiac myopathy led to regression of the hemangioma within 24 h, and since then, beta-blockers have become the standard of care for hemangiomas [165, 166]. Systemic propranolol can cause serious adverse effects including bradycardia, arrhythmia, bronchospasm, and hypotension ?hypoglycemia. Patients with PHACES syndrome may have cerebrovascular anomalies that put them at risk of cerebral ischemia with systemic propranolol use, especially those with moyamoya-like collaterals. Another viable option is topical timolol drops or gel for treatment for superficial and mixed lesions. Both 0.25% and 0.5% strengths with either twice or three times a day dosing have been shown to be effective in multiple studies [167–169]. Oral therapy may have a more rapid effect then topical (weeks vs. months).

Hypomelanosis of Ito

Hypomelanosis of Ito (HI), previously called incontinentia pigmenti achromians, is a sporadic neurocutaneous syndrome presenting in the first year of life [57, 170]. The use of the terminology is inconsistent at present, as it is not a specific syndrome but rather a descriptive term for mosaic or nevoid hypopigmentation with or without systemic abnormalities. HI has skin lesions that usually presents at birth but may be acquired in the first few years of life. Cutaneous findings include unilateral or bilateral hypopigmented streaks and whorls distributed along the lines of Blaschko.

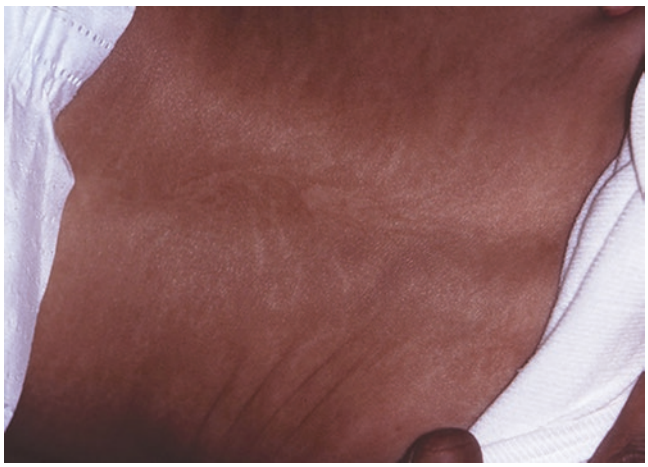

Fig. 8.13 Hypomelanosis of Ito, Skin Whorls

Palms, soles, and mucous membrane are spared [57] (Fig. 8.13). They do not change during childhood but may fade in adulthood. Skin histopathology shows decreased melanin content of the epidermis. Hypertrichosis and diffuse alopecia may be present. Scoliosis and limb deformities including hemihypertrophy are reported. Central nervous system involvement is common in reports of HI, along with mental retardation and seizures. Mircocephaly and muscular hypotonia are less common.

Ocular Manifestations

Ocular abnormalities have been reported in 20–25 % of patients and may involve both anterior and posterior segments [171]. Anterior segment abnormalities include heterochromic irides, iris coloboma, corneal pannus, cataracts, and Axenfeld-type anomalies [171–173]. Abnormal retinal and chorodial hypopigmentation and pigmentary pattern, optic nerve hypoplasia and atrophy have been described [173]. Strabismus, nystagmus, and significant refractive error may be present as well.

Nevus of Ota/Oculodermal Melanocytosis

Nevus of Ota is a typically unilateral pigmented lesion seen as permanently blue, brown and black macules on the face [125]. Ota first described ocular or oculodermal melanocytosis in 1939. It has also been referred to as nevus *fuscocaeruleus ophthalmomaxillaris*, melanosis oculi, congenital melanosis bulbi, and nevus of Ota. It is a developmental disorder of the embryonic neural crest. This congenital hyperpigmentation can involve the periocular skin, uvea, sclera, meninges, palate, and tympanic membrane . It is usually unilateral (90 %) and is due to excess melanocytes in those regions. The pigmentary abnormality can involve the skin or eye alone, but when seen in combination, it is referred to as oculodermal melanocytosis (ODM) [174]. In the study by Teekhasaenee of 194 patients, they reported skin involvement alone in 34.5 %, ocular involvement alone in 6.2 %, and 59.3 % with both skin and ocular involvement [175]. ODM is a rare condition. In 1982, Gonder found melanocytosis in 1 of 6915 African-American patients (0.014 %) and in 2 of 5251 white patients (0.038 %) [176].

Clinically, patients have a bluish-gray pigmentation involving the skin innervated by the first and the second divisions of the trigeminal nerve [177]. With ocular involvement, episclera is almost always involved and appear as discrete bluish to confluent dark patches that spares the limbus. Melanocytosis can affect the sclera or uvea diffusely or be present as sector pigmentation. Episcleral vessels that cross the pigmented areas are separated by a thin, nonpigmented band [177]. Choroid may appear dark compared to the fellow eye in about 80 % of cases [175]. Iris involvement can be diffuse or sectoral and is present in approximately 90 % [175]. It can vary in presentation from fine granular appearance on normal iris to dense pigmentation that obscures the underlying iris architecture [177]. Dense hyperpigmentation may be seen in the angle. There is no consistent correlation between the density of hyperpigmentation and elevated intraocular pressure (IOP) in ODM patients [178]. However, since glaucoma can be seen in 10 % of patients with ODM, close monitoring of IOP is recommended [178].

Patients with oculodermal melanocytosis have a higher risk for developing melanoma, especially in the uvea. For white patients with ODM, one of about 400 patients is estimated to develop uveal melanoma in their lifetime, compared with 1 in 13,000 for the general population [179]. Most developed melanoma at the age of 31 to 80 years [179]. In a series of 7872 patients with uveal melanoma, 230 patients (3 %) had evidence of melanocytosis [174]. They also found that patients with uveal melanoma and melanocytosis had 1.6 times higher relative risk for metastatsis compared to those without melanocytosis [174]. Because of these reasons, some experts recommend that patients with ODM undergo ophthalmic examination and imaging on a twice a year basis [174].

Appendix 1. Eye and Skin Findings in Phakomatosis

Phakomatosis	Skin lesion	Eye finding	Notes
Neurofibromatosis type 1 (Von Recklinghousen disease)	Café au lait spots, axillary freckling, neurofibromas	Lisch nodules, optic nerve gliomas	Associated with absence of greater wing of sphenoid, and neurofibromas of the lids
Sturge-Weber	Port wine stain, usually following a V1-V2 trigeminal nerve distribution or involving the forehead	Chorodial hemangioma, glaucoma	V1 assoc with seizures, V2 associated with eye findings
Tuberous Sclerosis (Bourneville disease)	Ash leaf spots, angiofibromas, shagreen patches, periungual fibromas	Hamartomas of the retina	Hamartomas in heart, brain lesions/seizure disorder
Ataxia Telangiectasia (Louis-Bar Syndrome)	Telangectasia face and then elsewhere. May have altered skin or hair pigmentation, including café au lait spots	Telangiectasia of bulbar conjunctiva	Ataxia and degeneration of CNS, deficiency in cellular immunity
Incontinentia pigmenti	Vesicles at birth becoming hyper keratotic on limbs and scalp, blisters become hyperpigmented linear lines, streaks and whorls on trunk. Many have minor hair abnormalities	Peripheral retinal ischemia and tractional detachment. Uveitis, keratitis and cataracts can occur	X-linked, dominant; usually lethal in males. Monthly retinal exams needed in first months of life

Appendix 2. Genetic Disorders Skin/Hair and Eye Findings

Disorder	Skin/hair findings	Eye findings (more prominent)	Other associated eye findings
Down Syndrome (trisomy 21)	Cutis marmorata, transient neonatal leukemoid reaction, elastosis performans serpiginosa, syringomas, milia-like calcinosis, alopecia areata, folliculitis, psoriasis	Brushfield spots, strabismus, blocked tear duct, cataracts/lens opacities, refractive errors	
Trisomy 13	Capillary hemangioma, especially forehead, loose skin posterior neck, transverse palmar creases, hyperconvex narrow fingernails, scalp defects	Microphthalmia, coloboma, retinal dysplasia	
Turner (45X0)	Excessive pigmented nevi, loose skin, congenital lymphedema, low posterior hair line, cutis vertices gyrate, hypoplastic concave nails	Ptosis, strabismus, blue sclera, cataracts	
Rubenstein-Taybi Syndrome	Hisuitism, capillary hemangioma, keloid	Heavy/arched eyebrows, long lashes, lacrimal duct obstruction, ptosis, strabismus, enophthalmus	Occasional cataracts and glaucoma
Dubowitz syndrome,	Eczema like skin disorder, sacral dimple	Telecanthus, ptosis blephrophimosis	Strabismus, microphthalmia, megalocornea, iris hypoplasia, coloboma
Johanson-Blizzard Syndrome	Sparse hair	Lacrimal fistula (hypoplastic sides of nose)	
Hallerman-Streiff Syndrome	Thin light hair with hypotrichosis	Microphthalmia, cataracts (which may reabsorb)	
Kabuki Syndrome	Vitiligo, low posterior hairline	Euryblepharon, blue sclera	
Williams Syndrome	Premature gray hair, soft lax skin	Stellate iris, blue iris	
Cardio-Facio-Cutaneous syndrome	Sparse, curly or slow growing hair, 100 %. Lack of eyebrows or lashes, sever atopic dermatitis, hyper keratosis	Ptosis, exophthalmos, hypertelorism	
Progeria	Alopecia, thin skin, scleroderma like appearance, perioral and nasolabial cyanosis, Dyspigmentation, early skin wrinkling	Microphthalmia	
Werner syndrome	Patches of stiffened skin, loss of subcutaneous fat, gray sparse hair at the temples, alopecia, telangiectasias, mottled and diffuse pigmentation, pressure ulcers	Cataract, retinal degeration	

(continued)

Disorder	Skin/hair findings	Eye findings (more prominent)	Other associated eye findings
Cockayne Syndrome	Photosensitive dermatitis, dry and sometimes scaly skin	Pigmentary retinopathy, optic atrophy, corneal opacity, cataract, strabismus, decreased lacrimation	
Rothmund-Thomson Syndrome	Irregular erythema progressing to telangiectasias and poikiloderma, hyperkeratotic lesions, sparse gray hair/alopecia, small nails	Juvenile cataracts, corneal dystrophy	
Marshall-Smith Syndrome	Hypertrichosis	Shallow orbits, blue sclera	
Cerebro-Oculo-Facio-Skelatal syndrome (COFS)	Hiruitism, arthogryposis	Microphthalmia and/or cataract	
Neu-Laxova Syndrome	Yellow edematous subcutaneous tissue, covered by thin transparent scaling skin (ichthyosis)	Cataracts, microphthalmia, protruding eyes, with no eyelids	
Restrictive Dermatopathy	Tightly adherent constrictive skin, prominent vessels	Sparse to no eyelashes	
Ataxia-Telangiectasia Syndorme	Telangiectasia	Telangiectasia of bulbar conjuntial	
Menkes (kinky hair) Syndrome	Sparse, stubby lightly pigmented hair, thick and relatively dry unequal skin pigmentation	Myopia, strabismus	
Angelman Syndrome (Happy Puppet)	Blond hair, oculocutaneous albinism type 2	Decreased eye pigmentation of iris and choroid	
		Oculocutaneous albinism type 2	
Prader-Willi Syndrome	Fair sun-sensitive skin, blond to light brown hair, Oculocutaneous albinism type 2	Blue irisis	
Cohen Syndrome	Thick hair	Retinochoroidal dystrophy, with bull's eye macula, high myopia	
Brachio-Oculo-Facial Syndrome	Premature graying of hair	Lacrimal duct obstruction, coloboma, microphthalmia / anophthalmia, myopia	White forelock, ptosis, orbital cyst, cataracts
Waardenburg syndrome (types I and II)	White eyelashes, bushy eyebrows, white forelock, premature graying, depigmented skin lesions	Hypochromic iris, hypopigmented ocular fundus (may be unilateral)	
Treacher Collins Syndrome	Hair extension down to cheek, partial to total absence of lower lashers	Lower lid coloboma	Dacryostenois, microphthalmia
Marshall Syndrome	Sparse scalp hair, eyelashes and eye brows	Myopia, cataracts, esotropia	
Oculodentodigital Syndrome	Fine, sparse, dry slow growing hair	Micriphthalmos, microcornea, fine porous iris	
Ectrodactyly-Ectodermal dysplasia-Clefting Syndrome	Light colored, thin, wiry sparse hair, nail dysplasia	Blue irides, photophobia, defects of lacrimal duct, blephrophimosis	
Hay-Wells Syndrome of Ectodermal dysplasia	Palmar/plantar keratoderma, hyperkeratosis, absent or dystrophic nails, wiry sparse hair, alopecia	Lacirmal duct atresia	
Robert's Syndrome (Pseuodthalidomide syndrome, hypomelia-hypotrichosis, hemangioma)	Sparse silvery blond hair, mid facial capillary hemangioma	Prominent eyes, bluish sclera, cornea clouding	
Fanconi Pancytopenia Syndrome	Purpura	Ptosis, strabismus, nystagmus, microphthalmia	
Chondrodysplasia Punctata, X-Linked Dominant type	Patterned erythroderma overlying psoriasiform scale. Severe cases demonstrate generalized ichtyosiform erythroderma with thick scale	Cataracts, hazy cornea, optic nerve and retinal atrophy	
Autosomal Recessive Chondrocysplasia Punctata (Rhizomelic Type)	Ichthyosiform skin dysplasia, lipomas	Cataracts	
Yunis-Varon Syndrome	Sparse scalp hair, eyebrows and lashes		Cataracts, sclerocornea
Crouzon Syndrome	Acanthosis nigricans of eyelids, perioral, perialar and neck skin	Optic atrophy, exposure keratitis, nystagmus	Keratoconus, Iris coloboma
Nail-Patella Syndrome (Hereditary Osteo-Onychodysplasia)	Nail hypoplasia, splitting, thin, with koilonychia	Irides with dark pigmentation centrally in clover leaf/flower pattern	

(continued)

Disorder	Skin/hair findings	Eye findings (more prominent)	Other associated eye findings
Generalized Gangliosidosis Syndrome, Type I, (Caffey Pseudo-Hurler Syndrome, Familial Neurovisceral lipidosis)	Angiokeratoma corpis diffusum, (telangiectasis or warty growths in groups, with thickening of epidermis) dermal melanocytosis	Cherry red spot in macula (50%)	
Hurler Syndrome (Mucopolysaccharidosis 1 H)	Coarse, thickened skin, Hirsutism	Hazy corneas, retinal pigmentation	Open angle glaucoma
Scheie Syndrome (Mucopolysaccharidosis I S, MPS I S)	Coarse, thickened skin, Body hirsuitism	Cloudy cornea	Edema like swelling of disc and macula
Marfan Syndrome	Striae no associated with weight gain/loss, skin laxity	Lens subluxation with phaco/iridodenesis, flat cornea, axial myopia, hypoplastic iris dilator	Coloboma
Ehlers-Danlos Syndrome	Widened atrophic scars, smooth velvety skin, molluscous pseudotumors	Scleral fragility, that can lead to rupture of globe	
Kyphoscoliosis type			
Osteogensis Imperfecta	Thin translucent skin	Blue sclera	
Sturge-Weber sequence	Port-wine capillary hemangioma of the face	Ketchup fundus, glaucoma	Coloboma
Linear Sebaceous Nevus Sequence (Nevus Sebaceous of Jadassohn, epidermal Nevus Syndrome)	Nevus sebaceous with hyperpigmentation and hyperkeratosis, most common mid facial	Lipodermoid of conjunctiva, coloboma of eyelid	Coloboma of the eye, optic nerve atrophy, microphthalmia, cloudy cornea, retinal neovascularization
Incognentia Pigmenti Syndrome (Bloch-Sulzberger Syndrome)	Blisters preceded by erythema, develop in linear distribution around limbs and trunk early in life, hyperkertotic lesions develop on limbs, trunk develops hyperpigmented whorls, Patchy sparse hair, alopecia, hyper to hypopigmented lesions with atrophy	Strabismus, retinal vessel abnormalities with ischemia and traction/detachmentuveitis, keratitis, cataract	
Hypomelanosis of Ito (Incontinentia Pigmentosa Achromians)	Hypopigmented streaks and whorls that follow the lines of Blashko, Hypertrichosis, diffuse alopecia	Iris heterochromia, abnormal retinal pigmentation, strabismus	
Tuberous Sclerosis Syndrome	Fibrous Angiomas, ash leaf lesions, café au lait spots, shagreen patches	Hamartomas of retina or optic nerve	
Neurofibromatosis Syndrome	6 or more café au lait spots, neurofibromas, axillary and inguinal freckling	Lisch nodules of iris	Sphenoid wing dysplasia, optic nerve gliomas
McCune-Albright Syndrome	Irregular brown skin pigmentation	Fibrous dysplasia facial bones	
Klippel-Trenaunay Syndrome	Vascular malformations of the capillary, venous and lymphatic in skin, hyperpigmented nevi and streaks, hemihypertrophy	Glaucoma, cataracts, Marcus-Gunn pupil, heterochromia	
Proteus Syndrome	Generalized thickening, epidermal nevi, vascular malformations, soft subcutaneous masses		Myopia, cataracts, microphthalmia, ptosis,epibulbar dermoid
Encephalocraniocutaneous Lipopatosis	Unilateral hairless fatty tissue nevus of the scalp with alopecia, café au lait spots	Hard pedunculated outgrowths attached to margin of upper lid	Microphthalmis, iris dysplasian, coloboma, cloudy cornea
Bannayan-Riley-Buvalcaba Syndrome	Lentigines on glans penis, Verruca vulgaris of face, angiokeratomas, café au lait spots, subcutaneous lipomas, oral and perianal papillomas, acrochordons, acanthosis nigricans	Strabismus, prominent Schwalbe lines and prominent corneal nerves	
Multiple Endocrine Neoplasia, Type 2B	Ganglioneuromatosis of mucosal surfaces	Medullated nerve fibers in cornea, subconjunctival neuromas, deficient lacrimation	
Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome)	Nevoid basal cell carcinomas, milia, dyskeratotic pitting on palms and soles		Cataract, coloboma of iris, prominent medullated retinal nerve fibers, retinal atrophy, glaucoma, strabismus
Goltz Syndrome	Linear areas of hypoplasia of the skin, telangiectasias, yellow to red or brown nodular outpouchings (herniation of subcutaneous fat), thin nails, sparse hair	Stabismus, coloboma of iris and aniridia, microphthalmia, anophthalmos, corioretinal coloboma	Bulbar angiofibroma of eye, optic atrophy

(continued)

Disorder	Skin/hair findings	Eye findings (more prominent)	Other associated eye findings
Microphthalmia-Linear skin defects syndrome	Dermal aplasia, that heals leaving hyperpigmented areas	Microphthalmia, sclerocornea	Anterior chamber abnormalities, pigmentary retinopathy
Hypohidrotic Ectodermal Dysplasia	Collodian membrane, Thin hypoplastic skin with decreased pigmentation, fine periorbital wrinkling, Sparse fine, dry and hypochromic hair	Hyperpigmentation around eyes and periorbital wrinkling.	
Clouston Syndrome	Palmoplantar keratoderma, hyperpigmentation over knuckles, elbows, axilla, groin. total alopecia, nail dystrophy	Strabismus, deficiency of eyebrows	
GAPO Syndrome (Growth deficiency, Alopecia, Pseudoanodontia, Optic atrophy)	Skin laxity, diminished scalp hair, with alopecia by age 2–3, sparse eye brows and lashes	Optic atrophy (progressive), cataracts, exophthalmos, keratoconus, glaucoma.	
Xeroderma Pigmentosa	Sunlight sensitivity, freckling, progressive skin atrophy, telangiectasia, angiomata, keatoses. Melanotic and non-melanotic skin cancers	Photophobia, conjunctival injection, exposure keratitis and scarring. neoplasms	
Senter-Kid Syndrome	Dry, red rough, erythematous, scaly skin. Erythrokeratoderma, non scaling plaques, follicular keratosis, especially on extensor surfaces, nail dystrophy	Corneal dystrophy, with progressive corneal neovascularizaion	
Environmental			
Fetal Varicella Syndrome	Cutaneous scars	Chorioretinitis, Horner syndrome, cataracts, microphthalia, optic nerve atrophy and hypoplasia	

Appendix 3. Rheumatology, Hematology and Oncology Conditions with Eye and Skin Findings

Condition	Cause	Skin lesion	Eye findings	Systemic findings
Lupus (SLE)	Rheumatic disease of unkown orgin	Malar rash, discoid rash, photo-sensitivity, vasculitic appearing erythematous maular eruptions	Iritis, vasculitis	Serositis of major organs, neuro-psychiatric manifestations
Behçet	Associated with HLA-B5 and HLA-B51 etiology uknown	Mucosal and genital ulcerations, folliculitis, papules, vesicles, pustules, pyoderma, acneiform lesions, furuncles, abscesses, erythema nodosum-like lesions, palpable purpura	Anterior and posteriour uveitis, retinal vasculitis	Polyarticular arthriris, central nervous system abnormalities
Polyarteritis nodosa	Cause unknown, often occurs after an infection	Purpura, erythema, linear edema, vasculitis, painful skin nodules, livedo reticularis, ulcerative skin lesions	Scleritis, peripheral ulcerative keratitis, nongranulomatous uveitis, retinal vasculitis, pseudotumor of the orbit, and central retinal artery occlusion associated with temporal arteritis	
Histiocytosis	Monoclonal proliferation of cells of histiocytes	Firm, round papules or nodules, Papular seborrheic dermatitis. may develop petechial or hemorrhagic exanthems	Bone destruction around eye	
Sarcoidosis	Unknown etiology	Yellowish brown, flesh colored, pink, red, and reddish brown lesions, subcutaneous nodules, infiltrated plaques, hypomelanotic macules and papules	Granulomatous uveitis	
Neuroblastoma	Paraneoplastic Mass effect on sympathetic nerve tract	Firm, blue-purple papules and nodules, hard subcutaneous nodules around the skull and orbital ridges, periortibal ecchymoses, proptosis	Opsoclonus, periorbital pigmentation	

(continued)

Condition	Cause	Skin lesion	Eye findings	Systemic findings
Porphyria	Due to deficient specific enzymes on the heme synthesis pathway	Cutaneous blisters secondary to plasma porhyrins	Photosensitization can affect the eyelids, conjunctiva, cornea, sclera and the retina	
		Inflammation can lead to vesicle and bulla formation, scarring, hyperpigmentation, and superinfection	Neuro-ophthalmological complications include optic neuritis, optic atrophy, ptosis, cranial nerve palsies and retinal hemorrhages	

Appendix 4. Infectious Conditions with Skin and Eye Findings

Condition	Skin lesion	Eye finding	Systemic tx	Ocular tx	Notes
Kawasaki's	Dry, fissured, crusted lips, polymorphous rash, swollen digits, strawberry tongue, non-pitting edema of the hands and feet, desquamation in later stages	Iritis, conjunctivitis	Symptomatic, aspirin, IVIG, NO oral steroids	Symptomatic, topical steroids for extreme cases	Etiology unknown
Cytomegalovirus (CMV) congenital	Blueberry rash in infants (petchiae and purpura), generalized maculopapular eruption, vesicular lesions may rarely occur	Retinitis	Ganciclovir	Intravitreal treatment, gancyclovir	Brain calcifications, most common congenital infection
Herpes (type 1 and 2) (HSV)	erythematous macules, vesicles, and bullae, may have diffuse edematous swelling of the scalp which may lead to necrosis	Primary infection vesicles around the eye (skin), recurrent dendrits and keratitis. Rarely acute retinal necrosis (ARN) and uveitis	Acyclovir	Topical ganciclovir Vidaribine	Congential can be fatal, spinal tap and IV meds and pCR required, acquired often from family member kissing child good night on cheek with first episode vesicles, recurrent episodes, kerititis
Syphilis (congenital)	Diffuse papulosquamous rash that includes the palms and soles, diffuse desquamation, weeping, fissuring at mucocutaneous junction	Glaucoma, uveitis chorioretinitis	Systemic penicillin	Systemic penicillin, steroids for uveitis	Treponema Pallidum
Rocky mountain spotted fever	Discrete, pale, blanching macules or papules, which begin peripherally and spread centripetally, can become petechial hemorrhagic or purpuric	Petechial lesions on the bulbar conjunctiva due to local vasculitis with conjunctivitis. Parinaud oculoglandular syndrome, corneal ulcers, uveitis, retinal vasculitis, endophthalmitis, and anterior ischemic optic neuropathy	Tetracycline, chloramphenicol	Treatment is directed at underlying eye pathology	

(continued)

Condition	Skin lesion	Eye finding	Systemic tx	Ocular tx	Notes
Lyme disease	Erythema migrans (single or multiple erythematous lesions with advancing borders and central clearing), late disease is associated with lymphocytoma cutis and acrodermatitis chronica atrophicans	Neuroretinis, bells palsey	Doxycycline Penicillin cefuroxime		Borrelia burgdorferi
Epstein barr virus (EBV)	Fine, maculopapular rash, occasionally symmetrical rash on cheeks, may have "atopic dermatitis" appearance	Rarely iritis, keratitis. lymphoma (usually in immune compromised), papillitis	Possible short course steroids	Symptomatic tx	Has been implicated in recalcitrant cases of uveitis and kerititis
Varicella infection	Primary: red macule or papule progressing to vesicles and crusting	Pseudoodendrites, followed by uveitis and sometimes corneal infiltrates, later is course of presentation (2 weeks), skin lesions may be healed	Acyclovir early in course	Iritis and glaucoma treatment as indicated, role of ocular antiviral unknown	May occur after Varicella vaccine
	Secondary: vesicles and erythema clustered in a dermatomal distribution of one or more sensory nerves	Microphthalmia, chorioretinitis, cataracts, optic atrophy		Congenital: anti VZV-immune globulin	
	Congenital: vesicles or scarring in a dermatomal distribution				
Toxoplasmosis (congenital)	Maculopapular eruption sparing the face, palms, and soles	Chorioretinal lesions (that may reactivate years later), uveitis, vitritis	Pyrimethamine plus sulfadiazine with leukovorin for significant active systemic disease. Newborns infected with disease should be treated even if asymptomatic or no findings	Pyrimethamine plus sulfadiazine with leukovorin for active eye disease (usually macula/sight threatening), which may include systemic steroids	Calcifications in brain
Rubella (congenital)	Blueberry muffin rash, generalized maculopapular eruption, reticulated erythema of the face and extremities	Eyes in acute phase: conjunctivitis, Congenital: (infection in mom before 16 weeks): cataracts, chronic uveitis, salt and pepper retinopathy	Usually short and self limited	Problems only in congential form	
Zika virus	Fine often asymptomatic rash, with mild fever and myalgia, associated with mesquito borne flavivrius	Macular and retinal and macular lesions, chorioretinal atrophy, optic disc abnormalities	None, prenatal dx	Ocular, retina evaluations, VEP?	Associated with congenital infection of mom, usually earlier in pregnancy neurocognitive degeneration, including microcephally
Condition	Skin lesion	Eye finding	Systemic tx	Ocular tx	Notes
Leprosy (Hansens Disease)	Tuberculoid-single flat lesion, large with well-dermarcated hypopigmented and thickened palpable peripheral nerves	Iritis, scleritis, keratopathy, corneal anesthesia	Systemic: clofazimine, steroids, (rifamipin, thalidomide and dapsone used in adults)	Eye, requires systemic treatment, artificial tears and hygiene lid and lashes	

(continued)

Condition	Skin lesion	Eye finding	Systemic tx	Ocular tx	Notes
	Lepramatous Leprosy- nodules on the eyebrows and ears and leonine facies				
Cutaneous Tuberculosis	Brownish red papule that develops into an indurated plaque that may ulcerate	Iritis granulomatous	Systemic: aminoglycoside, fluoroquinilones	Eye treatment directed toward uveitis	
Mycobacterium Tuberculosis					
Cat scratch disease	Skin, inoculation papule followed by 3–5 mm erythema papules developing at site of infection, localized lymph andenopthy	Parinaud ocular glandular syndrome	Tx : systemic: self limited and/ or azithromycin	Tx : ophthalmic doxycycline and rifampin	
Bartonella hensalae		Stellate macular retinopathy (neuroretinitis)			
Human Papilloma Virus (HPV)	Warts on skin and around eye		TX: removal by surgery, cryo, laser, topical, electro surgery		Have been found to be associated with malignant degeneration (some strains).
Typhus	Macular, papular, or petechial rash	Eye: Visual disturbances, photophobia	Tx: doxycycline, tetracycline		
Measles	Red maculopapular rash that begins on the head and chest and spreads peripherally, preceded by Koplik spots in mouth (discrete red lesion with bluish center)	Corneal ulcers, usually associated with vitamin A deficiency			Avoid secondary infections
Histoplasmosis	Skin findings are uncommon, papules, pustules, purpura, abscesses, severe dermatitis, verrucous lesions, erythema multiforme, and erythema nodosum	Keratoconjucntivitis, iridocyclitis, multifocal retininits,	Tx. For pulmonary involvement: Fuconazole or Itraconazole		
Lymphocytic Choromeningitis Virus (LCMV)	Occasionally maculopapular rash	Acute: papillademа, Chorioretinal scars	Tx: supportive care, avoid exposure to rodent hosts		
		Congenital (in first or second trimester): microphthalmia, vitritis, leukoria, cataracts, optic atrophy			
Trypanosomiasias (Trypanosoma Cruzi)	Acute form–localized signs of inflammation at parasite entery, with facial edema and lypmhandenopathy	Romana sign– (unilateral painless swelling of eye), conjunctivitis, preauricular lymphadenitis			

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Ocular Manifestations of Endocrinologic Diseases

9

Rebecca Sands Braverman and Sarah K. Bartz

Pituitary Gland Diseases

Introduction

The pituitary gland is considered the master gland and is divided anatomically into the anterior and posterior pituitary. The anterior pituitary is responsible for producing growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH). The posterior pituitary secretes oxytocin and vasopressin. The following pituitary disorders have significant systemic and ophthalmic manifestations and will be discussed in detail: growth hormone deficiency, pituitary adenoma, central diabetes insipidus, optic nerve hypoplasia syndrome and central precocious puberty.

Definition

Pituitary Gland Abnormalities

Hypopituitarism is defined as the diminished or absent secretion of one or more pituitary hormones. Examples include isolated hormone deficiencies such as growth hormone deficiency or multiple hormone deficiencies as often seen in optic nerve hypoplasia syndrome (septo-optic dysplasia). Excessive pituitary hormone production secondary to functional or secreting pituitary adenomas, may involve single or multiple hormones as well. The clinical presentation of pituitary hormone abnormalities vary depending on the age of onset, hormones involved, associated structural abnormalities of the brain and presence or absence of concomitant systemic/genetic syndromes.

Definition

Growth Hormone Deficiency

Human growth hormone is produced by the anterior pituitary. The hypothalamus controls secretion of GH from the pituitary. Growth hormone releasing hormone (GHRH) stimulates secretion of GH and somatostatin inhibits GH secretion. GH has direct anabolic effects on muscle, bone and liver tissue and indirect effects via insulin growth factor 1 (IGF-1).

History

Growth Hormone Deficiency

Research to treat pediatric GHD via the purification of GH started in the 1940s. Early preparations were composed of purified porcine and bovine GH. Genentech produced the first recombinant human GH in 1981.

Growth Hormone Deficiency

Growth hormone deficiency (GHD) may be congenital or acquired. Acquired GHD may be present in space occupying lesions such as suprasellar neoplastic diseases/pituitary-hypothalamus neoplasms such as craniopharyngioma that compress the pituitary gland. Other causes of acquired GHD include ischemic, infiltrative, severe head trauma, auto-immune (ie. Lymphocytic hypophysitis), iatrogenic (ie. Radiation, surgical), and idiopathic.

Growth hormone (GH) supplementation for the management of GHD or short stature has been available for decades and is used for growth restriction in the following syndromes: Turner, Prader-Willi and Noonan syndrome. Recombinant

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human growth hormone has been available since 1985. Diagnosis of GHD is largely dependent on comparing a child's growth pattern compared with standardized growth charts.

Epidemiology

Growth Hormone Deficiency

GHD affects 1 in 4000–10,000.

Systemic Manifestations

Growth Hormone Deficiency

The clinical manifestation of GHD depends on whether it is congenital, acquired, isolated GHD or associated with multiple pituitary hormone deficiencies. Infants with congenital GHD typically have a normal birth weight but begin to show growth failure by 6–12 months. Associated deficiencies of adrenocorticotropic hormone (ACTH) and gonadotropin hormone may result in perinatal hypoglycemia and urologic abnormalities respectively. The clinical features of acquired GHD are: severe growth failure, delayed bone age, infant like fat distribution, immature facial features, sparse hair, and delayed puberty.

Ophthalmic Manifestations

Growth Hormone Deficiency

Endocrine deficiencies including GHD may be present in optic nerve hypoplasia syndrome. Midline brain abnormalities including absent septum pellucidum, optic nerve hypoplasia and hypopituitarism have been termed septo-optic dysplasia or De Morsier syndrome for decades [1]. Optic nerve hypoplasia syndrome has superseded this terminology since optic nerve hypoplasia is often associated with hypopituitarism and neurodevelopmental abnormalities regardless of brain MRI findings and severity of optic nerve hypoplasia [2–4]. Optic nerve hypoplasia is evident on ocular examination by direct or indirect ophthalmoscopy. The optic nerves appear small, may have a rim of sclera around the nerve known as the "double ring sign" and retina vessel tortuosity Visual acuity varies depending on the severity of the optic nerve hypoplasia and can range from near normal to no light perception. Congenital nystagmus may be associated with severe, bilateral optic nerve hypoplasia.

Ocular malformations such as anophthalmia/microphthalmia associated with pituitary deficiencies including isolated GHD may be due to gene mutations of transcription factor genes (*PROP1*, *POU1F1*, *HESX1*, and *LHX4*) or the *OTX2* gene [5–7]. *PAX6* mutations responsible for aniridia, anterior segment dysgenesis of the cornea, lens and iris may result in abnormal glucose metabolism and borderline GHD [8, 9].

Morning glory disc (MGD) syndrome manifests as a variable excavation of the optic nerve and basal encephalocele. The affected eye in MGD often has poor vision and may be associated with retina detachment. Pituitary insufficiency and dwarfism may be associated with MGD syndrome [10–12].

GHD treated with exogenous administration of GH may result in neovascular retinopathy and macular edema in non-diabetics [13]. GH and IGF-1 have been implicated in the development of diabetic retinopathy for decades [14].

Idiopathic intracranial hypertension (IIH) may result from GH supplementation. Symptoms of headache, double vision due to cranial nerve VI palsy, blurred vision and visual field loss have been reported. Examination findings may include photophobia, reduced visual acuity and peripheral vision, esotropia due to unilateral or bilateral sixth nerve palsy, papilledema and elevated intracranial pressure (ICP). Patients with Turner syndrome, Prader-Willi syndrome and chronic renal insufficiency may be more prone to these side effects [13]. Discontinuation of GH typically results in resolution of IIH. However, there have been cases where vision loss occurs without associated headaches and may result in permanent vision loss [13, 15].

Diagnosis

Growth Hormone Deficiency

The diagnosis of GHD is based on the clinical exam, auxology (the study of growth and development), serum insulin growth factor levels (IGF-1, IGFBP-3), and GH stimulation tests. GH has pulsatile secretion so serum GH levels are difficult to interpret. Patients with GHD should have neuroimaging of the brain to rule out pituitary or pituitary-hypothalamic tumors or midline brain defects associated with optic nerve hypoplasia syndrome.

Management

Growth Hormone Deficiency

Subcutaneous aqueous recombinant GH is given daily. Dosages are adjusted based on response to therapy and IGF-1 level. Periodic ophthalmic examination is recommended to monitor for ocular signs of IIH and papilledema.

Pituitary Adenoma

Introduction

Pituitary adenomas are rare pediatric central nervous system tumors that may or may not secrete hormones. Tumor invasion into the optic chiasm and cavernous sinus may result in central vision loss, peripheral vision loss, cranial neuropathies, ophthalmoplegia and diplopia (Fig. 9.1).

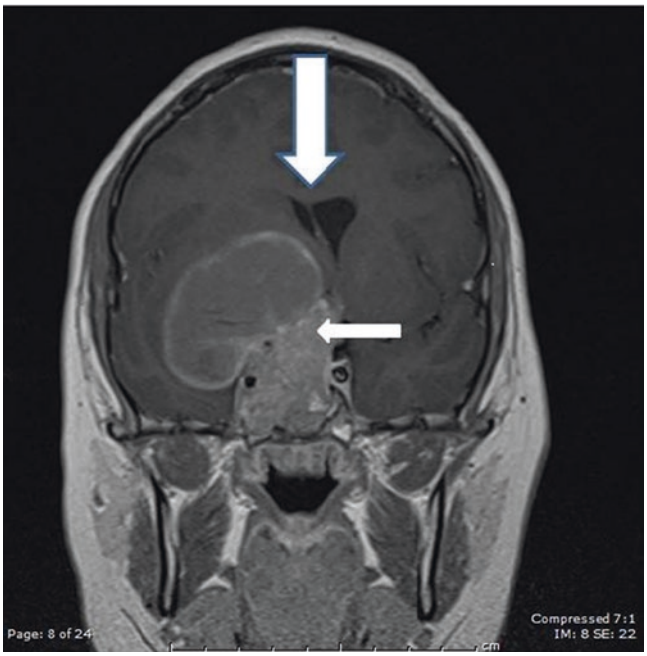

Fig. 9.1 Prolactinoma with invasion of sphenoid sinus (*small white arrow*) and midline shift (*large white arrow*)

Definition

Pituitary Adenoma

Pituitary tumors are defined by size and whether they secrete hormones. A microadenoma is less than 10 mm and a macroadenoma is equal to or >10 mm. A tumor is termed functional or secreting if it produces pituitary hormones including PRL, ACTH, GH, TSH, LH and FSH. The presentation of a functional tumor depends on the hormone it secretes. PRL secreting tumors with amenorrhea-galactorrhea or delayed puberty are most common followed by functional ACTH tumors that cause Cushing's disease and GH secreting tumors resulting in gigantism or acromegaly being very rare.

History

Pituitary Adenoma

The World Health Organization (WHO) first published *Histological Typing of Tumours of the Central Nervous System* in 1979 and is commonly referred to as the "WHO Blue Book". It has undergone three editions, most recently in 2007, to reflect increased understanding of tumor characteristics made possible by electronmicroscopy, immunocytochemistry and genetic testing [16].

Today, immunocytochemical classification of tumors include five main types: PRL, GH, ACTH, TSH and FSH-LH.

Pituitary adenomas have historically been considered benign due to the rarity of metastasis. However, some authors have recently suggested a revision in this characterization due to the 30–45 % rate of invasion of pituitary tumors into the cavernous and sphenoid sinus [17, 18], resistance to treatment and recurrence. Roverot et al. [19] suggested a new classification system that incorporates tumor size, type, grade and molecular prognostic markers that would aid clinicians identify tumors at high risk for recurrence and optimize treatment.

Epidemiology

Pituitary Adenoma

The pituitary adenoma is the most common intracranial tumor affecting 1 in 1000 individuals worldwide [20, 21]. Pituitary adenomas are more common in young adults but do occur in children and the elderly. About half to one third of all pituitary tumors are non-functioning. Prolactinomas are the most common secreting pituitary tumors [22]. Somatotropinomas resulting in GH excess are rare. The estimated prevalence of the acromegaly is 40 in 1,000,000 population with 3–4 new cases in 1,000,000 population per year [23].

Systemic Manifestations

Pituitary Adenoma

Functional pituitary tumors in young girls most commonly report oligoamenorrhoea and galactorrhoea, while headache and delay in pubertal development are the most common features in boys [24]. Prolactinomas may also result in delayed puberty in both girls and boys. Excess GH results in gigantism or acromegaly. Gigantism occurs in children due to excessive growth of long bones prior to closure of the epiphyses. Acromegaly typically affects adults and results in changes in the bones of the face hands and feet. Cushing syndrome results from ACTH secreting adenomas with affected individuals displaying signs of excess glucocorticoid namely growth failure, moon faces, truncal adiposity, purple striae, osteoporosis and diabetes mellitus.

Ophthalmic Manifestations

Pituitary Adenoma

Vision loss is the most common ocular symptom of pituitary adenomas and suprasellar masses in general [25]. Vision loss may be the first symptom of a pituitary adenoma especially if it is non-functional. Extrinsic compression of the optic chiasm by a pituitary adenoma/suprasellar mass may result in

chiasmal syndrome, bitemporal hemifield loss and bilateral optic atrophy. Invasion of the adenoma into the cavernous sinus may cause multiple cranial neuropathies resulting ophthalmoplegia, strabismus and diplopia. Other symptoms and signs include eye pain, nystagmus, visual hallucinations [26] and eyelid ptosis.

Excess GH and IGF-1 may play a role in the development of diabetic retinopathy and retina neovascularization [27]. There have been case reports of acromegaly presenting with enlargement of extraocular muscles [28, 29], restriction of eye movements [30, 31], tearing [28], increased cornea thickness and increased intraocular pressure [32–34].

Diagnosis

Pituitary Adenoma

A complete history, family history, review of systems and physical examination can illicit symptoms and signs of a pituitary adenoma. Central or peripheral vision loss, headaches, double vision, weight gain, short stature/tall stature, amenorrhea, galactorrhea, delayed signs of puberty are among the common presentations. Neuroimaging of the brain via CT or MRI is necessary delineate the presence of a pituitary tumor, it's size and involvement of local structures such as the optic chiasm and cavernous sinus. Laboratory studies may reveal elevated or decreased hormone levels. Gene testing may hold promise in the future for identifying individuals at risk for developing pituitary adenomas. Recent advances in the genetics of Familial Isolated Pituitary Adenoma (FIPA) may help identify individuals at risk for tumorogenesis. The aryl hydrocarbon receptor interacting protein (AIP) gene has been identified as causing a pituitary adenoma predisposition. FIPA associated adenomas only account for approximately 2 % of pituitary tumors but tend to present with large tumors at a young age [35].

Management

Pituitary Adenoma

Treatment of a pituitary adenoma must be individualized based on tumor size, functionality, hormones involved, systemic manifestations and symptoms. A team approach between ophthalmology, endocrinology and neurosurgery are often necessary. Transsphenoidal surgery and radiotherapy are the treatments of choice except in prolactinomas [36]. Prolactinoma pharmaceutical treatment consists of dopamine agonists such as cabergoline or bromocriptine. Pediatric gigantism is treated with somatostatin analogs (SSA), either alone or in combination with pegvisomant [37]. Temozolomide should be considered in aggressive pituitary tumors [36].

Central Diabetes Insipidus

Introduction

Central diabetes insipidus may be a congenital or acquired condition in which the hypothalamic-pituitary axis is deficient in the production of antidiuretic hormone (ADH/vasopressin) resulting in inability of kidneys to adequately retain free water.

Definition

Central Diabetes Insipidus

The etiology of central DI include: idiopathic, traumatic brain injury, iatrogenic, CNS neoplasm, midline brain malformations and genetic causes such as Wolfram syndrome. CNS neoplasms and infiltrative diseases associated with central DI include: Langerhans cell histiocytosis (LCH), germinomas, craniopharyngiomas, and optic pathway gliomas. Midline brain defects seen in optic nerve hypoplasia syndrome may result in panhypopituitarism and central DI. Wolfram syndrome type 1 (WS1) is an autosomal recessive or dominant disorder resulting in diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD). Wolfram syndrome type 2 is associated with early onset optic atrophy, diabetes mellitus and deafness but not DI (Fig. 9.2).

History

Central Diabetes Insipidus

Polyuria was identified by the ancient Greeks and termed *diabetes* meaning siphon or to pass through. It was not until the eighteenth century that it was recognized that there were

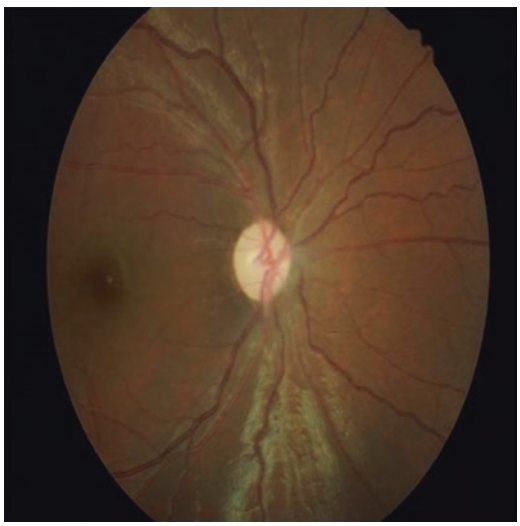

Fig. 9.2 Optic nerve atrophy associated with DIDMOAD

differences in the taste of the urine between diabetes insipidis (lacking strong flavor) and diabetes mellitus (sweet taste). The connection between the pituitary gland and diabetes insipidus was made in the twentieth century. Posterior pituitary extracts lead to the development of vasopressin which was used starting in the 1970s to treat diabetes insipidus and other hemodynamic disorders [38].

Epidemiology

Central Diabetes Insipidus

Diabetes insipidus (all types) affect infants, children and adults with a prevalence reported as 1 in 25,000 with <10 % hereditary [39]. The most common causes for central DI in children include CNS tumors, Langerhans cell histiocytosis, and congenital abnormalities of midline brain development such as holoprosencephaly and septo-optic dysplasia/optic nerve hypoplasia syndrome [40].

Systemic Manifestations

Central Diabetes Insipidus

Polydypsia, polyuria and hypernatremia are common sings of DI. Dehydration and hypovolemic shock may develop in severe cases. Associated problems with thermoregulation with alternating episodes of hypothermia and hyperthermia may be present. Hypopituitarism and neurodevelopmental delays are frequently associated with CNS neoplasms or congenital malformations of the brain.

Wolfram syndrome type 1 (WS1) presents with central DI, diabetes mellitus, optic atrophy and deafness (DIDMOAD). Wolfram syndrome type 2 (WS2) is similar to WS1 except for the lack of DI.

Ophthalmic Manifestations

Central Diabetes Insipidus

Ophthalmic manifestations depend on the underlying etiology of DI. Suprasellar masses may result in chiasmal syndrome, vision loss, bitemporal hemifield peripheral vision loss, and optic atrophy. Congenital brain anomalies may present with optic nerve hypoplasia which may be unilateral or bilateral. Patients with optic nerve hypoplasia may have near normal visual acuity to no light perception. Infants with low vision may have with poor visual tracking, lack of a social smile and nystagmus. An afferent papillary defect, sluggish pupil reactivity to light and reduced color vision are common. Examination of the optic nerve via ophthalmoscopy may reveal optic nerve head pallor in optic atrophy or unilateral or bilateral small optic nerves, a ring of sclera around the optic nerve known as the "double ring sign" and tortuous retina vessels in optic nerve hypoplasia. Optic atrophy associated with DIDMOAD results in bilateral reduced vision and optic nerve pallor during early childhood.

Diagnosis

Central Diabetes Insipidus

A history of polydypsia and polyuria associated with dilute urine (urine osmolality typically <300 mOsm/kg) and plasma hyperosmolality (>295–300 mOsm/kg) suggests diabetes insipidus. Central diabetes insipidus is confirmed by the response to vasopressin/desmopressin challenge test with >50 % increase in urine osmolality [39, 41, 42]. Neuroimaging is necessary to identify CNS neoplasms and malformations. Serum glucose and hearing tests for diabetes mellitus and deafness respectively should be completed if the clinician suspects Wolfram syndrome. Genetic testing for Wolfram syndrome type 1 (WS1) should be considered in cases of DI associated with diabetes mellitus, optic atrophy and deafness. The causative gene for WS1 maps to chromosome 4p16.1. The causative gene for WS2 maps to maps to chromosome 4q22 [43].

Management

Central Diabetes Insipidus

Management of DI aims to correct hypovolemia and hypernatremia. Desmopressin administration is the mainstay of pharmaceutical treatment but children may also be treated with a low solute and/or a thiazide diuretic. Additionally, acute dehydration and hypernatremia may be managed with free water intake orally or administration of intravenous fluids. Endocrinology consultation is recommended since other pituitary hormone abnormalities may be associated with central DI.

Individuals with low vision due to optic atrophy or optic nerve hypoplasia should be evaluated and managed by a Vision Rehabilitation/Low Vision eye care professional. School aged children with low vision benefit from the services of a Vision Teacher to optimize their learning experience using tools including Braille, magnifiers, closed circuit TV, tablets and computers while at school.

Optic Nerve Hypoplasia Syndrome/Septo-Optic Dysplasia

Introduction

Optic nerve hypoplasia syndrome also known as septo-optic dysplasia (SOD) or de Morsier syndrome is a constellation of midline brain abnormalities (absent septum pellucidum,

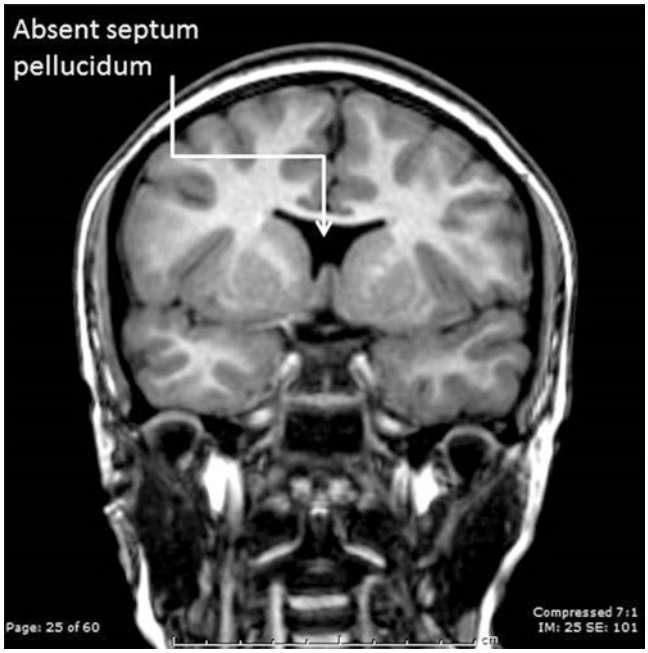

Fig. 9.3 Absence of septum pellucidum associated with optic nerve hypoplasia syndrome

thin or agenesis of the corpus callosum) various endocrine deficiencies, and variable optic nerve hypoplasia (Fig. 9.3).

Definition

Midline brain defects associated with optic nerve hypoplasia, hypoplasia of the optic chiasm and endocrine deficiencies.

History

Dr. David Reeves first described the association of optic nerve hypoplasia with agenesis of septum pellucidum in 1915. "La dysplasia septo—optique" has been credited to Georges de Morsier in 1956. de Morsier syndrome and associated pituitary dwarfism was first described by Dr William Hoyt in 1970.

Epidemiology

The incidence of optic nerve hypoplasia syndrome is 1 in 10,000 with equal sex distribution [44]. The condition is more commonly seen in children born to mothers who are very young, have diabetes or took illicit drugs or neuroleptics during their pregnancy. Most cases are considered spontaneous, but autosomal recessive and autosomal dominant cases of SOD have been reported. Less than 1 % of cases are considered to be secondary to mutations involving *HESX1*, *SOX2*, *SOX3* and *OTX2* genes [44].

Systemic Manifestations

Multiple hormone deficiencies or panhypopituitarism may be present. GH deficiency is the most common hormonal deficiency and may present with poor growth and neonatal hypoglycemia. Hypocortisolism may result in life threatening hypoglycemia during periods of stress such as fever. Additional signs of hypocortisolism include fatigue and weakness. Hypothyroidism may result in prolonged neonatal jaundice, developmental delay and poor growth. Diabetes insipidus (DI) may occur in addition to anterior pituitary deficiencies. Absence of the posterior pituitary and infundibulum on neuroimaging should alert the practitioner to the increased risk of DI.

Ophthalmic Manifestations

Visual acuity and the presence of nystagmus is variable depending on the severity of optic nerve hypoplasia. Typically optic nerve hypoplasia is bilateral in septo-optic dysplasia, but may be asymmetric in severity. Visual acuity may range from normal to no light perception. Nystagmus or roving eye movements are common. Ophthalmoscopy typically reveals a small optic nerve head, double ring sign and tortuous retinal vessels.

Diagnosis

Neuroimaging of the brain and orbits with a MRI is the best modality to delineate midline brain defects [45]. The severity of optic nerve hypoplasia is difficult to quantify via neuroimaging and is more accurately quantified by ophthalmoscopy. Ophthalmologists who evaluate an infant or child with optic nerve hypoplasia should do a complete review of systems to detect systemic abnormalities such as poor growth or developmental delay. Hormonal deficiencies are possible in individuals with unilateral optic nerve hypoplasia. Laboratory investigation to detect pituitary hormone deficiencies should be instituted by an Endocrinologist.

Management

Individuals with SOD should be under the care of an Endocrinologist since hormonal deficiencies may develop over time. Infants may develop life threatening adrenal crisis due to hypocortisolism. Untreated endocrine deficiencies

may result in significant neurodevelopmental abnormalities. Individuals with low vision benefit from vision rehabilitation starting at a young age.

Hypothalamic-Pituitary Neoplasms and Central Precocious Puberty

Introduction

Abnormalities of the hypothalamic-pituitary-gonadal axis can cause central precocious puberty (CPP). Lesions that result in CPP include craniopharyngioma, optic pathway glioma, suprasellar arachnoid cyst, hypothalamic hamartoma, germ cell tumors and hypothalamic-pituitary astrocytomas [46].

Definition

Precocious puberty manifests as the onset of puberty and inappropriate bone growth before age 8 years old in girls and 9 years old in boys [47] and ultimately short stature in adults. Central precocious puberty is gonadotropin dependent whereas peripheral precocious puberty is gonadotropin independent.

History

The normal age for the onset of puberty and the treatment of central precocious puberty (CPP) with gonadotropin releasing hormone agonists were under debate in the 1990s [48]. In 1997, the Lawson Wilkins Pediatric Endocrine Society published guidelines for the diagnosis and treatment of precocious puberty based on the review of available literature [49].

Epidemiology

Central precocious puberty (CPP) is a rare disease with female predominance [50]. Neoplasm-related precocious puberty (PP) is a rare presenting feature of childhood cancer and may be associated with neoplasms of the brain, hepatoblastoma and adrenocortical carcinomas [51]. CPP is a common cause of growth disorders in children with neurofibromatosis-1 and are commonly associated with optic chiasm and optic nerve gliomas [52].

Systemic Manifestations

Central PP may present with inappropriately early onset of puberty, tall stature, weight gain and bone age greater than chronologic age. Individuals with NF-1 may have associated short stature [53]. The type of CNS lesion influences the presentation of CPP [54]. Other pituitary deficiencies may be associated with CPP as a result of the primary lesion or it's treatment.

Ophthalmic Manifestations

Neuro-ophthalmic manifestations of hypothalamic-pituitary lesions depend on the size and location of the lesion. Suprasellar masses may compress the optic chiasm and result in chiasmal syndrome, namely central vision loss and bitemporal visual field loss. Optic pathway gliomas may result in unilateral or bilateral vision loss and optic nerve atrophy. Optic nerve gliomas may also cause proptosis of the affected eye (Fig. 9.4). Optic pathway gliomas may be isolated lesions or associated with NF-1. Assorted ocular manifestations of NF-1include: benign hamartomas of the iris (Lisch nodules), retina and eyelid.

Diagnosis

History and physical examination reveal premature signs of puberty and increased growth velocity. X-rays demonstrate advanced bone age compared to chronologic age. Laboratory testing for may reveal elevated testosterone or estradiol, elevated basal LH, and a pubertal response to GnRH agonist stimulation testing.

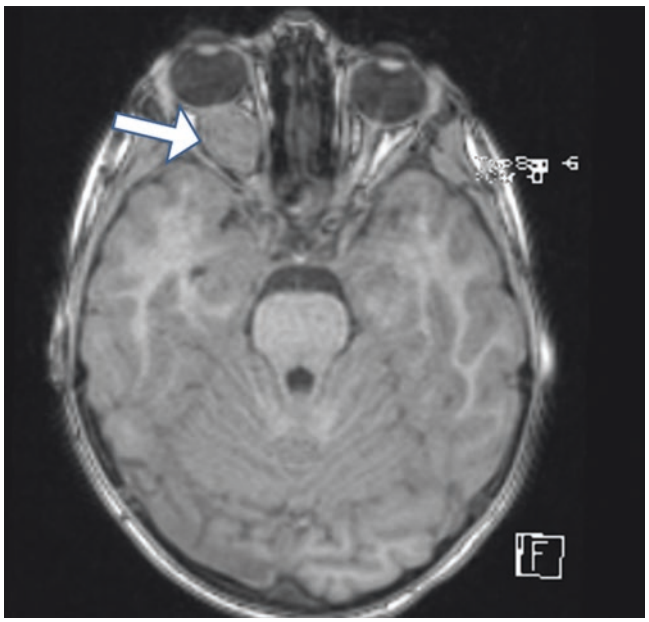

Fig. 9.4 Right optic nerve glioma (*arrow*) with proptosis

Management

Treatment should be aimed at the underlying cause. Children with CNS tumors should undergo appropriate neurosurgical and oncologic intervention. Pharmaceutical treatment with a GnRH agonist can be used to suppress central precocious puberty. Individuals with optic pathway gliomas resulting in vision loss are treated with vincristine/carboplatin based chemotherapy or proton-beam radiation. Typically, there is modest to no recovery of vision with treatment. A small case series of by Avery et al. of four children with vision loss due to optic pathway gliomas suggested that treatment with intravenous bevacizumab (monoclonal antibody against vascular endothelial growth factor) could result in vision recovery [55]. There is controversy as to when to initiate treatment for optic pathway gliomas. Large, controlled studies are necessary in order to standardize care [56].

Ophthalmic Manifestations of Thyroid Disease

Introduction

The ophthalmic manifestations of thyroid disease are commonly seen in individuals with hyperthyroidism. The severity of thyroid eye disease (TED) or thyroid associated ophthalmopathy (TAO) tends to be less in children than adults. Hypothyroidism does not typically result in eye disease but idiopathic intracranial hypertension associated with levothyroxine treatment has been reported [57]. Patients who have undergone treatment for thyroid disease and are clinically euthyroid may still have orbital signs and symptoms.

Definition

Thyroid Disease

Hyperthyroidism or thyrotoxicosis is a condition where inappropriately high thyroid hormone is produced and secreted. Graves disease is a multisystem autoimmune disorder resulting in hyperthyroidism, ophthalmopathy and diffuse goiter.

History

Thyroid Disease

Goiter, diffuse enlargement of the thyroid gland, and it's treatment with oral seaweed supplementation was first described by Chinese physicians nearly 3000 years BC. Leonardo Di Vinci was the first to identify and illustrate the thyroid gland in the 1500s. Dr. Robert Graves initially described a series of three female patients with exophthalmos, palpitations and goiter in the early 1800s. Shortly after Graves, C. von Basedow coined the classic triad of exophthalmos, tachycardia and goiter which became known as Basedow's disease. Dr. Charles H. Mayo, a founding member of the Mayo Clinic, first used the term hyperthyroidism to describe patients with exophthalmic goiter, toxic adenoma, and adenomatous goiter in association with clinical signs of inappropriately high thyroid hormone activity. Today, autoimmune hyperthyroidism is most commonly referred to as Graves disease, but Basedow disease is appropriate as well. The etiology of Graves disease caused by an immunoglobulin G autoantibody was discovered in the 1950s [58]. Stimulating antibodies against the thyrotropin receptor and possibly the insulin-like growth factor 1 receptor (IGF-1R) result in hyperthyroidism and the extra-thyroid manifestations of Graves disease [59]. Today, we understand thyroid associated ophthalmopathy is primarily a T and B-cell mediated disease. Cytokines stimulate orbital fibroblasts resulting in the accumulation of orbital extracellular matrix macromolecules, orbital inflammation and fibrosis [60].

The treatment of Graves disease has made great strides during the twentieth century. Radioiodine 131, betablockers and antithyroid drugs were developed and implemented in the medical treatment of Graves disease over the past century. Most recently, biologic agents or disease-modifying antirheumatic drugs (DMARD's) have been used in the medical management of TAO [60]. Further study on the effectiveness and safety of DMARDS in TAO, especially in children, are necessary. Thyroidectomy for the treatment of thyrotoxicosis was pioneered by surgeons from around the world including: Thomas Dunhill, Theodor Kocher, Charles Mayo, William Halsted and George Crile [61]. Dr H.C. Naffziger was an innovator in the surgical management of Graves ophthalmopathy via orbital decompression in the 1930s [62].

Epidemiology

Thyroid Disease

Graves disease is the most common cause of hyperthyroidism in children and peaks during adolescence. Girls are more commonly affected than boys. The prevalence of Graves disease in the United States is 1 in 10,000 children [63]. Half of children and adolescents will have eye manifestations of Graves disease.

Systemic Manifestations

Thyroid Disease

Symptoms of hyperthyroidism in Graves disease may be insidious and involve multiple organ systems. Behavior changes may include hyperactivity, declining school performance and sleep pattern changes. Patients may experience hair loss, heat intolerance, tremor, fullness or mass of the neck. Physical examination findings may include accelerated growth, goiter, tachycardia, hypertension, muscle weakness and weight loss.

Ophthalmic Manifestations

Thyroid Disease

Eyelid retraction and proptosis are the most common signs of pediatric Graves orbitopathy (Fig. 9.5) [64]. Eyelid retraction is secondary to increased Muller muscle tone. Dry eye and exposure keratopathy are secondary to lid retraction, reduced blink frequency and proptosis resulting in increased evaporative tear loss. Lid lag may be appreciated in downgaze. Orbital inflammation is not a predominant feature of pediatric thyroid eye disease in contrast with adult Graves orbitopathy. Diplopia secondary to restrictive strabismus and reduced visual acuity due to optic neuropathy are uncommon in children.

Diagnosis

Thyroid Disease

The lab evaluation of thyrotoxicosis should be guided by the patient's clinical presentation. In a patient with signs of thyrotoxicosis, goiter, and exophthalmos, the presumptive diagnosis of Graves Disease can be made. Confirmatory laboratory studies reveal elevated serum free thyroxine (FT4) and/or total triiodothyronine (T3), suppressed serum thyroid stimulating hormone (TSH), and presence of thyrotropin receptor stimulating antibody (TSHR-Ab). Radioactive iodine uptake is usually not necessary to make the diagnosis of Graves Disease but shows diffuse uptake throughout the gland if done. Euthyroid Graves disease consists of orbitopathy, positive TSHR-Ab but normal TSH and T4. Thyroid ultrasound imaging and radioiodine I-123 uptake testing are indicated if biochemical testing fails to confirm the diagnosis.

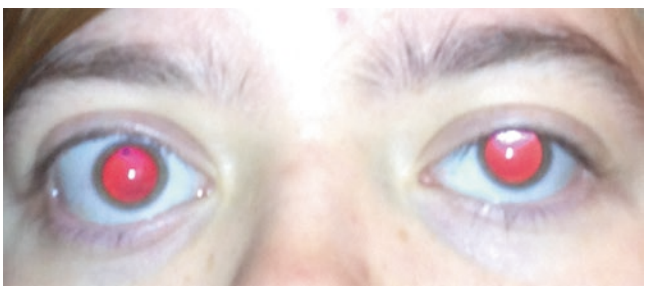

Fig. 9.5 Thyroid orbitopathy with bilateral lower eyelid retraction

Management

Thyroid Disease

Treatment of thyrotoxicosis associated with pediatric Graves disease is somewhat controversial and should be tailored for each individual child. The three most commonly used therapeutic options include anti-thyroid drugs (ATDs), radioactive iodine and thyroidectomy. Most pediatric endocrinologists prefer ATDs as the initial treatment of pediatric Graves disease. Methimazole is the recommended ATD since propylthiouracil (PTU) has more frequent and severe side effects, including the small risk of severe liver injury. Children tend to have a higher relapse rate after discontinuation of ATDs compared to adults. Only 30% of pediatric Graves patients achieve remission after 2 years of medical treatment with ATDs [10]. Alternative treatment with radioiodine 131 is considered when children have ATD toxicity, are non-compliant with ATDs or relapse after ATD discontinuation. Adjunct use of beta-blockers can control tachycardia, tremors, and anxiety associated with hyperthyroidism. A subtotal or total thyroidectomy may be considered in patients with Graves disease that presents prior to puberty, relapses after discontinuation of ATDs, is associated with severe orbitopathy or persistence of elevated TRAb levels. Reported complications after thyroidectomy in children with Graves disease include transient or permanent hypocalcemia, injury to the recurrent laryngeal nerve and keloid formation [65]. Avoidance of second hand smoke exposure may help prevent ophthalmopathy [66]. Graves orbitopathy tends to improve upon restoration of euthyroidism.

Graves orbitopathy (GO) in children presents predominantly with eyelid retraction and proptosis/exophthalmos. Systemic corticosteroid administration may be necessary if GO signs and symptoms progress despite ATDs or if they persist once the patient is euthyroid [67]. Somatostatin analogs have been reported to be of benefit in treating GO in adults, but limited information is available for children [68]. Newer treatments with B-lymphocyte depleting monoclonal antibody rituximab and anti-tumor necrosis factor-alpha agents etanercept and infliximab may play a role in the future treatment of pediatric GO but further studies to demonstrate safety and efficacy are necessary [69]. Orbital decompression is rarely needed in children as sight threatening complications secondary optic neuropathy and cornea exposure are rare compared to adults [64]. Orbit radiation is not recommended in children. Artificial tear drops and ointments may

be used to address dry eye symptoms. Anterior blepharotomy to manage lid retraction may be offered if dry eye symptoms or cornea exposure fail to respond to conservative measures or if poor cosmesis is objectionable to the patient [70].

Ocular Manifestations of Parathyroid Disease

Introduction

The parathyroid glands function to regulate serum systemic calcium levels via production of parathyroid hormone (PTH).

Definition

Parathyroid Disease

The four parathyroid glands located adjacent to the thyroid gland in the neck produce parathyroid hormone (PTH) to control serum calcium. PTH increases serum calcium by stimulation of calcium release from bone, increased calcium absorption from the gut via activation of vitamin D and increased renal calcium reabsorption. PTH also increases renal phosphate excretion. Hyperparathyroidism is caused by elevated PTH production resulting in elevated serum calcium and end organ damage involving the kidney, pancreas and bone as well as hypertension, neuromuscular, neuropsychiatric and gastrointestinal disorders.

Hypoparathyroidism is much more common than hyperparathyroidism in children. Hypoparathyroidism is most frequently caused by injury to the glands during thyroid surgery or may be syndromic. Hypoparathyroidism results in low serum and bone calcium as well as elevated serum phosphate. Hyperparathyroidism may be due to a single adenoma, multiple parathyroid gland hyperplasia or parathyroid neoplasia.

History

Parathyroid Disease

The parathyroid glands were discovered by Ivar Sandström and symptoms of hypocalcemia after parathyroidectomy were described by W. G. MacCallum and Carl Voegtlin in the late nineteenth century [71]. Surgery to excise the parathyroid glands to treat bone disease was first performed in the early part of the twentieth century. Fuller Albright's work established our current understanding of how the parathyroid glands regulate calcium and phosphate levels. He was the first to describe the etiology of primary hyperparathyroidism secondary to a solitary adenoma or hyperplasia of the parathyroid glands [72]. Albright also purified bovine parathyroid hormone for his research. Today, humanized truncated parathyroid hormone (Teriparatide, PTH) and intact parathyroid hormone (Preotact, PTH) are used for the treatment of osteoporosis and hypoparathyroidism [73]. However, PTH has a black box warning in pediatrics due to a possible link between its use and osteosarcoma.

Epidemiology

Parathyroid Disease

Hyperparathyroidism is rare in children with an incidence of 2–5 in 100,000 [74]. It is most often caused by a single adenoma but may be associated with genetic syndromes such as Multiple Endocrine Neoplasia (MEN), McCune Albright Syndrome (MAS), Kearns Sayre syndrome and Autoimmune Polyglandular Syndrome type 1.

Systemic Manifestations

Parathyroid Disease

Symptoms of hyperparathyroidsm are often vague and include fatigue, weight loss, abdominal pain, hypertension and polyuria. The most common presentation is asymptomatic mild hypercalcemia. A delay in diagnosis may result due to the rarity of the disease and vague symptoms [75]. Children may present with end organ damage secondary to hyperparathyroidism including renal calculi, pancreatitis and osteoporosis. Hypoparathyroidism may by asymptomatic or present with symptoms hypocalcemia including paresthesia, tetany, EKG changes and possibly seizures.

MEN syndromes are a group of inherited disorders characterized by tumors in multiple endocrine glands [76]. Systemic and ocular manifestations depend on the glands involved.

Kearns Sayre syndrome is a rare mitochondrial disease associated with chronic progressive external ophthalmoplegia, cardiac conduction abnormalities and retina degeneration within the first two decades of life [77]. The phenotypic presentation may be variable and include: myopathy, dystonia, cerebellar ataxia, dysarthria, nasal regurgitation, facial weakness, bilateral sensorineural deafness, dementia, proximal renal tubular acidosis, proximal skeletal muscle weakness and exercise intolerance [78]. Associated endocrinopathies include hypoparathyroidism, hypogonadism, diabetes mellitus, and hypopituitarism.

Autoimmune Polyglandular Syndrome type 1 is a rare autosomal recessive disease associated with hypoparathyroidism, adrenal insufficiency and chronic mucocutaneous candidiasis.

Ophthalmic Manifestations

Parathyroid Disease

Primary hyperparathyroidism results in the following ocular manifestations: band keratopathy, conjunctival calcification and scleritis. Syndromic parathyroid diseases have variable ocular presentations. MEN 2B may present with mucosal neuromas of the eyelid margins as well as anteverted eyelids and medullated nerve fibers of the cornea. Cataracts may be associated with hypoparathyroidism and are often described as having multicolored flecks.

Children with Kearns Sayre syndrome initially present with eyelid ptosis. Eyelid ptosis may be asymmetric, unilateral or bilateral [79]. Chronic progressive external ophthalmoplegia results in severe extraocular muscle dysfunction and strabismus. Double vision is encountered less frequently than expected despite the presence of severe ocular dysmotility. Orbicularis oculi weakness and lagophthalmos have been reported to result in severe exposure keratitis [80]. Retina abnormalities appear to be progressive over time. Initially, patients may have a normal fundus appearance which progresses to "salt and pepper retinopathy", chorioretinal atrophy and choroidal sclerosis [81]. Electroretinogram (ERG) testing may be normal initially but becomes extinguished over time. Visual acuity appears to parallel the development of retinopathy as vision loss progresses with time.

Chronic keratitis is the most common presenting ocular sign of Autoimmune Polyglandular Syndrome type 1. Chronic dry eye, cataracts, iritis, retina detachment and optic atrophy have been reported [82].

Diagnosis

Parathyroid Disease

Elevated serum and urine calcium and elevated PTH are diagnostic of hyperparathyroidism. Additional imaging modalities than can aid in the diagnosis of parathyroid disease include: ultrasonography, computed tomography, magnetic resonance imaging, and sestamibi nuclear scans [74].

A family history of genetic disorders including MEN syndrome should be elucidated as these disorders are autosomal dominant. Two or more endocrine tumors suggests the possibility of MEN. Other physical manifestations may help the clinician tailor their workup when investigating the possibility of other rare syndromes such as, Kearns Sayre, and autoimmune polyglandular syndrome type 1. Electrophysiologic testing of the retina via an electroretinogram (ERG), electromyography, electrocardiogram and muscle biopsy examination for ragged red fibers may be useful in patients suspected of having Kearns Sayre syndrome.

Management

Parathyroid Disease

Surgical resection of the parathyroid glands is the treatment of choice for hyperparathyroidism. Medical treatment involves administration of activated vitamin D (calcitriol) and calcium supplementation. A multidisciplinary approach is necessary to provide care for individuals with syndromic parathyroid disease.

Strabismus secondary to chronic progressive external ophthalmoplegia (CPEO) associated with Kearns Sayre syndrome is typically recalcitrant to treatment. Strabismus surgery with maximal resections and recessions of eye muscles augmented with botulinum toxin injection of the affected extraocular muscles typically fail to maintain ocular alignment long term [83]. Eyelid ptosis surgery for patients with Kearns Sayre syndrome should be undertaken with caution. The combination of external ophthalmoplegia and lagophthalmos make the eye vulnerable to injury, exposure keratopathy, corneal ulceration and perforation [84].

Ophthalmic Manifestations of Pancreatic Disease

Introduction

Pancreatic Disease

Diabetes mellitus is the most common pancreatic disease resulting in significant ocular complications. Cystic Fibrosis (CF) affects the exocrine function of the pancreas and can result in mal-absorption of vitamin A. Vitamin A deficiency results in xerophthalmia and retinopathy. Today, these sight threatening complications secondary to CF are uncommon due to vitamin supplementation.

Definition

Pancreatic Disease

Diabetes mellitus (DM) causes hyperglycemia and end organ damage to the eyes, kidneys, cardiovascular, central and peripheral nervous systems. The classification of diabetes is based on etiology. Type 1 DM results from insulin deficiency secondary to beta cell destruction within the pancreas. Type 1 DM usually results from cell-mediated destruction of beta cells but may be idiopathic. Type 2 DM results from insulin resistance and insulin deficiency. Maturity-Onset Diabetes of the Young (MODY) is a group of disorders of monogenic defects in beta cell function. Diabetes may also be drug-induced or caused by diffuse injury to the pancreas such as pancreatitis, trauma, and cystic fibrosis. Many endocrinopathies are associated with diabetes

including: Cushing syndrome, hyperthyroidism, pheochromocytoma, somatostatinoma and acromegaly.

History

Pancreatic Disease

The term diabetes means to siphon or pass through. Mellitus is used to describe the sweet taste of a diabetic's urine. The sweet taste of a diabetic's urine was documented in the literature of the ancient Greeks, Chinese and Egyptians. Prior to the development of insulin, various remedies were suggested to address the polyuria, polydypsia and polyphagia caused by diabetes including horseback riding, starvation and the consumption of wine.

The role of the pancreas and it's production of insulin was discovered at the end of the nineteenth century by Joesph von Mering and Oskar Minkowsi. They studied the effects of a total pancreatectomy on dogs and found that they developed signs and symptoms of diabetes postoperatively. Early in the twentieth century, Sir Edward Albert Sharpey-Schafer identified insulin production by the islets of Langerhans in the pancreas. In 1923, the team lead by Sir Frederick Grant Banting and Charles Best won the Nobel Prize for their production of insulin from purified cow pancreases. They developed the first effective treatment for diabetes which was administered to a 14 year old child in 1922. For the next 60 years, diabetics were treated with pancreas extracts from cows and pigs. In 1978 insulin became the first human protein to be manufactured through biotechnology and lead the way to mass production of human insulin (Humulin). Humulin became the first genetically engineered, recombinant DNA drug approved by the FDA in 1982.

Epidemiology

Pancreatic Disease

Diabetes affects >190,000 (1 of 433) youth aged <20 years in the United States according to the 2009 SEARCH for Diabetes in Youth Study Group. The prevalence of DM increases with age and is slightly higher in females than males. Race analysis suggests that DM is most prevalent in non-Hispanic White and least prevalent in Asian/Pacific Islanders, with Native American and black youth having the highest prevalence of type 2 diabetes [85]. The incidence of type 1 and 2 DM in children and adolescents increased from 2001 to 2009 across the United States but the cause is unclear [86]. However, the increase in prevalence of obesity in American children has likely contributed to the increase in pediatric type 2 DM.

One third of adults with diabetes have diabetic retinopathy and up to 7 % have diabetic macular edema with increased prevalence associated with longer duration of diabetes, hyperglycemia, and hypertension [87].

Systemic Manifestations

Pancreatic Disease

Diabetes Mellitus initially presents with signs and symptoms of polyuria, polydypsia, polyphagia and weight loss. Type 2 patients are typically overweight and present with similar symptoms but it can be difficult to distinguish type 1 and type 2 initially. The systemic manifestations of DM depends on it's duration and control of hyperglycemia, hypertension and hyperlipidemia. Hyperglycemia in poorly controlled DM leads to microvascular disease of the brain, heart, kidneys, and peripheral vascular system. Significant morbidity and mortality is associated with diabetic microvascular disease which may result in stroke, renal failure, myocardial infarction, lower limb amputations and death. Diabetics under treatment may experience episodes of hypoglycemia due to medication dosing errors, exercise, fasting and present with signs and symptoms of confusion, pallor, sweating, tremor, headache, hunger and tachycardia.

Ophthalmic Manifestations

Pancreatic Disease

Anterior segment complications of DM include diabetic keratopathy and cataracts. Diabetic keratopathy results in recurrent erosions, poor wound heeling and cornea ulcers. Posterior subcapsular cataracts can be seen in children with diabetes and present with reduced visual acuity. Transient refractive changes (hyperopic or myopic shift) due to hyperglycemia may result in subjective complaints of blurred vision.

Non-proliferative diabetic retinopathy results from microvascular changes to the retina. Funduscopic examination reveals retina hemorrhages, micro-aneurysms, cotton wool spots, intraretinal microvascular anomalies (IRMA), venous beading and hard exudates. Progression of diabetic retinopathy often occurs during puberty. Proliferative diabetic retinopathy (PDR) is associated with neovascularization of the retina, optic disc (NVD), peripheral retina elsewhere (NVE) and iris (NVI). Vascular Endothelial Growth Factor (VEGF) production in response to retina ischemia is responsible for neovascularization and increased vascular permeability. Epiretinal membrane formation and tractional retinal detachment are late sequela of PDR and often lead to severe vision loss and blindness.

Diabetic macular edema (DME) is caused by fluid and lipid extravasation by retina vessels within the macula. Macular edema typically presents with reduced vision. DME may coexist with proliferative retinopathy as well.

Neovascularization of the iris often causes increased intraocular pressure and neovascular glaucoma. Patients with neovascular glaucoma may have symptoms of ocular pain and vision reduction depending how quickly the intraocular pressure rises and the duration of high pressure. Optic nerve cupping and peripheral vision field loss may be present on examination.

Risk factors associated with diabetic retinopathy include duration of diabetes, nephropathy, hypertension and hyperglycemia [88–90].

Diagnosis

Pancreatic Disease

The American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus includes any of the following: fasting plasma glucose ≥ 126 mg/dL (7 mmol/L) (no caloric intake for ≥8 h), random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia, 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test.

Early detection of diabetic eye complications through screening programs and appropriate referral to an eye care provider knowledgeable in diabetic eye disease is essential. Screening guidelines for diabetic retinopathy have been published by the American Academy of Pediatrics (AAP), [91] the American Academy of Ophthalmology (AAO), [92] and the American Diabetes Association (ADA) [93]. The AAO recommends annual screening beginning 5 years after the onset of diabetes. The ADA recommends annual screening beginning 3–5 years after diagnosis of diabetes once the patient is 10 years or older. The AAP recommends an initial examination 3–5 years after diagnosis if older than 9 years, with annual follow-ups thereafter. Telemedicine may facilitate screening children with diabetes for retinopathy in the future. Nonmydriatic cameras have been reported to successfully screen for diabetic eye disease in children as young as 2 years old [94]. Despite screening programs and published guidelines, compliance with eye examinations by patients and physicians remains poor [95].

Identification of ocular complications secondary to diabetes begins with checking the visual acuity and refraction. Slit lamp examination can identify keratopathy, neovascularization of the iris and cataracts. A dilated retina examination is necessary to visualize diabetic macular edema and retinopathy. Optical coherence tomography (OCT) and fluorescein angiography are useful tools to confirm the presence of macular edema and proliferative retinopathy respectively. Neovascular glaucoma is diagnosed by the presence of increased intraocular pressure, neovascularization of the iris, and signs of optic nerve cupping. Peripheral vision loss associated with glaucoma may be detected by checking automated visual fields. Children tend to be cooperative enough to perform visual field tests around the age of 8–10 years old.

Management

Pancreatic Disease

Control of hyperglycemia and reduction of HBA1c reduces the rate of diabetic retinopathy development and progression. The Diabetes Control and Complications Trial (DCCT), [96] demonstrated a substantial decrease in the risk of progression of retinopathy with increased glycemic control. Treatment of proliferative diabetic retinopathy and macular edema with panretinal laser photocoagulation and focal laser respectively reduces vision loss [97, 98]. Other interventions to treat diabetic proliferative retinopathy and macular edema include intravitreal steroid and anti-VEGF injections, but pediatric safety and efficacy studies are necessary.

Ocular Manifestations of Adrenal Gland Disease

Introduction

Adrenal abnormalities may result from excess or deficient adrenal hormones. Excess cortisol may be caused by ACTH producing pituitary tumors (Cushing disease) or ACTH-independent causes such as adrenal tumors or iatrogenic Cushing syndrome. Pheochromocytomas and paragangliomas are catecholamine producing tumors that arise from the adrenal medulla or sympathetic ganglia. Numerous hereditary syndromes are associated with pheochromocytoma including: MEN and von Hippel-Lindau disease. Neuroblastoma is a malignant tumor derived from embryonal cells of sympathetic nervous system seen almost exclusively in children. Neuroblastomas may be located in the adrenal gland and have the capacity to synthesize and secrete catecholamines. There are many causes of adrenal insufficiency, including adrenoleukodystrophy which also has significant visual dysfunction.

Definition

Adrenal Gland Disease

The adrenal gland is made of two parts, the cortex and medulla. The adrenal cortex produces three categories of hormones: mineralocorticoids, glucocorticoids, and adrenal androgens. The adrenal medulla synthesizes and secretes catecholamines. The pituitary gland controls glucocorticoid production via adrenocorticotropic hormone (ACTH). The renin-angiotensin system controls mineralocorticoid release.

Cushing Syndrome describes any form of glucocorticoid excess. Cushing Disease defines hypercortisolism due to pituitary overproduction of ACTH.

History

Adrenal Gland Disease

The discovery of the adrenal glands is somewhat controversial. Batholemeus Eustachius, an anatomist at the Collegio della Sapienza in Rome, was the first to describe the anatomic details of the adrenal glands in 1552. Baron George Cuvier, a French zoologist, described the difference between the cortex and the medulla of the adrenal gland in 1805. The function of the adrenal glands remained a matter of debate until 1855, when Thomas Addison of Guy's Hospital, London published a monograph where he described the findings of 11 patients with destruction of both adrenal glands. His series of patients all had "anemia, debility, feebleness of the heart, irritability of the stomach, and peculiar changes of the color in the skin." Armand Trousseau, an internist from Paris, proposed the name Addison's disease after he cared for a patient with tuberculosis involving the sympathetic ganglia and similar findings as described by Dr Addison. Adrenaline was identified in the late nineteenth century by two English physiologists, George Oliver and Edward Sharpey-Schafer. In 1886 Felix Frankel was the first to describe a patient with a pheochromocytoma in the adrenal medulla at autopsy. Harvey Cushing described the clinical features of hypercortisolism in 1912. The 1950 Nobel Prize for Physiology and Medicine was awarded jointly to Edward Calvin Kendall, Tadeus Reichstein and Philip Showalter Hench for their description of the structure and function of adrenal cortex hormones.

Epidemiology

Adrenal Gland Disease

Except for iatrogenic Cushing syndrome, this disease is rare in the pediatric population. Endogenous Cushing syndrome has an incidence estimated at 0.7–2.4/million/year in general population but is more common in adults than children [99]. The incidence of pheochromocytomas and paragangliomas is 0.3/million/year with approximately 10–20 % diagnosed during childhood [100]. Neuroblastoma has an incidence 1/100,000 children in United State[s] and accounts for 8 % of all tumors in children <15 years old and 15 % of pediatric cancer deaths [101]. Children with Neuroblastoma present with symptoms of metastases in approximately 50 % of cases and with Opsoclonus Myoclonus Syndrome in about 2–4 % of cases. X-linked adrenoleukodystrophy (X-ALD), caused by mutations in the ABCD1 gene resulting in defective peroxisomal transmembrane transport of very long-chain fatty acids is the most common peroxisomal disorder. Males typically present in early childhood whereas females may present in adulthood. The estimated population frequency of hemizygotes for X-linked adrenoleukodystrophy (ALD) is 1 in 42,000 [102].

Systemic Manifestations

Adrenal Gland Disease

Cushing syndrome manifestations are a result of inappropriately high levels of glucocorticoids, also termed hypercortisolism. Symptoms may include irritability, difficulty sleeping, depression, weight gain, irregular menses and changes in appetite. Examination may reveal hypertension, weight gain with reduced growth velocity, short stature, facial plethora (moon facies), dorsal cervical fat pad (buffalo hump), obesity, precocious puberty or delayed puberty, hirsutism, proximal muscle wasting, osteoporosis, purple skin striae and ecchymosis.

Pheochromocytoma is a catecholamine producing tumor of the adrenal medulla. Patients may be asymptomatic or present with episodic headaches, sweating, palpitations, tremor, anxiety, polydypsia, polyuria and weight loss. An adrenal mass may be an incidental finding on abdominal imaging. Pheochromocytoma may be sporadic or familial, therefore systemic manifestations vary based on the presence or absence of an associated syndrome. Hereditary syndromes associated with pheochromocytoma include multiple endocrine neoplasia syndrome (MEN) IIa and IIb, Von Hippel-Lindau syndrome (VHLS) and Neurofibromatosis-1 (NF-1). MEN IIa is associated with medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism. MEN IIb is associated with medullary thyroid carcinoma, pheochromocytoma, ganglioneuromatosis and Marfan like phenotype. Von Hippel-Lindau syndrome is associated with hemangioblastomas that can affect multiple organs including the retina, brain and spinal cord. In addition to pheochromocytoma and clear cell renal carcinoma, VHL is associated with renal, pancreatic, endolymphatic sac tumors resulting in hearing loss and epididymal cystadenomas in males. Individuals with NF1 have variable systemic manifestations of the disease. Affected patients may have café au lait spots of the skin, Lisch nodules of the iris, optic pathway gliomas, axillary or inguinal freckling, multiple neurofibromas, CNS vascular abnormalities including moyamoya, scoliosis, long bone abnormalities, short stature, and delayed or precocious puberty.

Neuroblastoma arises from neural crest cells anywhere along the sympathetic nervous system including the adrenal gland. Signs and symptoms vary depending on the location and size of the tumor. Children commonly present with metastatic disease to the liver, bone, lymph nodes and orbit. Patients may present with nonspecific findings such as lethargy, irritability, abdominal distension, spinal cord compression, proptosis, and periorbital ecchymosis (raccoon eyes). Rarely a paraneoplastic process results in Opsoclonus Myoclonus Syndrome. The tumors usually produce catecholamines or catecholamine metabolites but only rarely cause symptoms of catecholamine excess

X-linked adrenoleukodystrophy (ALD) typically affects young boys resulting in progressive motor and cognitive decline due to CNS white matter degeneration. The diagnosis of ALD may prove challenging as the phenotype of ALD is variable in both males and females. Patients may present with adrenal insufficiency (Addison disease), hepatomegaly, spastic gait, hearing loss and behavior changes which can progress to dementia and death. Neonatal adrenoleukodystrophy results in severe infantile seizures.

Ophthalmic Manifestations

Adrenal Gland Disease

Cushing syndrome may present with ocular hypertension, open angle glaucoma, and posterior subcapsular cataracts. Hypertensive and diabetic retinopathy may be present if secondary hypertension and type 2 diabetes develop as a result of hypercortisolism.

Pheochromocytoma may present with bilateral papilledema [103], hypertensive retinopathy [104], and optic neuropathy [105]. Macular star formation associated with optic nerve edema similar in appearance to neuroretinitis has been reported [106].

Syndromic pheochromocytomas associated with MEN II b may present with ocular pain, enlarged cornea nerves and conjunctival neuromas on examination [107]. Ocular abnormalities associated with VHLS include the presence of retina hemangioblastomas or capillary angiomas, decreased retina thickness on ocular coherence tomography (OCT) and electroretinogram abnormalities [108]. NF-1 may present with Lisch nodules of the iris, optic pathway gliomas, cutaneous neurofibroma of the eyelid and sphenoid wing abnormalities. Orbital gliomas can progress and result in proptosis and blindness. Vision loss is associated with optic pathway gliomas is variable. Associated congenital glaucoma with NF-1 is rare.

Neuroblastoma may present with periorbital ecchymosis (raccoon eyes) due to orbital metastasis [109]. Opsoclonus is a paraneoplastic process resulting chaotic and random eye movements. Autoantibodies and lymphocytic infiltration may play a role in the development of Opsoclonus Myoclonus Syndrome in neuroblastoma [110].

X-linked adrenoleukodystrophy (ALD) presents with progressive vision loss due to optic atrophy and cortical visual impairment. Exotropia may be present as well.

Diagnosis

Adrenal Gland Disease

A history of symptoms and examination findings of Cushing syndrome should prompt the clinician to initiate a workup. The condition is suspected in children especially if they are noted to have weight gain with reduced growth velocity. A history of systemic glucocorticoid use, such as oral prednisone, should be elucidated. Blood pressure measurements are necessary to establish the presence of hypertension. Laboratory studies to investigate the possibility of Cushing syndrome include: midnight salivary cortisol levels, 24-h urine free cortisol levels, low dose dexamethasone suppression test and serum ACTH levels. Serum ACTH levels are elevated in the presence of a functional pituitary adenoma producing ACTH and are reduced if hypercortisolism is due to autonomous adrenal production. Identification of a pituitary adenoma as the cause of Cushing disease may be done via brain MRI or inferior petrosal sinus sampling [111].

Pheochromocytoma should be suspected in patients with labile or refractory hypertension or other signs or symptoms of excess catecholamines. Paroxysmal symptoms may make the diagnosis of pheochromocytoma challenging. Serum or urine tests for catecholamines and their metabolites (metanephrines) are sensitive.. Imaging of the abdomen will help identify abdominal masses due to pheochromocytoma. A complete family history is necessary to identify pheochromocytomas associated with genetic syndromes. Genetic testing to identify germline mutations may be warranted [112]. Genes implicated in syndromic forms of paragangliomas include: *VHL* gene (von Hippel-Lindau), *RET* gene MEN2), and *NF1* gene (Neurofibromatosis type 1), and ten novel genes for paragangliomas/pheochromocytomas: *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *TMEM127*, *MAX*, *EGLN1*, *HIF2A*, and *KIF1B* [113].

Neuroblastoma should be suspected in patients with, an abdominal mass and signs of systemic metastases. Diagnosis can be made via urine catecholamine testing, abdominal imaging revealing a mass in the adrenals or parasympathetic chain, and by tissue examination after tumor biopsy. Open or image guided needle biopsy appear to yield adequate tissue

sampling for diagnosis, risk classification and staging of neuroblastoma [114].

X-linked adrenoleukodystrophy (ALD) is diagnosed by elevated serum levels of very long-chain fatty acids, genetic testing to identify gene mutations of the *ABCD1gene* and shrinkage of white matter on CNS neuroimaging.

Management

Adrenal Gland Disease

Treatment of Cushing syndrome caused by a pituitary adenoma is primarily surgical. Pituitary transsphenoidal adenoma resection with adjunctive pituitary irradiation and medications, somatostatin analogues and pasireotide, may be necessary to control the disease [115]. Ophthalmic surgery may be necessary to address visually significant cataracts. Glaucoma may require topical medications and/or surgery to control intraocular pressure and prevent progression of glaucomatous optic neuropathy.

Pheochromocytoma is treated with surgical resection. Blood pressure should be controlled prior to surgery. Preoperative pharmacological blockade of catecholamine effects and synthesis is required. Pharmacological agents include α-adrenergic blocking agents (i.e., phenoxybenazmine, prazosin, doxazosin) followed by a β-adrenergic blockade (i.e., propranolol, atenolol). Additional agents including channel blockers (i.e., nicardipine, nifedipine) may be required to control BP. Oral and sublingual short-acting nifedipine are potentially dangerous in patients with hypertensive emergencies and are not recommend [116].

Neuroblastoma treatment is based on the stage/risk and consists of surgical resection, chemotherapy, radiation, myeloablative and immunotherapy [117].

Treatment of X-linked adrenoleukodystrophy (ALD) remains challenging. Bone marrow transplantation and stem cell therapy are the treatment of choice [118].

Ocular Manifestations of Gonadal Disease

Introduction

Genetic diseases with associated gonadal and ocular abnormalities include: Bardet Biedl, Turner and Klinefelter syndromes. There are 14 different gene mutations that cause BBS but the two most common accounting for nearly 50% of cases are mutations in the *BBS1* and *BBS10* genes. Klinefelter syndrome is a result of aneuploidy of the X chromosome. Affected males have at least one extra X chromosome (47, XXY) but may have more. Turner syndrome patients are females with one defective or absent X chromosome (45, X). Mosaicism can be seen in Turner syndrome.

Definition

Gonadal Disease

Hypogonadism results from insufficient or absent production of hormones from the testes in males and ovaries from females. Hypogonadism may be primary or central. Primary hypogonadism occurs when the ovaries or testes are abnormal and fail to produce sufficient hormones. Central hypogonadism occurs when there is an abnormality in the stimulation of the gonads by the hypothalamus or pituitary gland. Hypogonadism results in abnormalities in the development of secondary sexual characteristics and puberty in children.

History

Gonadal Disease

Bardet-Biedl syndrome (BBS) was first described by Laurence and Moon in 1866 and additional cases were described by Bardet and Biedl between 1920 and 1922 [119]. Henry Turner was the first to describe a series of patients with dwarfism and lack of sexual development in 1938 which later became known as Turner syndrome [120]. Klinefelter syndrome was described, as was the development of testosterone for the treatment of hypogonadism in males, in the 1940s [121].

Epidemiology

Gonadal Disease

Klinefelter and Turner syndromes are the most common causes of primary hypogonadism. Turner syndrome occurs in approximately 1 in 3000 births. Klinefelter syndrome has an incidence of 1 in every 500–1000 births. BBS has a prevalence of 1 in 140,000–1 in 160,000 newborns in North America and Europe.

Systemic Manifestations

Gonadal Disease

Bardet Biedl syndrome (BBS) is an autosomal recessive disease with heterogeneous phenotypic manifestations. Individuals typically have retinal dystrophy, hypogonadism, obesity, polydactyly, renal disease, behavior abnormalities and cognitive delays. Other manifestations may include diabetes mellitus and short stature. Laurence Moon syndrome is similar to Bardet Biedl syndrome but has progressive

spastic paraparesis and distal muscle weakness without polydactyly [122].

Females with Turner syndrome have short stature, ovarian dysgenesis and congenital left-sided heart defects. Delayed puberty, primary and secondary amenorrhea along with short stature should alert the clinician to the possibility of Turner syndrome. Additional features of Turner syndrome include webbed neck, low hairline and hand/feet edema. Skeletal and structural renal abnormalities may be present as well.

Male children and adolescents with Klinefelter syndrome have small testes, gynecomastia, delayed or incomplete puberty, central obesity, learning disabilities and behavior problems.

Ophthalmic Manifestations

Gonadal Disease

BBS is a ciliopathy that primarily affects photoreceptors within the retina and results in the development of rod-cone retinal dystrophy. Individuals typically become symptomatic with night blindness and constricted visual fields within the first decade of life. Reduction of visual acuity is severe and usually results in legal blindness in the second decade of life [123]. Ophthalmic examination of the retina reveals a phenotypic appearance similar to retinitis pigmentosa with peripheral retina "bone spicule" pigment clumping. Other ocular abnormalities include myopia, strabismus and cataracts.

Patients with Turner syndrome may have strabismus, red-green color vision deficiency and strabismus. Myopia and hyperopia occur in Turner syndrome more frequently than the general population [124]. Eyelid and orbit abnormalities include epicanthus, ptosis and hypertelorism. There have been reports in the literature of anterior segment dysgenesis, glaucoma and Axenfeld-Rieger [125].

Ocular abnormalities seen in Klinefelter syndrome are relatively rare but include refractive errors, strabismus, cataracts, microphthalmia and colobomatous malformations of the iris, choroid and optic nerve [126]. Glaucoma has been reported in juveniles and adults with Klinefelter syndrome [127].

Diagnosis

Gonadal Disease

Phenotypic abnormalities can guide the clinician towards targeted genetic testing for BBS. Genetic testing can identify known gene mutations but an underlying genetic mutation may not be identified in every cases. Electrophysiologic testing of the retina via an electroretinogram can identify retina dysfunction consistent with a rod-cone dystrophy. Electroretinogram results typically reveal non-detectable rod more than cone responses [128]. Visual field testing can identify peripheral visual field constriction but may be difficult to perform in patients with cognitive delays.

Turner syndrome is definitively diagnosed by karyotype. Cardiac abnormalities should be investigated with an electrocardiogram and echocardiogram. Renal ultrasonography can identify structural renal abnormalities.

Klinefelter syndrome should be suspected in boys or adolescent males with small testes, gynecomastia, delayed or incomplete puberty, central obesity, learning disabilities and behavior problems. Karyotype will identify aneuploidy of the X chromosome. Elevated follicle-stimulating hormone and luteinizing hormone and low to normal testosterone levels support the diagnosis of primary hypogonadism.

Management

Gonadal Disease

Patients with BBS may need hormonal replacement for hypogonadism, weight management through diet and exercise for obesity and low vision services for legal blindness. Co-morbidities secondary to obesity including hypertension, diabetes mellitus and hypercholesterolemia should be screened for and treated medically.

Management of Turner syndrome involves growth hormone supplementation for short stature and ovarian hormone replacement. Treatment of Klinefelter syndrome with testosterone replacement therapy is not recommended in prepubertal boys except for the treatment of microphallus. Testosterone replacement therapy is usually initiated in the peripubertal age range and continued into adulthood to prevent secondary disorders including osteoporosis, metabolic syndrome and type 2 diabetes.

Routine eye examinations are recommended for patients with Bardet Biedl (BBS) and Turner syndromes. Low vision services are necessary for individuals with BBS. Correction of refractive errors, surgical management of strabismus and screening for glaucoma in the presence of anterior segment abnormalities are recommended for patients with Turner syndrome. Ocular abnormalities are rare in Klinefelter syndrome but a baseline ophthalmic examination should be considered to rule out potentially sight threatening conditions including glaucoma.

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Ocular Manifestations of Gastrointestinal Disease

10

James E. Elder and Winita Hardikar

Introduction

There are numerous immune-mediated disorders that affect both the gastrointestinal and visual systems and numerous genetic disorders that have both gastrointestinal and ocular features. Ophthalmic assessment may help to establish a gastrointestinal diagnosis.

This chapter reviews the ocular manifestations of liver, intestinal and pancreatic disorders in children. Wilson disease is discussed in the chapter on the Ocular Manifestations of Metabolic Disorders.

Liver Disease

All pediatric liver diseases are rare and require an extensive work up to identify the etiology. The overall incidence of liver disease in infants is thought to be one in 2500 live births. Many pediatric liver diseases have characteristic or supportive ocular manifestations and hence the ophthalmologist is often called upon to assist in the diagnostic workup as well as ongoing management of these conditions.

Children with liver disease may present with any of the following clinical or biochemical features: jaundice, hepatomegaly, splenomegaly, pale stools, coagulopathy, abnormal liver function tests. Spider nevi are seen when liver disease has been chronic, which is considered greater than 6 months duration. Children may also present simply with aberrant liver function tests and no clinical features.

As late 1970, 65 % of children with liver disease were described as 'idiopathic' neonatal hepatitis. In the last 20 years, there has been a significant expansion in the identification and characterisation of disease entities including bile acid transport disorders, disorders of structural proteins in the biliary tree and hepatocytes as well as metabolic and mitochondrial diseases. At present, the majority of disorders in infants can be diagnosed with the idiopathic component now being 15 % [1].

Investigation of liver disease in children follows a common diagnostic algorithm depending on the presentation of the patient and whether liver functions tests show the predominant pattern to be that of hepatocellular injury or obstruction of the biliary tree. The diagnostic work up is tiered according to the most likely diagnoses from a clinical point of view and those which require urgent treatment. Diagnosis requires a combination of biochemical, haematological and metabolic testing. Common investigations include include viral serology (hepatitis A, hepatitis B, hepatitis C, Epstein- Barr virus and cytomegalovirus), autoantibodies (ANA, SMA, LKM), alpha-1 antitrypsin and Pi type, iron studies, serum copper and ceruloplasmin. Other investigations may urine metabolic screen, serum and urine amino and organic acids, alpha fetoprotein, and urine succinyl acetone. In the setting of acute liver failure, a urine drug screen, serum paracetamol level and other testing may be required. Liver biopsy is a key diagnostic modality with the sample being subjected to histology including special stains, electron microscopy and frozen sample obtained for enzyme or DNA analysis where required. Imaging of the liver and biliary tree by means of ultrasound, MRI and CT scan may be required. Systemic investigations looking for ocular, neurological, cardiac, renal and bony manifestations are often performed. Management is disease specific.

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Alagille Syndrome

Definition

Alagille syndrome is an autosomal dominant multisystem disorder characterised by liver, heart, skeleton, eye, kidney and central nervous system abnormalities [2]. It was originally recognised as a cause of neonatal conjugated hyperbilirubinemia secondary to a paucity of intrahepatic bile ducts in association with congenital heart disease [3–5]. This association gave rise to the alternative name of arteriohepatic dysplasia [5]. It is now known to be the result of abnormalities in the NOTCH signalling pathway, which has a major role in angiogenesis [2]. Mutations or deletion of the *JAG1* (OMIM 601920, 20p12.2) gene or mutation in the *NOTCH2* (OMIM 610205, 1p12-p11) gene are believed to give rise to almost all cases [2, 6].

History

While jaundice was probably noted in infants for centuries, one of the earliest scientific studies was by Jean Baptiste Baumes in 1785, following the course of ten babies with jaundice [7]. Most of the individual diagnoses remained elusive apart from biliary atresia first described in 1817 by Professor John Burns [8]. Daniel Alagille's first description appeared in the French literature in 1969 with his first publication in English appearing in 1975 [4]. He drew attention to the association of neonatal jaundice secondary to paucity of intrahepatic bile ducts, characteristic facial appearance, cardiac abnormalities consistent with pulmonary artery stenosis, vertebral arch defects, growth retardation, low IQ and hypogonadism [4]. Watson and Miller coined the term "arteriohepatic dyplasia" to describe a similar group of patients in 1973 and clearly delineated the associated pulmonary artery stenosis with angiography [5]. Ophthalmic abnormalities were first described by Riely et al. in 1979 [9]. There have been many subsequent publications confirming these observations and describing less frequent ophthalmic abnormalities [9–28].

Epidemiology

The estimated incidence of one in 70,000 births [29]. Given the heterogeneity in the clinical features of *JAG1* and *NOTCH2* mutations this may well be an underestimate [2]. Alagille syndrome appears to affect all population groups.

The proportion of patients with ophthalmic abnormalities varies between different reports Subramaniam et al. pooled data from 6 series [3, 30–34] with a total of 385 patients with Alagille syndrome [34]. Of these 320 had eye examinations with 234 having ophthalmic abnormalities being detected giving a weighted average of 73 %. The lowest percentage reported was 56 % [30] and the highest was 88 % [3]. Hingorani reported on a series of 22 children with Alagille syndrome who had a very detailed ophthalmic assessment and found 95 % had posterior embryotoxon [15].

Systemic Manifestations

Alagille syndrome is a highly variable condition as demonstrated by Guegan et al. who showed that 34 % of patients with one or two clinical characteristics of Alagille had a mutation in the *JAG1* gene and thus genetically had a confirmed diagnosis of Alagille while not fulfilling the clinical criteria for the diagnosis outlined above [35]. Many patients may be completely asymptomatic and the cause for this extreme variability in expression is unknown. A number or authors have reported a lack of genotyp-phenotype correlation with abnormalities in *JAG1* and *NOTCH2* [36, 37]. Severe pulmonary vascular disease or cerebral haemorrhage associated with vascular malformations may be life limiting [31, 38].

Hepatic

The typical hepatic features of Alagille syndrome are neonatal conjugated hyperbilirubinemia with a paucity of intrahepatic bile ducts being demonstrated on liver biopsy [3–5]. 95 % of children with Alagille syndrome will present with cholestasis prior to 3 months of age [31]. The percentage of affected individuals with paucity of intrahepatic bile ducts increases with age with 95 % showing this pathological feature by 6 months of age [2]. A small number of children with Alagille syndrome do not have liver disease [39, 40]. It is estimated that 15 % eventually require liver transplantation [31].

Cardiac

Over 90 % of patients with Alagille syndrome have a cardiac anomaly [37]. The most common cardiac abnormality is peripheral pulmnonary artery stenosis affecting two thirds of affected individuals [31, 37]. Other reported cardiac abnormalities are tetralogy of Fallot, ventricular septal defect, atrial septal defect, aortic stenosis, and coarctation of the aorta, and hypoplastic left heart [31, 37, 41]. It is suggested that the presence of complex congenital heart disease in children with Alagille syndrome is indicator of risk of early death [2]. Mutations in *JAG1* may cause isolated congential heart disease without liver disease [40].

Skeletal

Failure of fusion of the anterior vertebral arches gives rise to the "butterfly" vertebral anomaly seen in Alagille syndrome [2]. This was identified in the initial reports describing Alagille syndrome [3–5] and is present in at least 80 % of patients with the syndrome [42]. Abnormalities in vertebral body segmentation are seen in a wide variety of disorders [43] and are remarkable for the relative symmetry in Alagille syndrome [2]. A number of other abnormalities of the axial skeleton have been reported [44, 45]. Unicoronal craniosynostosis has been described in two children with Alagille syndrome due to *JAG1* mutation with no mutations being detected in *FGFR1* (OMIM 136350, 8p11.23-p11.22), *FGFR2* (OMIM 176943, 10q26.13), *FGFR3* (OMIM

134934, 4p16.3) or *TWIST1* (OMIM 601622, 7p21.1) genes [46]. A further child with Alagille syndrome with scaphocephaly related to premature fusion of the sagittal and lamboid sutures has been reported [47]. Animal studies have suggested that *JAG1* may have a role downstream from *TWIST1* in coronal suture formation [48]. Other non-axial skeletal abnormalities including radioulnar synostosis [49] and fusiform distal phalanges [2] and supernumerary digital flexion creases [50] have been described. Long bone fractures related to poor nutrition occur in some more severely affected children with Alagille syndrome [32, 33, 51]. There is evidence of reduced bone mass in children with Alagille syndrome [52].

Facial

Krantz et al. described the characteristic facial appearance as "…prominent forehead, deep-set eyes with moderate hypertelorism, pointed chin, and saddle or straight nose with a bulbous tip. The combination of these features gives the face a triangular appearance" [53]. It has been argued that this appearance is a specific consequence of childhood cholestasis [54]. More recent analysis by Kamath et al. suggested that the facial appearance is specific to Alagille syndrome and is useful in the diagnosis [55]. The facial appearance may be significantly influenced by the degree to which the eyes are deep-set [2].

Renal

Kamath et al. have reviewed the renal involvement in Alagille syndrome and suggest that renal abnormalities are seen in 40 % of individuals with *JAG1* mutations [36]. Renal failure is common in cases of end-stage liver failure. Renal dysplasia, proteinuria, tubular acidosis and renal vascular hypertension are all reported in cases of Alagille syndrome [36]. *JAG1* and *NOTCH2* have significant roles in nephron formation [36].

Central Nervous System Abnormalities

Idiopathic intracranial hypertension [19, 20] and Moyamoya disease [10, 24, 56, 57] have been described in association with Alagille syndrome. In the cases reported by Narula et al. benign intracranial hypertension was associated with papilledema and had a successful treatment outcome in three cases [20]. Two of these children were post-liver transplantation and one of the three required lumboperitoneal shunt in addition to medical treatment. In a fourth case they reported a child with optic atrophy and visual loss they believe was related to undiagnosed idiopathic intracranial hypertension [20]. Mouzaki et al. reported two cases of idiopathic intracranial hypertension with documented raised intracranial pressure and good outcome with medical treatment with acetazolamide [19]. Elevated levels of serum vitamin A has been described in adults with idiopathic intracranial hypertension [58]. The two children reported by Mouzaki et al. had modestly elevated serum vitamin A and the authors believe this may have contributed to their idiopathic intracranial hypertension [19]. Yilmaz et al. reported papilledema in a child with Alagille syndrome and Chiari malformation believed to be secondary to craniosynostosis of the sagittal and lamboid sutures [47].

Pancreatic

Deficiency of pancreatic enzyme production has been reported and is thought to contribute to steatorrhea and failure to thrive in children with Alagille syndrome [59]. Pancreatic enzyme replacement therapy was noted to be of benefit in some of these children. There is a single case report of diabetes mellitus in association with Alagille syndrome that was believed to be the result of pancreatic atrophy [60].

Growth

Growth retardation and short stature are well recognized in Alagille syndrome [61, 62]. Malabsorption is considered to be the main cause [62] but hypothyroidism [62] and growth hormone insensitivity may contribute [63].

Ophthalmic Manifestations

Vision

Visual acuity is usually normal in individuals with Alagille syndrome [15]. Infrequently reduced vision is reported and is most commonly associated with retinal pathology, optic nerve abnormality or CNS lesions. Strabismus has rarely been reported [9, 15, 22, 25] and may be associated with amblyopia [15]. Significant refractive error has been described [15, 22, 25, 26]. Visual field defects have been reported in association with retinal pathology [22, 26] and the CNS consequences of associated Moyamoya syndrome [10]. Baird et al. described a 2 year old boy with Alagille and Moyamoya syndromes who suffered a posterior cerebral artery stroke and has a residual (unspecified) field defect [10]. It has been suggested that Moyamoya syndrome in association with Alagille syndrome may be part of a common or synergistic vasculopathic process [24, 56].

Anterior Segment

Since the association between posterior embryotoxon and Alagille syndrome was first described in 1979 [9] it has been reported in virtually all series of patients with Alagille syndrome. Posterior embryotoxon is seen in the in 6–32 % of the normal population [64]. It is a thickened and visible Schwalbe's line which is the junction of the uveal meshwork and Descemet's membrane [65]. Some authors suggest it may only be visible on gonioscopy [66]. It may be associated with iris processes (previously known as Axenfeld anomaly) [9, 15, 22, 25, 26, 31] and less frequently corectopia [12, 15, 25, 67]

which suggests an overlap with Axenfeld-Rieger spectrum. The iris processes may be better seen on gonioscopy. The proportion of patients who have posterior embryotoxon has been reported to vary between 58 % [30] and 95 % [15] and reflects the variability of expression in Alagille syndrome and possibly how carefully the abnormality is sought on examination. Posterior embryotoxon has no impact on vision but remains an important clinical criterion for the diagnosis of Alagille syndrome in combination with neonatal jaundice [15].

Other corneal abnormalities are rarely described in association with Alagille syndrome. Microcornea [12, 15], keratoconus [23, 31, 68], band keratopathy [25], pannus [12, 25] and xerophthalmia [18] have all been reported. The child with keratoconus reported by Traboulsi et al. had no other ophthalmic features of Alagille syndrome and required penetrating keratoplasty at 14 years in one eye and 19 years in the other [68]. The visual results were not reported. The patient with xerophthamlia had a known diagnosis of Alagille and despite vitamin A supplementation developed keratomalcia and corneal ulceration requiring amniotic membrane grafting [18]. This child was described to having "a few retinal pigmentary changes" but development delay made it impossible to measure vision or determine if there was nyctalopia [18]. Microphthalmia [67] and reduced axial length [21, 28] have also been reported.

Shallowed anterior chambers have been described [28, 67] but glaucoma has not been reported. Heathcote et al. described a child with intrahepatic cholestasis, pulmonary stenosis and congenital glaucoma in 1976 but suggested that the child had congenital rubella and not Alagille syndrome [69].

Iris hypoplasia is relatively commonly described [12, 15, 22, 25, 28, 67]. On occasions there are very prominent iris trabeculae similar to that seen in William syndrome and there may be white dots reminiscent of Brushfield spots.

Cataracts have rarely been described [14, 15, 22]. Most are not visually significant [15, 22]. The case of Fukumoto is of interest as apparently uncomplicated cataract surgery in a 15 year old girl was followed by intraocular lens subluxation and then retinal detachment both of which were successfully treated [14]. It is not clear if these complications were in any way related to the underlying Alagille syndrome.

Retina and Choroid

Abnormalities in pigmentation of the retina and choroid in children with Alagille syndrome have been commonly described [9, 11, 12, 15, 20, 22, 23, 25, 26, 28, 31]. Any part of the retina can be affected and is most commonly a diffuse hypopigmentation [15]. Earlier reports generally described areas of alternating pigment clumping and hypopigmentation in the retinal periphery [9, 22]. It would appear that the pigment clumping in the retina increases with age. Wells et al. described pigmentary changes in seven affected individuals, five older than 10 years and two under 10 years old, with the pigment clumping being more severe in the older patients [28]. Hingorani et al. reported retinal findings in 21 children with diffuse hypopigmentation in 12/21 and no clear association with age [15]. In this series pigment clumping was seen in 8/21 with six being more than 10 years old. Discrete macular pigmentary disturbance had been described in children with Alagille syndrome [12, 15, 28]. This does not appear to be visually significant and is variously described as a reddish brown discoloration of the macula [12], retinal pigment epithelial clumping and yellow deposits [28] or speckling [15].

It has been suggested that the pigmentary changes may be related to hypovitaminosis A but investigations have not supported this [15, 28]. White spots are often described in the retina of individuals with nyctalopia secondary to hypovitaminosis A [70, 71] and these have only been described in one patient with Alagille syndrome who did not have systemic symptoms of hypovitaminosis A [15]. The case of xerophthalmia and Alagille syndrome reported by Moisseiev et al. did not have positive retinal findings [18].

Given the underlying mutation in genes of the NOTCH signalling pathway a localised retinal or choroidal vasculopathy may be in part responsible for the changes observed [2]. Pathological examination of the eyes of children with Alagille syndrome have shown abnormal accumulation of lipofuscin within the retina and this may indicate a metabolic abnormality directly contributing to the observed retinal changes [72].

Peripapillary choroidal atrophy and focal hypopigmentation has been described [11, 15, 22] and has been associated with progressive loss of vision in one case [11]. This individual was an adult with a mutation in the *JAG1* but had no liver disease who had two nephews with confirmed Alagille syndrome with no ophthalmic abnormality.

Choroidal folds are seen occasionally in adults with Alagille syndrome [12, 15, 25, 28] and have only been described in a child with Alagille syndrome once and this was only seen on fluorescein angiography [15].

Retinitis pigmentosa has been reported twice in children with Alagille syndrome [20, 31]. In the first case no further details or age provided [31]. In the second there was reduced visual acuity, diffuse loss of the retinal pigment epithelium and extinguished electroretinogram "consistent with a rod cone dystrophy" [20]. There is no discussion of the vitamin A status of this child. Tanino reported three siblings with marked chorioretinal degeneration, constricted visual field, variable reduction in visual acuity and reduced amplitude electroretinogram [26]. No description of vitamin or nutritional status or follow-up is given. Puklin et al. described an adult with pigmentary abnormality, constricted fields, maintained visual acuity, reduced amplitude electroretinogram "compatible, however, with rod and cone involvement" and normal vitamin A levels [22].

Pathological myopia has been reported [22, 25, 26] and in one case this was complicated by retinal detachment [22]. It is not clear if the myopia is etiologically related to the Alagille syndrome or is just coincidence. A further case of retinal detachment has been reported as a complication of cataract surgery [14] and is probably not related to the Alagille syndrome.

Retinal vascular abnormalities have been described and include abnormal branching [15], kinking [66] and tortuosity [15, 22, 25, 28]. Tortuosity is most often associated with optic disc anomalies such as buried drusen [15, 21, 22].

Optic Disc

Optic disc anomalies including hypoplasia [12, 21, 31], abnormalities of shape [15, 21], tilting [12], peripapillary crescent [12, 26], elevation [21, 22, 25, 28], papilledema [19, 20, 47] and atrophy [22] have been recognised in association with Alagille syndrome. Elevation and abnormal appearance are frequently related to buried drusen [15, 21]. Nischal and colleagues have demonstrated this is using ultrasound in at least one eye of 18/20 (90 %) of children with Alagille syndrome [21]. The pathophysiology of the association between Alagille syndrome and drusen is uncertain [21]. Optic nerve head drusen are thought to occur because of impaired axoplasmic flow and axonal degeneration at the optic nerve head [73] with a possible contribution of reduced scleral ring size [74]. Metabolic abnormalities secondary to impaired fat soluble vitamins [21], dilated optic nerve sheath associated with Alagille syndrome [28] and vasculopathy secondary to the underlying abnormality in the NOTCH signalling pathway may all contribute [2]. There is a single report of myelinated nerve fibres in a child with Alagille syndrome [27]. Optic pit has also been described once [13]. The significance of these associations is uncertain.

Diagnosis

The clinical diagnostic criteria for Alagille syndrome are the histologic finding of bile duct paucity and three of the following five characteristics; (a) cholestasis, (b) cardiac abnormality (most often peripheral pulmonary artery stenosis), (c) skeletal abnormality (most commonly butterfly vertebra), (d) ocular abnormality (most frequently posterior embryotoxon) and (e) typical facial features (prominent forehead, deep-set eyes, hypertelorism, pointed chin and saddle or straight nose with bulbous tip) [75]. Renal, neurovascular and pancreatic abnormalities are important characteristics is some patients with Alagille syndrome [2].

The diagnosis of Alagille's syndrome may be supported by investigations such as radiography of the spine and echocardiography. Liver biopsy may be utilised to demonstrate bile duct paucity but is no longer mandatory to make the diagnosis. Many of the diagnostic ophthalmic features of Alagille syndrome are readily elicited with standard clinical examination. Genetic testing is available and particularly useful where there are insufficient clinical features or to identify asymptomatic parents or siblings [35]. Mutation in *JAG1*, and less frequently in *NOTCH2* will confirm the diagnosis of Alagille syndrome in most cases [2, 75].

Management

Liver disease may present predominantly with pruritus. Several medical therapies including oral antihistamines, cholesterol binding resins, rifampicin and naltrexone are available. An orally administered ileal bile salt transport inhibitor is currently being trialled (Evaluation of LUM001 in the Reduction of Pruritus in Alagille Syndrome https://clinicaltrials.gov/ct2/show/NCT02057692). Biliary diversion surgery and nasobiliary drainage are also used to treat pruritus. Liver transplantation can be considered for chronic progressive cholestatic liver disease associated with malnutrition and liver failure seen in some patients. Liver disease is treatable by liver transplantation and has a good prognosis with an 87 % 1 year survival. Notably vascular renal and CNS complications are increased in patients with Alagille syndrome post-transplant compared to patients with biliary atresia [76].

Most of the ophthalmic manifestations of Alagille syndrome do not need specific intervention or are not amenable to any known treatment. General measures of correcting any refractive error and treating any amblyopia apply as usual. Infrequently cataract surgery may be required and given the report of subsequent intraocular lens subluxation [14] careful follow-up would be indicated. The literature suggests that idiopathic intracranial hypertension in association with Alagille syndrome can usually be managed medically with a successful outcome [19, 20].

Hepatitis Autoimmune Hepatitis

Definition

Autoimmune hepatitis involves severe inflammation of the liver with the presence of raised serum immunoglobulins and auto-antibodies [77]. Autoimmune hepatitis is divided into two types; type 1 occurs in adults and children and is characterised by antinuclear antibodies and/or smooth muscle antibodies and type 2 is more common in children and typically has liver and/or kidney antibodies [78].

History

Autoimmune hepatitis was first described by Waldenström in 1950 [79]. It was identified as a form of unremitting hepatitis more common in females [79] and was initially thought to be the result of chronic viral infection [80] before the loss of immune tolerance was recognised as a more likely etiology [81]. Earlier reports refer to autoimmune hepatitis as "chronic active hepatitis or active chronic hepatitis" [80].

Epidemiology

The precise epidemiology of autoimmune hepatitis in children remains uncertain [82]. A population study from New Zealand suggests incidence and prevalence were 1.7 and 18.9 per 100,000, respectively with less than 20 % being in the pediatric age range [83].

Systemic Manifestations

Three broad patterns of presentation are recognised with pediatric autoimmune hepatitis [82]. The first mimics the onset of infective hepatitis with non-specific symptoms of malaise, nausea/vomiting, anorexia, and abdominal pain, followed by jaundice, dark urine and pale stools with a small number progressing to fulminant liver failure [82]. The second is more insidious, with progressive fatigue, relapsing jaundice, headache, anorexia, amenorrhoea, and weight loss, lasting for several months to years [82]. The least common presentation is with signs of chronic liver disease such as upper gastrointestinal bleeding or hypersplenism [82]. The natural history can be fluctuating but most children will manifest evidence of chronic liver disease (such as spider naevi, palmar erythema, leukonychia, striae) and have a firm liver to palpation with splenomegaly [82].

Ophthalmic Manifestations

Uveitis

Panuveitis has been described twice in children with autoimmune hepatitis [84, 85]. Bloom et al. reported an 8 year old girl with chronic hepatitis (presumed to be autoimmune) who developed pan uveitis and a serous retinal detachment [84]. This responded to treatment with oral prednisolone and then azathioprine with one ocular relapse that settled with the reintroduction of oral prednisolone. Lim et al. described an 8 year old boy with autoimmune hepatitis who had raised intraocular pressure, vitritis and retinal vasculitis what was treated with topical and systemic corticosteroid, methotrexate and cyclosporine [85]. Despite this treatment the ocular disease was complicated further by cataract, glaucoma, peripheral anterior synechiae, hypotony, band keratopathy and phthisis bulbi (in one eye) with visual acuity at latest follow-up (9 years) of 20/63 and hand movements.

Orbital Involvement

Sires et al. reported a 13 year old boy who presented with a spontaneous orbital haemorrhage in the inferior rectus muscle who was subsequently found to have autoimmune hepatitis with clotting defects [86]. The orbital haemorrhage cleared spontaneously with oral prednisolone and vitamin K supplementation. A case of mild Grave's disease in association with autoimmune hepatitis and nonocular myasthenia gravis in a 13 year old girl has been reported [87].

Diagnosis

The International Autoimmune Hepatitis Group published a scoring system for autoimmune hepatitis in the 1990s and this continues to be used clinically [79]. The diagnostic work-up is complex and often involves liver and kidney biopsy in addition to more routine laboratory tests of liver function and circulating antibodies. The scoring system incorporates a number of parameters of clinical, immunologic, pathologic findings and treatment response to derive a numerical score and determine the likely diagnosis. Detailed discussion of this is beyond the scope of this text and further details are available in Liberal et al. [79].

Management

Autoimmune hepatitis is usually responsive to steroid treatment and most patients will require long term immunosuppression with at least one medication [88]. In cases of fulminate liver failure or severe chronic liver failure liver transplantation may be required (estimated to be 10 % of children with autoimmune hepatitis) [82]. The ocular manifestations usually respond to similar immunosuppressive treatments [84–86].

Hepatitis A

Definition

Hepatitis A is caused by a picornavirus (RNA virus) and is a faecal-orally transmitted viral infection which is usually self-limiting [89, 90].

History

The illness we now know is hepatitis A infection was recognised in ancient Greece and Rome and in the older literature was referred to as "catarrhal jaundice" [91]. A viral etiology was acknowledged in the 1930s [91] with the viral particle finally being identified in the 1970s [92].

Epidemiology

In high income countries where vaccination for hepatitis A is routine the rate of infection is now extremely low [89]. Endemic hepatitis A remains common in some parts of south Asia and sub-Saharan Africa [93].

Systemic Manifestations

Sporadic, endemic and epidemic hepatitis A infections are recognised. There is an incubation period of 15–30 days followed by nonspecific symptoms and then gastrointestinal symptoms of anorexia, nausea, vomiting and abdominal pain with the subsequent development of dark urine and jaundice. The jaundice lasts a variable length of time and is often accompanied by tender heapatomegaly and splenomegaly.

Most infected individuals recover spontaneously and perhaps as many as 10–15 % do not develop jaundice. A small number develop acute liver failure. The mortality for hospitalised cases of hepatitis A is estimated to be less than 1.5 % [91].

Ophthalmic Manifestations

Varona et al. described a 15 year old girl with the acute onset of unilateral oculomotor (pupil sparing) and facial nerve palsy who soon afterward developed hepatitis A with severe and transient liver failure [94]. The cranial nerve palsies resolved as her hepatitis settled. Jouhadi et al. reported the case of an 8 year old girl who developed Devic's disease with bilateral optic neuritis and transverse myelitis secondary to presumed hepatitis A infection [95]. Serological testing was positive for IgM for hepatitis A and no other infections. Visual acuity was reduced to count fingers bilaterally and recovered completely following treatment with intravenous methylprednisolone followed by oral corticosteroid. There was only partial recovery of spinal cord function with persistence of lower limb paralysis [95].

Diagnosis

Hepatitis A infection is confirmed by positive serology [91]. There is a variable abnormality of liver function tests and the virus can be recovered from the stool of infected individuals [91].

Management

No specific management is required for the majority of cases of hepatitis A infection [91]. The management of the fulminant liver failure depends on the severity and the availability of liver transplantation.

Hepatitis B

Definition

Hepatitis B is caused by hepadnavirus (a DNA virus) and is spread parenterally either percutaneously, sexually or perinatally [96]. Hepatitis B infection is a major cause of cirrhosis, liver failure and hepatocellular carcinoma worldwide [96].

History

The hepatitis B virus (HBV) was the first of the hepatitis viruses to be identified [97, 98]. Baruch Blumberg and others had hypothesised that individuals who had received multiple transfusions would express antibodies to proteins that originated from the blood donor and in 1960 were able to demonstrate this [99]. Using this technique he then discovered an antigen in the serum in an indigenous Australian (later called the Australia antigen) that was also found in individuals with a history of leukemia. The connection with hepatitis was finally made when a child was noted to become Australia antigen positive at the same time as developing evidence of hepatitis and ultimately this lead to the identification of the hepatitis B virus [99]. This sequence of events lead Blumberg to state in his Nobel Prize lecture; "This experience does not encourage an approach to basic research that is based exclusively on specific-goal-directed programs for the solution of biologic problems" [99].

Epidemiology

Hepatitis B is a significant cause of liver disease worldwide in adults and children. In countries where vaccination is not given at birth, the main source of transmission is perinatal and results in chronic infection in 90 % of infants [89]. In developed countries most infection is via sexual transmission, intravenous drug use or occupational exposure [98]. Globally it is estimated 3.6 % of the population is seropositive for hepatitis B with rate varying from 0.2 % in Mexico to 22.4 % in South Sudan [100].

Systemic Manifestations

Hepatitis B is predominantly a liver disease which follows four phases according to the interaction between the virus and the host immune system. In perinatally acquired disease, there is a predominance of viral replication with almost no host immune response. HBV DNA levels are very high and liver function tests are normal. This is known as the immunotolerant phase and may last for 2–3 decades. Activation of the host immune response together with a reduction in viral antigens is associated with liver inflammation and abnormal liver function tests and is known as the immune clearance phase. This usually results in loss of e antigen and development of e antibody, a process known as seroconversion and is associated with low viral loads and less inflammatory activity known as the immune control phase. The emergence of an e antigen negative viral population or immune escape phase once again causes liver inflammation, abnormal liver function tests and is known as e antigen negative hepatitis. Chronic hepatitis B is associated with a risk of cirrhosis in up to 20–40 % of patients and hepatocellular cancer [101].

Several extrahepatic manifestations of acute and chronic hepatitis B have also been described. These are uncommon and thought to be immune mediated in etiology. They include a serum-sickness like syndrome, glomerulonephritis, polyarteritis nodosa, cryoglobulinemia, Guillian Barre syndrome and various dermatological manifestations [102].

Ophthalmic Manifestations

Kwon et al. reported the case of a 15 year old boy with hepatitis B that developed open angle glaucoma while being treated with interferon alpha [103]. The intraocular pressure returned to normal off all glaucoma treatment once the interferon was discontinued.

Table 10.1 Diagnosis of hepatitis B

	Interpretation	HBsAg	Anti HBs	HBeAg	Anti HBe	Anti HBc	HBV DNA
Stage of HBV infection	Acute HBV	+	–	+	–	IgM	+
	Chronic HBV						
	• Immunotolerant	+	–	+	–	IgG	>20,000 IU/mL
	• Immune clearance	+	–	+	–	IgG/IgM	2000–20,000 IU/mL
	• Reactivation/Flare	+	–	+/–	–	IgM	>20,000 IU/mL
	• HBeAg (–) chronic HBV	+	–	–	+	IgG	>20,000 IU/mL
	• Inactive disease	+	–	–	+	IgG	<2000 IU/mL
	Resolved past infection	–	+	–	–	IgG	–
	Vaccinated	–	+	–	–	–	–

Diagnosis

Diagnosis of the presence of hepatitis B infection and its phase is based on a series of blood tests which detect parts of the virus and the host immune response. The various markers and their interpretation are summarised in Table 10.1.

Management

The best management strategy for hepatitis B is prevention by vaccination at birth of all children, but particularly those born to hepatitis B infected mothers.

Once hepatitis infection has occurred treatment depends on the stage of the infection and the presence and severity of liver disease and or hepatocellular cancer. Viral replication can be suppressed with a number of new potent nucleoside analogues with high barriers to viral resistance. Unfortunately treatment is required long term with eventual development of resistance and treatment paradigms including response guided therapy are still under evaluation. Pegylated Interferon is also used as an alternative therapy with a limited duration of treatment, no resistance but a significant side effect profile.

Viral eradication is not yet achievable with current treatments, so the goals of therapy are to prevent serious liver disease including cirrhosis and hepatocellular cancer [101].

Hepatitis C

Definition

Hepatitis C is a flavivirus (RNA virus) and causes a blood borne viral infection which may progress to chronic liver disease, cirrhosis and hepatocellular cancer [104]. Now oral treatment regimens which achieve a 90 % clearance are available [89].

History

Hepatitis following blood transfusion was a major problem before screening became possible in the 1970s for hepatitis A and B [104]. Following this transfusion hepatitis persisted and was referred to as "non A and non B hepatitis" until the discovery of the hepatitis C virus (HCV) in 1989 [105].

Epidemiology

Hepatitis C infection is often asymptomatic and thus precise estimates of incidence and prevalence are difficult. The WHO estimates that 3 % of the world population has been infected with hepatitis C and there are 170,000,000 chronic carriers of the infection that are at risk of cirrhosis and liver cancer [104].

Systemic Manifestations

Hepatitis C causes a chronic hepatitis which can lead to cirrhosis and hepatocellular cancer. The exact rate of progression depends on other comorbid factors such as alcohol, iron deposition, fatty liver disease and other concomitant hepatitis virus infection e.g. hepatitis B.

In addition hepatitis C is associated with a number of extrahepatic manifestations including mixed cryoglobulinemia, porphyria cutanea tarda, thyroid disease and polyarteritis [106].

Ophthalmic Manifestations

Ertekin and Tan reported a 9 year old boy who presented with opsiclonus-myoclonus syndrome and on subsequent investigation was found to have hepatitis C with no evidence of neuroblastoma nor encephalitis [107]. He responded to treatment with clonazepam with resolution of the opsoclonus and myoclonus. The etiology of opsiclonus-myoclonus is uncertain but thought to be immune mediated [108, 109] and this is presumed to be the case with the extra-hepatic manifestations of hepatitis C infection [110].

Diagnosis

The presence of HCV RNA in the blood implies HCV infection. Serum HCV antibody implies exposure to HCV virus but cannot distinguish between current or past infection and hence is used as a screening test.

Management

The management of hepatitis C infection has undergone a paradigm shift in the last 5–10 years with the development of all oral pangenotypic regimens which can eradicate the virus.

The duration and type of treatment depend on the virus genotype. At present the cost of these treatments are very high and hence their availability may be restricted to those with the most severe disease until they become more affordable [111].

Hepatitis E

Definition

Hepatitis E is a faecal-oral transmitted viral infection [89] caused by a hepevirus (RNA virus) which has a very varied clinical spectrum from asymptomatic infection or clinical hepatitis to liver failure with a high mortality rate in pregnant women and immune-compromised patients [112]. It most commonly occurs as an epidemic disease in areas of poor sanitation but is a recognised cause of post-transfusion hepatitis [113].

History

A water-borne non A and non B form of hepatitis was recognised in large epidemics in the 1980s [113] with the hepatitis E virus (HEV) being identified in 1990 [114]. For many years if was thought to be a disease of countries with poor sanitation but is now recognised as an infrequent cause of hepatitis in all countries [113].

Epidemiology

The incidence and prevalence of hepatitis E is uncertain as there is significant variation around the world and varying sensitivity of serological tests [113].

Systemic Manifestations

Hepatitis E in developing countries presents in a similar fashion to other types of acute viral hepatitis with fever, icterus, abdominal pain, anorexia and pruritus. It may produce fulminant liver failure in pregnant women, young children and a chronic transaminitis in transplant recipients. Alternatively it may be totally asymptomatic and recognised only by serological testing in developed countries [115].

Ophthalmic Manifestations

Yadav et al. have describe a 13 year old girl who presented with altered conscious state as part of the onset of hepatitis E [116]. As she regained consciousness after 5 days she was noted to have a unilateral pupil sparing third nerve palsy and no other focal neurologic findings. Over 2 months there was only partial recovery of the third nerve function [116].

Diagnosis

Diagnosis is based on serological assays which detect anti-HEV IgM in the days prior to clinical infection and may last for 6 months. Anti-HEV IgG may last for up to 12 years and indicates past infection. HEV RNA can also be detected in the stool and blood of patients with acute HEV infection [115].

Management

Management of hepatitis E infection is supportive. Prevention however involves improved hygiene and provision of safe drinking water. There are several candidate vaccines for hepatitis E currently under trial [115].

Congenital Hepatic Fibrosis

Definition

Congenital hepatic fibrosis is a histopathological diagnosis and is defined as "a developmental disorder of the portobiliary system characterized histologically by defective remodelling of the ductal plate (ductal plate malformation), abnormal branching of the intrahepatic portal veins, and progressive fibrosis of the portal tracts" [117]. If there are macroscopic cysts contiguous with the biliary tree it is sometimes called Caroli syndrome and Caroli disease is the much less common occurrence of macroscopic cysts without hepatic fibrosis [117]. The typical clinical features are an enlarged liver with a palpable left lobe, ultrasound evidence of increased echogenicity, with or without macrocysts, good liver function in infancy (often) and evidence of portal hypertension later [117]. Most frequently congenital hepatic fibrosis is associated with the ciliopathies that have renal disease [117, 118]. This group of disorders sometimes referred to as "hepatobiliary fibropolycystic diseases".

Joubert syndrome is one of these disorders and a subtype of Joubert syndrome, COACH syndrome, presents with congenital hepatic fibrosis and ocular manifestations [119, 120]. COACH is an acronym that stands for Cerebellar vermis hypo/aplasia, Oligophrenia, congenital Ataxia, ocular Coloboma, Hepatic fibrosis and is autosomal recessive [120].

Most cases of COACH syndrome are the result of mutations in *TMEM67* (alterative name *MKS3*, OMIM 609884, 8q22.1) and less commonly mutations in *CC2D2A* (OMIM 612013, 4p15.32) and *RPGRIP1L* (OMIM 610937, 16q12.2) [121–123].

History

Congenital hepatic fibrosis was first described by Kerr et al. in 1961 [124]. The association of hepatic fibrosis and ocular manifestations was first described by Hunter et al. in 1974 [125] with a more complete description by Verloes and Lambotte in 1989 [120]. These authors also proposed the acronym COACH.

Epidemiology

The incidence of congenital hepatic fibrosis is thought to be one in 10,000–20,000 and the incidence of COACH syndrome is estimated to be one in 1,000,000 births [117, 118].

Systemic Manifestations

This discussion will be limited to a the systemic features of COACH syndrome. A discussion of the systemic features of the other hepatobiliary fibropolycystic diseases is beyond the scope of this chapter.

Hepatic

Congenital hepatic fibrosis is seen in all cases and may present with signs of portal hypertension such as hematemesis [117, 126]. Liver function is commonly relatively well preserved initially with early onset liver abnormalities being rarely reported [127, 128]. In older affected individuals liver failure may occur [126].

Neurologic

Developmental delay and intellectual disability (oligophrenia) is present to varying degree [117, 123]. Neonatal tachypnoea (as would be expected with Joubert syndrome) has been described [122, 125]. Early onset ataxia is frequently observed with choreo-dystonic movement disorders being seen less often [120, 122]. Imaging frequently shows cerebellar vermal hypoplasia or aplasia with the typical molar tooth sign [120–122, 129].

Renal

Renal involvement was documented in the original cases reports [125]. Progressive renal failure due to due to fibrocystic renal changes is now recognised as a common manifestation [130].

Ophthalmic Manifestations

Retina and Optic Nerve

Chorioretinal and optic disc colobomas are detected in 42–71 % of cases in two larger series [121, 122]. It has been suggested that abnormal optic disc cupping and pallor may be part of a spectrum of optic disc abnormalities seen in COACH syndrome [122]. Optic disc hypoplasia and septo-optic dysplasia has been described in a 7 year old girl with hepatic fibrosis [131]. This child had developmental delay but there is no description of cerebellar findings on imaging. This child did not have neonatal jaundice which is more commonly associated with septo-optic dysplasia [132, 133]. The underlying diagnosis remained uncertain in this child. There is a single case report of congenital hepatic fibrosis and retinal dystrophy (given the diagnosis of Leber congenital amaurosis in the report) [134]. Mutation detection was not performed in this case. Other authors of commented on the rarity of retinal dystrophy in association with COACH syndrome [122].

Eye Movement Abnormality

Nystagmus and oculomotor apraxia are described in association with COACH syndrome [121, 128, 135]. The nystagmus has not been well characterised in the literature but one report describes it as “gaze-evoked” [120].

Strabismus and Ptosis

Ptosis is described in up to 25 % of cases [121, 128]. Strabismus has been rarely described [120].

Diagnosis

The clinical diagnosis is made on the basis of examination findings, liver and renal imaging, brain MRI and confirmed with mutation analysis for in *TMEM67*, *CC2D2A* and *RPGRIP1L*.

Management

Management is determined largely by the severity of the associated liver disease. Liver transplantation may be required [121, 122, 136].

Neonatal Hemochromatosis

Definition

Neonatal hemochromatosis is an allo-immune disorder unrelated to hereditary hemochromatosis. It is due to transplacental transfer of a maternally derived antibody directed at fetal liver and resulting in severe fetal liver injury and extrahepatic deposition of iron [137].

History

Neonatal hemochromatosis was formally considered to be part of the spectrum of familial hemochromatosis but in 2010 it was finally recognised that it is the result of liver damage induced by maternally derived antibodies now referred to as gestational allo-immune liver disease [138].

Epidemiology

Neonatal hemochromatosis is a rare cause of liver failure in the neonatal period [139] but more precise incidence and prevalence estimates are not available.

Systemic Manifestations

Neonatal hemochromatosis presents as liver failure at birth with jaundice, coagulopathy, hypoglycaemia and ascites. Many babies show evidence of an intrauterine insult such as oligohydramnios or intrauterine growth retardation [137].

Ophthalmic Manifestations

Maldonado et al. reported a case of neonatal hemochromatosis complicated by severe bilateral retinal edema and subretinal fluid [140]. The retinal edema was so severe that the retinal appearance mimicked the cherry-red spot of metabolic disorders. The ocular manifestations resolved completely after successful liver transplantation. It is of interest in this case report that the authors did not discuss the most likely etiology of the liver disease being gestational allo-immune liver disease.

Diagnosis
Diagnosis is based upon the demonstration of extrahepatic siderosis in a newborn with liver failure. Extrahepatic siderosis may be demonstrated by an oral mucosal biopsy to show iron deposition in submucosal glands. MRI can also be used to demonstrate iron in various tissues in particular pancreas and liver [141]. More recently immunohistochemistry of the liver for C5b-9 has been used to demonstrate complement mediated hepatocyte injury, but use of this modality requires further study [142].

Management
As this is an allo-immune disorder the first affected infant will present with liver failure. Treatment is extremely difficult but entails the use of an anti-oxidant cocktail from birth together with supportive therapy for liver failure. Survival with this treatment is reported between 10 and 20 %. Liver transplantation can be offered but is associated with all the risk of transplantation in growth retarded infants [141]. Once the index case has been identified, the mother can undergo pre-emptive treatment during subsequent pregnancies with intravenous immunoglobulin. This therapy has been remarkably successful and has resulted in survival of the infants without liver disease in 48 of 52 mothers treated [143].

Hypopituitism and Neonatal Jaundice

Definition
Neonatal jaundice secondary to hypopituitism.

History
The association between neonatal jaundice and hypopituitism was first described by de Morsier in 1956 [144]. Since then this association has become clearly recognised [133].

Epidemiology
Neonatal hypopituitism occurs in about one in 53,000 births and is a rare cause of neonatal cholestasis [145]. The exact frequency of this association is uncertain but a retrospective study over 20 years found that 7 of 20 patients (35 %) with hypopituitarism presented with cholestatic jaundice [146].

Systemic Manifestations
Hyperbilirubinemia may be conjugated or unconjugated and presents at around 7 weeks of age. Other clinical manifestations include microphallus, persistent hypoglycaemia, hepatosplenomegaly and ophthalmic manifestations as described below [145].

Ophthalmic Manifestations
Optic nerve hypoplasia is frequently seen in this situation (as would be expected in cases of hypopituitism) [132, 133].

Diagnosis
Hypopituitism as a cause of neonatal jaundice may be difficult to diagnose and the detection of optic nerve hypoplasia may be useful [132, 133]. The diagnosis is usually made on the basis of endocrine investigations.

Management
Hormone supplementation is the mainstay of treatment [133].

Hardikar Syndrome

Definition
This is a multisystem disorder with features including neonatal cholestasis, cleft lip/palate, intestinal malrotation, obstructive uropathy, vaginal atresia and choledochal cyst [147–150]. The etiology remains unknown [151].

History
First described by Hardikar et al. in 1992 [148] there have to date been five cases reported [147–150].

Epidemiology
Hardikar syndrome is an extremely rare disorder.

Systemic Manifestations
Hepatic
Neonatal jaundice and abnormalities of the biliary drainage system with late complications of cirrhosis (varices) and liver failure have been reported [151].

Gastrointestinal
Malrotation, jejunal septum, gastroesophageal reflux and celiac disease have all been reported [151].

Renal
Hydronephrosis secondary to obstruction and vesico-uretic reflux have been described [151].

Cardiac
Patent foramen ovale, mild pulmonary artery stenosis and anomalous pulmonary venous drainage have been described [151].

Facial
Cleft lip and palate and preauricular pits have been described [151].

Vertebral
Scoliosis requiring surgery has been described once [151].

Central Nervous System
Minor narrowing of the basilar and vertebral arteries and hearing loss have also been described [151].

Ophthalmic Manifestations

Retinopathy

Pigmentary retinopathy was described in the original case report and has been described in all subsequent cases [147–150]. The fundus is described as being albinotic with areas of pigmentary clumping in the shape of a cat's paw (bear tracks) [148]. In the peripheral retina there may be focal areas of chorioretinal degeneration.

Strabismus

Esotropia has been described in two cases [147, 148].

Diagnosis

There is no diagnostic test and diagnosis is made on the basis of pattern recognition.

Management

Liver transplantation is sometimes required for severe liver disease [149, 150].

Intestinal Disease

Polyposis Syndromes

This is a group of genetic disorders associated with multiple bowel polyps and variable extra-intestinal manifestations, often classified according to the histological types of polyps found in the bowel and the underlying genetic mutation. Most of these disorders are associated with a risk of both intestinal and non-intestinal malignancy. Of these syndromes, the following conditions are discussed in this chapter: Familial adenomatous polyposis, Peutz-Jegher syndrome and Cowden syndrome.

Familial Adenomatous Polyposis

Definition

Familial adenomatous polyposis is an autosomal disorder associated with the development of hundreds to thousands of adenomatous polyps in the intestine. It is cause by a mutation in the *APC* (adenomatous polyposis coli) gene (OMIM 611731, 5q22.2) [152]. For many years Gardner syndrome was the expression used to describe familial adenomatous polyposis with extra-colonic features but it is now know that most people with familial adenomatous polyposis have at least one extra-colonic feature and Gardner syndrome is considered to be a variant of familial adenomatous polyposis [153]. They are both the result of mutations in the *APC* gene. There is some overlap between familial adenomatous polyposis and the mismatch repair cancer syndrome (Turcot syndrome) [154]. This syndrome is manifest as intestinal polyposis with brain tumours. Four loci have been identified, none of which suggest that this disorder is allelic with *APC*.

History

In 1951, Gardner described the association of intestinal polyposis colonic and carcinoma of the colon in a large family [155]. Subsequently he and others recognised many extracolonic manifestations including desmoids, dental anomalies, osteomas and epidermoid cysts [156].

The association between familial adenomatous polyposis and pigmented fundal lesions was first noted by Blair and Trempe in 1980 [157]. McKittrick et al. almost certainly described an isolated case of familial adenomatous polyposis in 1935 with the fundal lesions being noted as well [158].

Epidemiology

Familial adenomatous polyposis is the most common inherited polyposis syndrome in childhood with the prevalence being between one in 5000 and one in 17,000 [159].

Systemic Manifestations

The lifetime risk for colorectal neoplasia is 100 %. Familial adenomatous polyposis can be associated with extra-colonic manifestations including tumours in the duodenum, thyroid, pancreas, brain and hepatoblastoma. In addition, bony lesions, desmoid tumours, nasopharyngeal angiofibromas, dental anomalies, and adenomas in the stomach, duodenum, jejunum and ileum may occur. *APC* gene mutations are considered to be highly penetrant with variable expressivity [152, 160, 161].

Ophthalmic Manifestations

Retina

The pigmented ocular fundal lesions seen in familial adenomatous polyposis are often called congenital hypertrophy of the retinal pigment epithelium (CHRPE) (see Fig. 10.1). Typical CHRPE are pigmented lesions with a variable area of depigmentation within (lacuna) or around the lesion [162–164]. The hypopigmentation may form a "tail" to the lesion directed towards the macula [163]. The lesions vary in size and photography and fluorescein angiography may reveal lesions not easily seen with an indirect ophthalmoscope [165]. OCT shows some photoreceptor loss over these lesions [166, 167]. These may occur singly or be multiple. The presence multiple pigmented fundal lesions is considered to be highly specific for familial adenomatous polyposis if there is a family history of familial adenomatous polyposis [168–170]. The incidence of isolated CHRPE in the general population is approximately 1 % with Coleman and Barnard identifying 25 CHRPE in 21 patients from a population of 1745 [171]. CHRPE tend to enlarge slowly

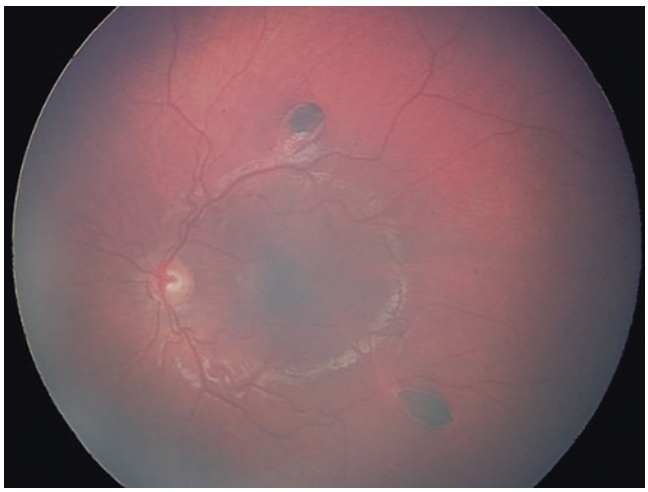

Fig. 10.1 Multifocal congenital hypertrophy of retinal pigment epithelium in a patient with familial adenomatous polyposis. (Courtesy of Dr. Carol Shields)

[164] with occasional development of a nodular appearance or even tumours in adulthood [172, 173].

The association of CHRPE with familial adenomatous polyposis has been discussed in many reports [157, 168–170, 174–191]. Traboulsi et al. showed bilateral pigmented lesions or greater than four lesions or both had a high specificity and sensitivity for familial adenomatous polyposis [168]. There are clear differences between pedigrees with familial adenomatous polyposis and controls families with the familial adenomatous polyposis family members having more pigmented lesions than controls [177, 179]. There is not a perfect correlation between the presence of CHRPE and familial adenomatous polyposis within families [175, 179, 182]. This is thought to be due to differing genotype-phenotype correlation for different mutations within *APC* [187, 188, 190]. There is little doubt that the finding multiple pigmented lesions in a possible carrier of an *APC* gene mutation greatly increases the risk of subsequent development of polyps and later carcinomas [169, 178, 183]. The lack of pigmented lesions in a possible carrier is less significant and such individuals still require monitoring for the development of polyps or mutation detection [152, 185, 191]. The finding of an isolated or even multiple CHRPE in an individual is probably of little value in assigning a risk of developing familial adenomatous polyposis [162, 181]. In a younger individual a family history of polyps or bowel cancer should be sought. Aiello et al. reported a premature baby who was found to have multiple pigmented lesions during assessment for retinopathy of prematurity and a positive family history for probable familial adenomatous polyposis was elicited [184]. Ganesh et al. described a 3 year old boy with exotropia who was found to have multiple pigmented lesions of varying size and an epiretinal membrane in the presence of an *APC* mutation [192].

Tumours

There are reports of less frequent ocular manifestations of familial adenomatous polyposis. Kochhar et al. reports a 16 year old girl with proptosis secondary to an orbital osteoma as her presenting feature of Gardner syndrome [193]. While being investigated for her proptosis she had painless rectal bleeding and was found to have intestinal polyposis. Retinal examination was described as normal and there is no mention of a family history of gastrointestinal malignancy [193]. Armstrong et al. described a 16 year old girl with orbital rhabdomyosarcoma who developed bloody diarrhoea during treatment and was then found to have colon polyps and a 5q- deletion [194]. The relationship between her orbital tumour and her familial adenomatous polyposis remains uncertain. An association with 5q deletion has been demonstrated with some rhabdomyosarcomas [195]. Kiratli et al. reported a case of sporadic unilateral retinoblastoma that was then followed by acute lymphoblastic leukemia and then the discovery of bowel polyps [196]. There is unfortunately no mention of any retinal findings in the fellow eye nor was any genetics undertaken.

There have been two reports of ophthalmic presentations of Turcot syndrome. The first involves a 14 year old girl who had a history of intestinal polyposis and then developed a juvenile pilocytic astrocytoma of one optic nerve with loss of vision [197]. There was no mention of retinal examination, family history nor genetic studies to help determine the etiology of this girl's condition. Lima et al. reported the case of a 17 year old boy with a history of intestinal polyposis who presented with diplopia due to a fourth nerve palsy and was found to have a germinoma in the tectal plate [198]. He was subsequently found to have a mutation in the *APC* gene. There was a family history of polyposis with his mother requiring a colectomy. He had a single pigmented lesion in each retina [198]. This case is much more in keeping with familial adenomatous polyposis.

Diagnosis

Diagnosis should be considered after the finding of numerous adenomatous polyps (usually >100) which develop after the first decade. A careful family history of polyposis, colorectal and other cancers should be sought. Genetic testing can identify a wide variety of mutations in the *APC* gene which cause familial adenomatous polyposis.

Management

Individuals with *APC* mutations have a 90 % risk of developing colonic adenomas, with the risk increasing with age. Management involves careful surveillance for colorectal cancers and colectomy. Patients with *APC* mutations also have a significantly increased risk of developing other cancers including desmoid tumours, ampullary cancers, hepatoblastoma and duodenal cancers. Regular surveillance for these cancers is also recommended according to the American College of Gastroenterology guidelines [199].

Peutz-Jeghers Syndrome

Definition

Peutz-Jeghers syndrome is an autosomal dominant familial polyposis disorder due to mutations of the *STK11* gene (OMIM 602216, 19p13.3). It is characterised by mucocutanous melanosis, gastrointestinal polyposis, gastrointestinal cancer and extra-intestinal cancer [200].

History

The association of perioral and mucosal pigmentation and familial polyposis was first described by Peutz in the Dutch literature in 1921 [201] and then again in the 1940s by Jeghers [202–204]. The *STK11* gene was identified by Jenne et al. in 1998 [205].

Epidemiology

The incidence of Peutz-Jeghers syndrome is estimated to be between one in 8300 and one in 200,000 births and has a lifetime risk of developing cancer of between 37 and 93 % [201].

Systemic Manifestations

Peutz-Jeghers syndrome is associated with the development of hamartomatous polyps in the gastrointestinal tract, together with skin pigmentation and a significant life time risk of cancer in the gastrointestinal tract as well as in breast, testicle, ovary, uterus, cervix and pancreas [200]. Ninety-five percent of children with Peutz-Jeghers syndrome have pigmentation of the lips, buccal mucosa or perianal skin [200]. Presentation is often in infancy because of the pigmentary changes or with rectal bleeding, intussusception or anemia [200]. The polyps have a characteristic histological appearance being multilobated with a papillary surface epithelium covering a core of arborizing smooth muscle resembling a branching tree [206].

Ophthalmic Manifestations

There is a single report of ocular manifestation in a child with Peutz-Jeghers syndrome. Raizis et al. reported the case of a girl who was diagnosed with bilateral retinoblastoma at 6 months of age and then was found to have a pineal tumour [207]. She survived with appropriate treatment and at 9 years of age was noted to develop buccal pigmentation. At 17 years of age she had an intussusception and at operation was found to have multiple intestinal polyps. Subsequent genetic testing confirmed a mutation in the *STK11* gene but not evidence of any abnormality in the *RB1* gene (OMIM 614041, 13q14.2) or its product pRB. The authors suggest that a mutation in the *STK11* gene and subsequent altered gene product may have interacted with pRB to cause the development of trilateral retinoblastoma. They were unable to completely exclude the possibility of an in-frame, intronic mutation in *RB1* or mosaicism [207].

Diagnosis

Diagnosis is based on the combination of clinical features described above including hamartomatous gastrointestinal polyps and peri-oral pigmentation. Genetic testing for mutations in *SRK11* can be performed.

Management

Management of this condition involves regular surveillance endoscopy and removal of polyps which can cause obstruction and intussusception as well as lifelong surveillance for the high risk of other systemic cancers. As these conditions are rare, guidelines for surveillance are based on expert consensus [199].

Cowden Syndrome

Definition

Cowden syndrome is a an autosomal dominant hereditary cancer syndrome caused by mutations in the *PTEN* gene (OMIM 601728, 10q23.31) in 80 % of cases [208]. It results in increased risk for breast, thyroid, renal, uterine, intestinal and other cancers as well as benign neoplasias and neurodevelopmental abnormalities [208]. Lhermitte–Duclos disease or dysplastic cerebellar gangliocytoma is a phenotypic variant of Cowden syndrome and is also caused by *PTEN* mutations [209]. Bannayan–Riley–Ruvalcaba syndrome (characterized by macrocephaly, benign hamartomas, pigmented macules of the glans penis, lipomas, hemangiomas, and the developmental delay) is allelic in 60 % of cases [209]. It has been suggested that these three condition should be referred to as the '*PTEN* hamartoma-tumour syndromes' [209, 210]. It has also been suggested that Proteus syndrome may overlap with Cowden syndrome [209] while others have suggested there is no overlap and cases of "Proteus syndrome" with PTEN mutations are in fact misdiagnosed Cowden syndrome [211].

History

Cowden syndrome was first described by Lloyd and Dennis and is named after the first patient recognised to have the disorder [212]. Mutations in the *PTEN* gene were identified as the cause of Cowden syndrome in 1997 [213].

Epidemiology

Cowden syndrome is rare with an estimated prevalence of between one in 200,000 and one in 250,000 in the Dutch population [214]. Other authors have suggested it may be more common as the phenotypic variability may result in under-diagnosis [209].

Systemic Manifestations

Patients with Cowden syndrome develop multiple hamartomas most commonly on the skin and mucous membranes but they can be anywhere including the intestines. Other features include gastrointestinal polyps, ovarian cysts and leiomyomas.

Patients are also at risk of other cancers including breast, thyroid, and uterine cancers. Affected individuals may have macrocephaly and a small percentage have intellectual disability.

Ophthalmic Manifestations

Optic Disc

Nuss et al. reported an 24 year old man diagnosed with Cowden syndrome who had "pseudotumour cerebri" at 16 years of age [215]. No further clinical details were given. Wells et al. described a 16 year old girl in 1994 who presented with signs of raised intracranial pressure and a sixth nerve palsy who was found to have a cerebellar mass that on biopsy was consistent with Lhermitte–Duclos disease [216]. On subsequent ophthalmic assessment she was noted to have choroidal hamartoma and conjunctival papilloma. She had a past history of partial thyroidectomy. These findings were considered to be consistent with a diagnosis of Cowden syndrome [216]. Arch et al. reported a 18 month old boy with Bannayan–Riley–Ruvalcaba syndrome who was noted to have pseudopapilledema and anisometropia [217]. Subsequent testing revealed a mutation in *PTEN* and the authors suggested Bannayan–Riley–Ruvalcaba syndrome and Cowden syndrome are allelic [217].

Cornea

Schaffer et al. reported a 5 year old boy with multiple nonencapsulated neuromas of the vermillion border of the upper lip, digits, palms and shins with prominent corneal nerves and *PTEN* mutation [218]. No other features of Cowden syndrome were reported.

Diagnosis

Clinical Diagnosis is made by a combination of three or more major criteria or two major and three minor criteria based on a systematic review by Pilarski and colleagues. Recommendations for which patients should undergo genetic testing are also contained in these guidelines [219].

Management

As with other syndromes in which the cancer risk is significant, management involves a program of regular screening for cancers including breast, thyroid, uterine etc. Surgery, laser therapy and chemical peels may be used to treat some of the skin lesions. Clinical trials using rapamycin and sirolimus are currently underway after the demonstration of regression of cutaneous lesions and other features in a mouse model with a PTEN deletion.

Inflammatory Bowel Disease

Definition

Crohn disease and ulcerative colitis are chronic, inflammatory diseases of the bowel with some unique and some overlapping features. Crohn disease is manifested by inflammation of the bowel anywhere from mouth to anus. The child may present with diarrhoea, abdominal pain, PR bleeding and weight loss [220]. The disease is characteristically not continuous and commonly involves extra-intestinal manifestations including musculoskeletal, hepatobiliary, skin and eye involvement. Crohn disease may predominantly involve the oral cavity and lips-, so called orofacial granulomatosis. It may also be predominantly perianal with fistulas and skin tags and relatively little in the way of bowel involvement. Histologically, Crohn disease is characterised by discontinuous involvement and granulomas. In contrast, ulcerative colitis is limited to the colon and is usually continuous starting distally and becoming more proximal. It can also be associated with extra-intestinal manifestations of the same spectrum as seen in Crohn disease. In children, the distinction between Crohn disease and ulcerative colitis maybe difficult at diagnosis. The presence of certain antibodies may assist. Anti- saccharomyces cerevisiae (ASCA) IgG is a specific but not sensitive marker in patients with Crohn disease while Anti-neutrophil cytoplasmic antibodies (pANCA) are present in more than half of patients with ulcerative colitis [221]. If the distinction cannot be made, patients are labelled as "IBDU"- inflammatory bowel disease unclassified until the clinical pattern becomes clearer with time.

The pathogenesis of these extra-intestinal manifestations is poorly understood and given the nature of inflammatory bowel disease is thought to be immune mediated [222, 223].

History

Crohn disease was first distinguished from other inflammatory bowel diseases by Crohn et al. in 1932 [224]. In the original description only involvement of the ileum was identified and the name "regional ileitis" was suggested. Ulcerative colitis was first described by Samuel Wilks in 1859 as chronic continuous inflammation limited to the large bowel, starting distally in the rectum and continuing proximally to a variable extent [225].

The association between gastrointestinal disease and ocular inflammation has long been known with the 1918 report of Maxwell and Kiep linking infective dysentery and uveitis being the earliest in the English literature [226]. Paradoxically Crohn reported the association between ulcerative colitis and ocular lesions in 1925 [227] some 7 years before he published his description of the disease that bears his name [224].

The earliest series of patients with ulcerative colitis and ocular manifestations was published in 1967 by Billson et al. [228]. They described 3.7 % of 465 patients with ulcerative colitis having ocular manifestations. Their patients were predominately adults.

The first reference to uveitis in association with Crohn disease is probably that of Korelitz and Coles in 1967 [229]. These authors report 13 individual's with inflammatory bowel disease and uveitis four of whom probably had Crohn disease ("granulomatous colitis"), though there is some diagnostic uncertainty. The first systematic documentation of a

large series of patient's with ocular disease and Crohn disease was that of Hopkins et al. published in 1974 [230]. In this series 21/332 (6.3 %) had one or more ocular complaints [230]. Sixty-seven of the 332 (20 %) patients studied were under 19 years of age and four of these were reported to have "eye lesions" but not uveitis.

Epidemiology

The prevalence of Crohn disease and ulcerative colitis is increasing, with large scale, population based studies from several countries demonstrating this phenomenon [231–234].

There is extremely wide geographic variation in the incidence of extra-intestinal manifestations of Crohn disease with estimates varying from 7 % in a Korean population [235] to 42 % in a Spanish population [236]. The Korean study reported no ocular manifestations while the Spanish study noted 2 % had ocular manifestations. The Korean study was only adults while the Spanish study did include some children (age range 10–80 years). In one study from Turkey a prevalence of 60 % of Crohn disease patients with ophthalmic abnormalities was ascribed to the ascertainment bias of a tertiary referral centre [237].

Systemic Manifestations

Bowel

The main features of inflammatory bowel disease depend on the distribution of the disease in an individual patient. Inflammation of the colon, either in Crohn disease or ulcerative colitis, presents with diarrhoea, abdominal pain and PR bleeding. This may be accompanied by systemic symptoms of fever, weight loss and malaise. Crohn disease may associated with mouth ulcers, small bowel strictures, isolated oral involvement (orofacial granulomatosis) or isolated perianal disease.

Musculoskeletal

Musculoskeletal pain is the most common extra-intestinal manifestations of inflammatory bowel disease and occurs in up to 50 % of patients. Arthritis may involve peripheral joints, or the axial skeleton such as the spine and sacroiliac joints. The peripheral arthritis may be pauciarticular and correlate well with disease activity or polyarticular, long lasting, and independent of disease activity [238].

Dermatological

A number of skin manifestations are associated with inflammatory bowel disease and the most common are erythema nodosum, pyoderma gangrenosum and psoriasis. Erythema nodosum occurs in 7 % of patients and presents with painful erythematous or bruise like nodules often on the anterior shins. Their presence parallels disease activity in the bowel and treatment is directed at managing bowel inflammation [239]. Pyoderma gangrenosum consists of a papule or nodule which breaks down into an ulcerated lesion. It can occur anywhere on the body, most commonly on the legs and can be seen in up to 10 % of patients with ulcerative colitis and up to 20 % of patients with Crohn disease [240].

Hepatobiliary

Primary sclerosing cholangitis is the most common and severe hepatobiliary manifestation of inflammatory bowel disease and may precede or follow the development of bowel disease. It is found in 5 % of patients with ulcerative colitis and 2 % of patients with Crohn disease. It causes progressive structuring of bile ducts, cholestasis and end stage liver disease which may require transplantation. Primary sclerosing cholangitis may also recur in the transplanted liver graft. Other hepatobiliary manifestations include choledocholithiasis and portal vein thrombosis.

Ophthalmic Manifestations

Ophthalmic extra-intestinal manifestations of inflammatory bowel disease are relatively common and in the majority of cases mild and often asymptomatic [223]. These complications may be a primary feature of inflammatory bowel disease or secondary to treatment (most commonly corticosteroid therapy) or co-incidental observations [241]. Ocular involvement can occur prior to the diagnosis of inflammatory bowel disease, be diagnosed at the same time or some time subsequently. In a large Italian series, ocular manifestations were diagnosed prior to systemic diagnosis in 11 % of cases of inflammatory bowel disease, at the same time in 19 % and following diagnosis in 70 % [242].

With the exception of anterior uveitis, cataract and ocular hypertension reports of reports of ocular manifestations have been in small case series or single case reports. There are two prospective cross-sectional studies of the ophthalmic manifestations of inflammatory bowel disease in paediatric populations [243, 244].

Anterior Uveitis

Asymptomatic uveitis in children is the most commonly reported ocular manifestation of inflammatory bowel disease with reported prevalence of 0–32 % [230, 243–245]. Hofley et al. assessed 97 children with Crohn's disease and reported 6/97 (6.2 %) had asymptomatic uveitis (defined as flare or inflammatory cells in the anterior chamber) [243]. No patients with ulcerative colitis in this series were reported to have uveitis and no other ophthalmic abnormalities were reported by these authors [243]. Rychwalski et al. examined 18 children with Crohn's disease and 14 with ulcerative colitis [244]. 3/18 (17 %) of the Crohn's disease patients and 1/14 (7 %) of the ulcerative colitis patients had asymptomatic uveitis with cells and flare [244]. In the majority of children reported to have anterior uveitis and inflammatory

bowel disease the uveitis is mild and often asymptomatic and consists of mild flare and cells [228, 230, 243–245].

The association between activity of inflammatory bowel disease and presence of anterior uveitis is uncertain. Hofley et al. reported no association between the activity of the Crohn disease and uveitis [243]. Rychwalski et al. reported three of four children with anterior uveitis who had active systemic disease at the time of detection of uveitis [244]. The principle location of the Crohn disease was reported to be the colon in 4/6 children with uveitis in one series [243]. This is similar to the association reported in adults [246]. Anterior uveitis may precede bowel disease with Korelitz and Cole reporting three of the four patients with granulomatous colitis (Crohn disease) developing iritis before the diagnosis of the bowel disease [229].

The natural history of asymptomatic uveitis associated with inflammatory bowel disease is uncertain [243, 244, 247]. Daum et al. examined five children 6 months after the detection of asymptomatic uveitis and found 4/5 had resolved and the remaining one was improving (the sixth patient was lost to follow-up) [245]. None of these patients had received any treatment specifically for their uveitis.

Conjunctival Lesions

Conjunctival lesions have been described in children with Crohn disease on two occasions.

Blase et al. described a 13 year old boy who developed granulomatous conjunctivitis at the same time as his gastrointestinal symptoms [248]. He was noted to have normal vision, moderate bilateral conjunctival injection and gelatinous nodules at the limbus with mild anterior uveitis. Biopsy of a conjunctival lesion revealed "chronic round cell infiltration of the substantia propria with discrete nodules of epithelial and giant cells"[248]. The conjunctival changes revolved rapidly with systemic corticosteroid therapy. Knox et al. reported a 17 year old boy with a small limbal infiltrate in association with episcleritis and mild anterior uveitis [241]. Biopsy showed acute inflammation and no granuloma. This boy had a history of recurrent iritis and this episode was preceded by a flare-up of this gastrointestinal symptoms.

Episcleritis

Episcleritis is infrequently reported as an extra-intestinal manifestation of inflammatory bowel disease. This may be because it is mild and self-limited. Hopkins et al. found a prevalence of 0.6 % for episcleritis in a series of 332 adult and paediatric patients with Crohn disease [230] and Billson et al. reported an incidence of 1.5 % in a similar population with ulcerative colitis [228]. Pediatric patients with episcleritis have been described by Ellis and Gentry [249] Salmon et al. [250] and Knox et al. [241]. The case reported by Ellis and Gentry was an 11 year old girl with ulcerative colitis [249]. She had a protracted course with respect to ocular manifestations having episcleritis followed by iridocyclitis, neuroretinitis, lateral rectus weakness, further iritis, episcleritis and scleritis and ultimately inflammatory mass around the trochlea. She developed a mild posterior subcapsular cataract as the result of steroid therapy [249]. The case reported by Salmon et al. was described as nodular episcleritis and it was noted that episcleritis was seen in association with active bowel disease and settled with systemic therapy for this [250].

Scleritis

Scleritis is infrequently described in adults with Crohn disease and to date has not been reported in the pediatric population. Salmon et al. describe 19 and 20 year old female patients with diffuse and necrotizing scleritis respectively [250]. In both patients the onset of the scleritis was after tapering systemic corticosteroid treatment for long-term treatment of recurrent bowel inflammation.

Blepharitis

Blepharitis is relatively commonly described in association with inflammatory bowel disease in adults [230, 251] but has only been specifically described in the pediatric age group as a complication of anti-tumor necrosis factor treatment [252].

Keratitis

Keratitis is infrequently reported in the pediatric population with inflammatory bowel disease. The case of Blase et al. had unilateral superficial corneal infiltrates in association with conjunctival granulomas [248]. In their prevalence study Hopkins et al. report a 0.3 % rate of keratitis [230]. Lind reported 2 cases of keratitis in their series of 214 cases of Crohn disease [253]. Macoul described a 17 year old male with Crohn disease who developed marginal corneal infiltrates after a complex preceding ocular history of bilateral iridocyclitis followed by bilateral posterior uveitis with bilateral papillitis [254]. Sahel described a 12 year old girl who had corneal infiltrates (as well as episcleritis and scleritis) 4 years prior to her diagnosis of Crohn disease [255]. Severe corneal pathology has been described as a complication of anti-tumor necrosis factor treatment by Fasci-Spurio et al. [252]. This 16 year old boy with Crohn disease had keratitis, corneal scar formation and corneal melts.

Cataract

The most frequently describe cataract morphology seen in association with inflammatory bowel disease is posterior subcapsular. It is generally assumed this is a complication of long-term corticosteroid use [244, 256]. In the report of Rychwalski et al. 3/18 patients with Crohn disease had posterior subcapsular cataract but no comment is made about the vision of these children other than to state "No patient had … photophobia, or visual disturbance" [244]. Tripathi et al.

described 12/58 (21 %) children with inflammatory bowel disease who developed posterior subcapsular cataract following treatment with corticosteroid [256]. The development of these cataracts "was not correlated …. with the total dose of prednisone, duration of treatment, average daily dose, or number of days on high doses" though it was assumed that the development of cataract was secondary to corticosteroid treatment.

Visually significant cataract in children with inflammatory bowel disease has not been described.

Ocular Hypertension

Ocular hypertension secondary to systemic corticosteroid use has been described in children with Crohn disease [257]. There have been no reports of steroid induced glaucoma in children with Crohn's disease.

Vitritis

Vitritis has only been described in the report of Macoul of a 17 year old boy with Crohn disease who had protracted pan uveitis, papillitis and reduced vision [254].

Papillitis and Papilledema

Papillitis has been described twice in children with inflammatory bowel disease [254, 258]. Both children had reduced visual acuity with marked disc swelling and hemorrhages. The case of Hutnik et al. was investigated with CT and MRI scan and lumbar puncture all of which were normal [258]. This 17 year old boy was diagnosed with Crohn disease immediately following his presentation with reduced vision.

There is a case report of pseudotumour cerebri and associated papilledema in a 16 year old boy with Crohn disease [259]. This occurred following steroid withdrawal on four occasions and necessitated long term diuretic treatment.

Central Retinal Artery Occlusion

There is a single case report of central retinal artery occlusion in a 9 year old boy with Crohn disease [260]. Fortunately this child had a cilioretinal vessel and central vision was preserved.

Serous Retinal Detachment

Ernst et al. described one child with serous retinal detachment in their small series of patients with inflammatory bowel disease and posterior segment pathology [261]. This 15 year old boy noted slightly reduced vision in one eye 2 weeks after the diagnosis Crohn disease. Despite resolution of the retinal detachment following treatment with systemic corticosteroid he was left with slightly reduced visual acuity of 20/40.

Dacryoadenitis

Dacryoadenitis has been reported twice in children with Crohn disease [262, 263]. Dutt et al. reported 16 year old boy who developed bilateral dacryoadenitis at the same time as a relapse of his Crohn disease [262]. The diagnosis in this case was made on clinical finding and imaging only. The 10 year old girl reported by Rafiei et al. had bilateral dacryoadenitis as part of her initial presentation of Crohn disease [263]. The diagnosis in this case was made on examination findings alone.

Nasolacrimal Duct Obstruction

Acquired nasolacrimal duct obstruction is well known to occur in adults with inflammatory bowel disease [264]. but has only been reported in a child once [265]. This 16 year old boy had bilateral nasolacrimal duct obstruction that required dacryocystorhinostomy procedures. Nodular tissue was found in both lacrimal sacs and histopathology showed granulomatous inflammation.

Orbital Pseudotumour

Orbital pseudotumour has been reported on five occasions in the pediatric age group [249, 266–269]. Interestingly all cases have been in girls and with one exception all have been in association with Crohn disease [249]. In all cases there was involvement of extraocular muscles and in four cases this was well seen on imaging [266–269]. In the earlier report of Ellis and Gentry a mass was described as being over the trochlea and superior oblique sheath and no imaging was performed [249]. This report gave no other details about eye movement findings.

Co-incidental Ophthalmic Findings (Strabismus, Amblyopia and Refractive Error)

One child was found to have esotropia and amblyopia and another unilateral high myopia both of which were probably co-incidental findings [244].

Diagnosis

The diagnosis of Crohn disease and ulcerative colitis relies predominantly on endoscopy of the upper and lower bowel and histology of biopsies. Supportive evidence of small bowel or perianal involvement in Crohn disease is obtained by MRI and capsule endoscopy (tiny camera that is swallowed and wirelessly transmits images of the small intestine). A new screening tool, stool calprotectin has excellent sensitivity and specificity in identifying inflammation of the bowel and is also used in disease monitoring [270]. Some authors have recommended routine screening for ophthalmic manifestations [244, 247] while others have commented that the evidence base for doing this is uncertain and the disease impact is low as the uveitis is usually so mild. Further long-term study of these patients is needed [243].

Management

The goal of treatment is to attain mucosal healing. The treatment of inflammatory bowel disease involves immunosuppression and immunomodulation. The mainstay of paediatric management includes steroids, 5ASA preparations, thiopurines,

methotrexate and anti-TNF preparations including infliximab and adalimumab. Tacrolimus is also used for refractory colitis. An 8 week trail of exclusive enteral nutrition has been shown to be as effective as steroids in attaining mucosal healing in children with Crohn disease [271]. Colectomy may be required if colitis cannot be controlled with medical therapy. In Crohn disease, stricturing of the bowel may be amenable to balloon dilatation or may requires resection. In addition, perianal disease and fistulas may require the placement of setons to aid healing. With the newer therapies, the long term survival in children with inflammatory bowel disease is excellent. However there is a significant increased risk of cancer [272].

Ophthalmic management may be observation alone for asymptomatic anterior uveitis [243–245]. Other more significant inflammatory processes such as episcleritis, scleritis, conjunctival granuloma, keratitis, papillitis, dacryoadenitis or orbital pseudotumour respond well to topical and systemic corticosteroids [249, 250, 254, 258, 262, 263, 266–269]. Visual outcomes are usually excellent.

Hirschsprung Disease

Definition

Hirschsprung disease is the result of a failure of development of the enteric nervous system resulting in a congenital absence of parasympathetic ganglia in the submucosal and myenteric plexi of the distal bowel extending for a variable distance continuously from the internal anal sphincter [273]. The genetics of this condition are complex and may involve mutations of one of several genes including *RET* (OMIM 164761, 10q11.21), *EDNRB* (OMIM 131244, 13q22.3) and *EDN3* (OMIM 131242, 20q13.32) [273].

History

Harald Hirschsprung described two infants with constipation and megacolon in a detailed autopsy study published in 1888 [274]. The exact aetiology was unclear until two independent reports of the absence of ganglion cells in the colon of affected individuals [275, 276].

Epidemiology

Hirschsprung disease is estimated to have an incidence of one in 5000 live births with a male:female ratio of approximately 4:1 [277].

Systemic Manifestations

Hirschsprung disease usually presents within the first few months of life with constipation, delayed passage of meconium, feed intolerance or uncommonly as enterocolitis with bowel perforation. Children with very short segment disease may present later in life with constipation.

Long term complications include the risk of enterocolitis which is more common in patients with Down syndrome, ongoing constipation and faecal incontinence [278].

Ocular Manifestations

Many ocular manifestations have been reported in association with syndromic Hirschsprung disease and these are tabulated in Table 10.2 [280–293].

Diagnosis

The diagnosis of Hirschsprung disease is made by rectal biopsy.

Management

The management of Hirschsprung disease is primarily surgical with removal of the most of the aganglionic segment and anastomosis distally with four main "pull-through" operations (Swenson, Soave, Duhamel and Rehbein) [294].

Celiac Disease

Definition

Celiac disease is defined as "an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterised by the presence of a variable combination of gluten-dependent clinical manifestations, celiac disease-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy" [295]. The celiac disease specific antibodies are autoantibodies against tissue transglutaminase type 2 (anti-TG2), endomysial antibodies (EMA) and antibodies against deamidated forms of gliadin peptides (anti-DGP) [295]. In children and adolescents the presentation of celiac disease can be quite non-specific and testing is recommended for chronic or intermittent diarrhea, unexplained weight loss, chronic fatigue, etc. Testing is also recommended in children and adolescents with conditions that are known to have increased risk of developing celiac disease such as type 1 diabetes mellitus, Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective immunoglobulin A (IgA) deficiency, autoimmune liver disease, and first-degree relatives with celiac disease [295, 296]. The understanding of the pathogenesis of this disease continues to improve with evidence that changes in the microbiome, antirotavirus VP7 antibodies and the Parkinson's disease seven gene may all have a role in the development of the celiac disease [297].

History

The clear first modern description is said to be by Samuel Gee in a 1887 lecture but the disease was well known at least 1800 years earlier [298].

Table 10.2 Syndromes associated with Hirschsprung Disease with ocular findings

Syndrome	Systemic features	Ocular manifestations
Bardet-Biedl	Obesity, intellectual disability, polydactyly, hypogenitalism, renal abnormalities	Retinal dystrophy [280], cataract, strabismus
Congenital central hypoventilation	Hypoxia, reduced ventilatory drive, neuroblastoma	Fixed dilated pupils, strabismus, Marcus Gunn jaw winking [281]
Familial dysautonomia (Riley-Day syndrome)	Sensory and autonomic dysfunction (including abnormal sweat, tear, and saliva production)	Alacrimia, corneal surface abnormalities [282]
Fryns syndrome	Distal digital hypoplasia, diaphragmatic hernia, congenital heart disease, craniofacial, intellectual disability	Congenital glaucoma, microphthalmia, coloboma [283]
Goldberg-Shprintzen syndrome	Craniofacial, microcephaly, intellectual disability, polymicrogyria	Megalocornea, ptosis, hyperopia, iris coloboma [284], corneal hypoesthesia [285]
Intestinal neuronal dysplasia	Abnormal intestinal innervation with giant ganglia	Miosis with denervation pupillary hypersensitivity [286]
Multiple endocrine neoplasia 2A	Medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism, lip/tongue nodules	Prominent corneal nerves [287]
Multiple endocrine neoplasia 2B	Medullary thyroid carcinoma, pheochromocytoma, mucosal and intestinal neuromas, skeletal abnormalities	Prominent corneal nerves, eyelid neuromas, lid margin eversion or thickening, subconjunctival neuroma, and ptosis [288]
Mowat-Wilson syndrome	Intellectual disability, microcephaly, craniofacial, congenital heart disease, agenesis of the corpus callosum, epilepsy, short stature	Microphthalmia, coloboma, cataract, Axenfeld-Rieger spectrum anomalies, myopia, strabismus, ptosis [289]
Neurofibromatosis 1	Café-au-lait spots, axillary/inguinal freckling, neurofibromas, bony dysplasia, developmental delay	Lisch nodules, thickened corneal nerves, optic pathway glioma, glaucoma, sphenoid wing aplasia [290]
Smith-Lemli-Opitz	Intellectual disability, hypospadias, syndactyly, congenital heart disease, craniofacial abnormalities	Ptosis, cataract, strabismus, optic nerve hypoplasia, atrophy and swelling [291]
Waardenburg syndrome type 4 (Waardenburg-Shah syndrome)	Pigmentary abnormalities, deafness	Heterochromia iridis, bicolored or brilliant blue iris, telecanthus [292, 293]

Adapted from Parisi MA. Hirschsprung Disease Overview. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews(R). Seattle, WA: University of Washington, Seattle; 2011 [279]. With permission from University of Washington, Seattle, © 1993–2015

Epidemiology

It is estimated that approximately 1 % of the population may have some form of celiac disease [297].

Systemic Manifestations

Gastrointestinal

The patient with celiac disease may present with diarrhoea, abdominal pain, weight loss, malaise, and iron deficiency anemia. These symptoms are secondary to malabsorption caused by small bowel mucosal injury. Curiously patients may also be totally asymptomatic.

Hepatobiliary

Mild liver function test abnormalities can be seen in patients with celiac disease and usually resolve with commencement of a gluten free diet. Clinically significant auto-immune type liver diseases however are associated with celiac disease including auto-immune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis [299].

Skin

Dermatitis herpetiformis is the characteristic skin lesion of celiac disease. It can be seen in up to 25 % of patients and consists of erythematous papules, pustules or urticarial plaques. The lesions are itchy and excoriation from scratching may produce secondary damage. The disorder responds to a gluten free diet [300].

Endocrine

Type 1 diabetes is closely associated with celiac disease, with 2–11 % of patients with Type 1 diabetes developing celiac disease. Conversely, celiac disease is associated with a two-fold risk of the development of type 1 diabetes before the age of 20 years [301]. Serological signs of auto-immune thyroid disease (Graves and Hashimoto) can be found in up to 26 % of patients with celiac disease [302]. Patients with Addison disease are at risk of developing celiac disease and vice versa. In the latter group, a gluten free diet has not modified the natural history of Addison disease [303].

Central Nervous System

There is evidence that celiac disease is associated with idiopathic cerebellar ataxia [304] but the nature of this association is debated [305]. Versino et al. documented cerebellar abnormalities in a largely adult group patients with celiac disease (on gluten free diets) and with no symptoms of neurological disorder [306]. Seven of 42 (17 %) subjects had eye movement abnormalities on clinical assessment, five with gaze-evoked nystagmus (one upbeat nystagmus as well as hozizontal) and two with positional down beat nystagmus on lateral gaze when supine. Eleven of 42 (26 %) were found to have saccadic dysmetria of which three had gaze evoked nystagmus as well [306]. These authors concluded that there is a cerebellar background in individuals with celiac disease that is independent of gluten intake and may represent a differing immune reaction from that which mediates gut symptoms [306]. Cortical atrophy has been reported in older adults with celiac disease [307].

Ocular Manifestations

Given the involvement of immune mechanisms and specific HLA types it is no surprise that ocular disorders that have similar pathogenesis may coexist with celiac disease. The earliest reports of ocular manifestations however were related to nutritional deficiency secondary to malabsorption. The first reports were of retinal [308] and corneal pathology [309] related to hypovitaminosis A.

Urganci and Kalyoncu prospectively examined 67 children aged 1–16 years with celiac disease and found that none had cataract or uveitis at presentation or during follow-up [310].

Orbitopathy and Myopathy

Both case reports [311, 312] and larger clinical series [313, 314] have shown an association between autoimmune thyroid disease and celiac disease. Ruch et al. reported a 17 year old girl with Down syndrome, celiac disease and thyroid ophthalmopathy presenting with mild proptosis [311]. She subsequently developed diabetes mellitus as well and her ophthalmopathy was controlled with carbimazole and dietary avoidance of gluten. Gora-Gebka described a girl who developed Grave's disease with relatively severe ophthalmopathy requiring systemic steroid and other therapies at 8 years old [312]. She subsequently developed cholestatic jaundice and on investigation was found to have celiac disease. With avoidance of gluten her liver and thyroid disease improved dramatically [312]. Spadaccino and colleagues have shown in a mixed pediatric and adult population of 276 patients with autoimmune thyroid disorders of whom 1.8 % have a prior diagnosis of celiac disease and 3.6 % were positive to celiac antibodies with half of these having a positive duodenal biopsy for celiac disease [313]. Ponto et al. have shown in patients with "thyroid-associated orbitopathy" 14 % have evidence of celiac disease making it the most common autoimmune comorbidity in this condition [314].

There is a single report of orbital myopathy with a 12 year old girl who presented with a 3 month history of diplopia secondary to bilateral medial rectus weakness with subsequent investigation revealing a diagnosis of celiac disease [315]. Investigation for thyroid disease and myasthenia gravis was negative and CT scan revealed cortical atrophy. A biopsy of one medial rectus revealed muscle atrophy and fatty infiltrate. Her eye movement abnormality resolved completely with a gluten free diet and remained improved over the next 6 months [315]. The authors suggested these findings may be consistent with a local myositic process.

Uveitis

There have been a number of case reports of uveitis associated with celiac disease [316–319] and a recent population study in Sweden suggested a moderate increased risk of developing uveitis of any form with celiac disease [320]. The first report of uveitis in a child with celiac disease is that of Laghmari et al. in 2003 [316]. Al Hemidan reported the association of Vogt-Koyanagi-Harada, diabetes mellitius and celiac disease in a 3 year old girl [317]. Krifa et al. reported a 9 year old girl with diabetes mellitus who developed anterior uveitis with reduced vision [318]. Her uveitis settled once she was treated with a gluten free diet. Arikan-Ayyildiz et al. drescribed a 11 year old girl who was diagnosed as have anterior uveitis 1 month before investigation for short stature revealed a diagnosis of celiac disease [319]. There was no recurrence of her uveitis during 2 years of follow-up on a gluten free diet.

Cataract

Bilateral total cataracts have been reported as part of the presentation of an 18 year old boy with severe malnutrition and multiple long bone abnormalities attributed to malabsorption secondary to celiac disease [321]. Given the severity of the skeletal abnormality, hypodontia and osteoporosis it is possible that there may be two co-existing disorders in this child; celiac disease and an ill-defined skeletal abnormality.

Conjunctiva

There are two reports of conjunctival abnormalities in association with celiac disease [322, 323]. Kanwar et al. reported a 14 year old girl with an 8 year history of celiac disease who developed cicatricial pemphigoid that presented with conjunctival symblepharon amongst over complaints [322]. She was commenced on systemic therapy of prednisolone and dapsone but no follow-up data was published. Tuncer et al. described a 3 year old girl who presented with a fleshy conjunctival lesion soon after the diagnosis of celiac disease [323]. The lesion settled with topical steroids and a gluten free diet. The authors' clinical diagnosis was Kaposi sarcoma. Neither biopsy nor HIV1 testing was performed.

Retinitis Pigmentosa

Retinitis pigmentosa has been reported once in association with celiac disease [324]. This 9 year old boy had idiopathic pulmonary hemosiderosis and celiac disease in addition to early onset retinitis pigmentosa. His retinitis pigmentosa progressed despite improvement in his respiratory disease with the introduction of a gluten free diet. His 13 year old brother had a similar history of retinitis pigmentosa and was found to have celiac disease on subsequent investigation. In both boys hypovitaminosis A was excluded [324]. It is possible that this represents a chance association of celiac disease and autosomal recessive retinitis pigmentosa.

Eye Movement Abnormalities

Mohn et al. reported an 11 year old girl who presented with vertigo and nystagmus and subsequent investigation confirmed a diagnosis of celiac disease [325]. The vertigo but not the nystagmus improved on gluten elimination and the vertigo returned on gluten rechallenge. It is of interest that his girl had normal visual acuity and no oscillopsia was mentioned in the report. This may suggest that the nystagmus was of longstanding and not related to the vertigo or alternatively may have been gaze-evoked only as has been reported in association with celiac disease [306]. Deconinck et al. described a 2 year old boy who developed cerebellar ataxia, myoclonus, palpebral flutter and opsiclonus over a 3 week period associated with diarrhoea [326]. Subsequent testing confirmed a diagnosis of celiac disease and his opsiclonus-myoclonus and other neurological abnormalities settled completely on a gluten free diet.

Optic Neuritis

There is a single report of neuromyelitis optica and celiac disease with recurrent optic neuritis over a 4 year period in a child [327]. A gluten free diet did not modify the neurological symptoms which required immunosuppression with tacrolimus. This girl had partial IgA and IgG3 deficiency in the context of anti-aquaporin-4 auto-immunity and familial IgA deficiency in addition to her celiac disease suggesting a complex series of abnormalities in immune regulation and auto-antibodies [327].

Diagnosis

Diagnostic paradigms for celiac disease are in evolution. Traditionally the diagnosis has been made by a combination of positive serology (presence of transglutaminase IgA, deamidated gliadin peptide antibody and/or anti-endomysial antibody), confirmed by typical histological changes in a duodenal biopsy. Recently, several groups have developed algorithms to avoid duodenal biopsies in certain children when a number of other strict diagnostic criteria are met [295].

Management

Treatment of celiac disease involves a lifelong strict gluten free diet. This is associated with mucosal healing, resolution of clinical symptoms and a reduction in all causes of mortality if mucosal recovery is achieved [328]. Serology correlates with, but is not a reliable marker of mucosal recovery in adults. A recent study in children has shown that a combination of two negative serological tests is a strong predictor of mucosal recovery in children [329]. New therapies for coeliac disease are currently undergoing clinical trials. These include gluten specific proteases and vaccines designed to restore immune tolerance to gluten [330].

Pancreatitis

Definition

Pancreatitis is defined as "an insult to the pancreas that leads to the presence of acute inflammatory cells, edema, and necrosis that may result in organ damage or fibrosis" [331]. Pancreatitis is further subdivided into acute, acute relapsing and chronic forms. Acute pancreatitis is defined as two of the following: abdominal pain compatible with acute pancreatitis, serum amylase and/or lipase values at least three times upper limits of normal and imaging findings of acute pancreatitis [332]. Acute relapsing pancreatitis is defined as two or more distinct episodes of acute pancreatitis with intervening return to baseline [332]. Chronic pancreatitis is defined as the presence of typical abdominal pain plus characteristic imaging findings, or exocrine insufficiency plus imaging findings, or endocrine insufficiency plus imaging findings [332]. In the majority of children the cause remains unknown, however infections, trauma and medications account for most of the remaining cases. A small percentage may be due to cholelithiasis, inherited disorders of pancreatic enzyme metabolism or other metabolic disorders [333, 334]. The *PRSS1* (OMIM 276000, 7q34), *SPINK1* (OMIM 167790, 5q32) and *CFTR* (OMIM 602421, 7q31.2) genes have all been associated with an increased risk of developing chronic pancreatitis [333]. Diabetic ketoacidosis, hypertriglyceridemia and hypercalcemia have all been associated with the development of acute pancreatitis [335].

History

Historical descriptions of probable pancreatitis go back as far as the fatal illness of Alexander the Great in 323 BC [336]. The first modern description was by Fitz in 1889 with Chiari recognising the importance of pancreatic "autodigestion" in 1896 [336].

Epidemiology

Pancreatitis is relatively uncommon in children but may be becoming more common with a North American study suggesting an incidence of 13 per 100,000 children [337]. Greater physician awareness of the possible diagnosis of pancreatitis and subsequent testing may explain some of this increase [338].

Systemic Manifestations

Acute pancreatitis can be complicated by severe systemic illness leading to multi-organ failure and intra-abdominal complications including pancreatic pseudocyst formation [339, 340]. Chronic pancreatitis may result in pancreatic failure with pancreatic exocrine and or endocrine deficiency. Exocrine deficiency will result in maldigestion, malnutrition, weight loss, flatulence, and steatorrhea and can be treated with oral pancreatic enzyme supplementation [340, 341]. Diabetes mellitus will result from pancreatic endocrine failure and may take decades to develop [340]. Pancreatic neoplasia can be a late complication of chronic pancreatitis [340].

Ophthalmic Manifestations

Retina

Mudumbai and Bhandari reported the case of an 18 year old girl with acute pancreatitis who developed a thrombotic microangiopathy and subsequently was found to have bilateral haemorrhagic infarct of the lateral geniculate bodies [342]. She had a single small retinal hemorrhage and a few cotton wool spots in the retina of one eye and hour glass homonymous hemianopic field defects as would be expected for lateral geniculate damage. It is possible that this may have been mild Purtscher retinopathy although it is not clear that the retinal findings met the definition of this condition [343].

Nystagmus

Basit and colleagues described an 11 year old boy with a history of recurrent pancreatitis who developed thiamine deficiency and signs of Wernicke encephalopathy with nystagmus and slight ptosis [344]. His MRI scan was consistent with this diagnosis and he was show to be thiamine deficient and responded promptly to supplementation.

Diagnosis

Acute pancreatitis is diagnosed on the typical history of acute abdominal pain, nausea, vomiting, or back pain; serum levels of pancreatic amylase and/or lipase three times the upper limit of normal; radiographic evidence of acute pancreatitis including pancreatic edema on ultrasound or computed tomography [331]. Less frequently MRI or endoscopic retrograde cholangiopancreatography (ERCP) are required to more accurately delineate the anatomy of the hepatobiliary tract and pancreas [331].

Management

The management of pediatric acute pancreatitis is based on extrapolation from adult studies and guidelines [331, 345]. Management for acute pancreatitis consists of pain relief, fluid resuscitation and nutritional support [331]. The role of other pharmacological intervention is uncertain and surgical intervention (ERCP) is occasionally required in the rare instance of cholelithiasis [331] and in the management of hereditary chronic pancreatitis [333].

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Hematologic Disorders of the Eye

11

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Introduction

Hematological disease may affect the eye by loss of vessel integrity, vascular occlusion, altered blood viscosity, loss of function of a particular blood cell line or blood component, infiltration of perivascular tissue by an abnormal blood constituent, or by any combination of the preceding. Ready access to the ocular fundus enables the observation of the affects of hematological diseases on the microcirculation.

Hematological malignancy, inherited or acquired disorders of hemoglobin production and coagulation are amongst the most common and serious of pediatric blood disorders. All may have significant ocular involvement. We will narrow our discussion here to sickle cell disease, related diseases and leukemia.

Sickle Cell Disease

Definition

Sickle cell disease refers to a heterogeneous group of genetic blood disorders characterized by a predominant production of mutant hemoglobin: sickle hemoglobin (HbS). HbS production results from a single point mutation (adenine → thymine in the sixth codon of the β globin gene) causing valine to be substituted for glutamic acid. In sufficient concentrations, HbS forms polymers in deoxygenated conditions and deforms the red blood cell (RBC) into the classic 'sickle-shape,' which is stiff and sticky. The clinical consequences of this polymerization are severe with sickled cells causing vaso-occlusion of the microcirculation resulting in tissue ischemia and aberration of multiple downstream systems (inflammatory, coagulation, and vaso-regulation). This chronic and episodic vaso-occlusion is characterized clinically by acute pain and results in the accumulation of multi-organ system damage and dysfunction over time.

In sickle cell trait, the HbS is inherited in the compound heterozygous state with normal globin allele (HbAS); however, it is rarely associated with systemic or ocular pathology. The most clinically severe form of the disease results from homozygosity at the HbS allele (HbSS). Compound heterozygosity for HbS and β thalassemia (HbSβthal) or HbC can also have significant systemic and ocular complications [1]. Other less frequent mutations in hemoglobin (HbE, and thalassemia variants) are recognized to occur in conjunction with HbS and be associated with systemic pathology. Clinically, and in this chapter, we use the general term "sickle cell disease" except when a particular variant is the subject of discussion. The abbreviations we use to denote the different variants of sickle cell disease (or anemia) are as follows: someone with the HbSS mutation (homozygosity) has SS disease; someone with the HbAS mutation has AS disease, otherwise known as sickle cell trait; someone with the compound heterozygous mutation (HbC) has SC disease; and someone with the compound heterozygous mutation HbS and β thalassemia has S β thalassemia; if some β globulin is still produced, the disease is designated S β+ thalassemia; if there is no β globin it is S β^0 thalassemia and the clinical problems tend to be more severe.

The sickle mutation is believed to create some immunity to malaria, especially in the neonatal period, which may explain the retention of this mutation in the human genome. The morbidity caused by sickle cell disease has been greatly

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reduced and life expectancy increased with advances in medical care. In the 1970s, sickle cell patients could expect to live into their teens. Now, life expectancy has increased to 50 years [2].

History

Sickle cell disease was first described in the medical literature in an African dental student in 1910 [3], although it was known in African and Middle Eastern peoples long before. Sydenstricked [4] then described it in two children, one of whom died, and autopsy findings were reported. In the late 1940s, the disease was defined as having a molecular basis by Pauling [5]. Followed by Neel [6], who explained the autosomal recessive nature of the disease and showed the milder form to be the heterozygous state, HbAS. The ocular complications were first reported in the 1950s [7–9]. Angioid streaks were first noted in sickle cell disease in 1960 [10]. Duke-Elder described early reports of vascular tortuosity in both sickle cell trait (1957) and sickle cell disease (1937) [11]. Welch and Goldberg first described proliferative retinopathy as "sea fans" in 1966 [12].

Epidemiology

The CDC estimates that approximately 100,000 Americans have sickle cell disease and that 1 in 12 Americans of African descent carry the trait. They further estimate that it occurs in one of every 500 persons of African descent and one in every 36,000 people of Hispanic descent [13]. Sickle cell disease and thalassemia can also exist in people of Mediterranean heritage.

Systemic Manifestations

The systemic manifestations of sickle cell disease are diverse. They can be acute events or chronic problems. They vary widely from patient to patient, some suffering near constant problems and others experiencing a seemingly benign course. The acute episodes may relapse and remit, but almost all patients experience significant morbidity and early mortality.

The classic example of an acute event for a sickle cell patient is vaso-occlusive pain. Resulting from RBC sickling, vaso-occlusion and infarction of tissue can occur anywhere in the body and commonly occurs in the lungs, bones, liver, and penis. Various factors may precipitate a vaso-occlusive event; such as temperature changes, infection, or stress; but often no inciting factor is described [1]. Treatment of vaso-occlusion is mostly supportive with non-steroidal anti-inflammatory agents, hydration and opiate therapy [14]. Daily administration of hydroxyurea therapy has been shown to safely protect against these vaso-occlusive events and prevent hospitalizations [15]. It is offered to patients 9 months old or older.

Increased Risk of Infection

Because of "functional asplenia" (either through autoinfarction or surgical removal to prevent recurrent splenic sequestration), patients with sickle cell disease are more susceptible to infection, especially with encapsulated organisms such as *S. pneumoniae* and *H. influenzae. S. aureus*, *V. streptococci*, *E. coli*, or *C. trachomatis* (Chlamydia), Mycoplasma and Salmonella species are also common pathogens [1]. Pneumococcal and influenza vaccines are recommended to commence as early as possible for all patients with sickle cell disease. Penicillin prophylaxis for infants and young children (until age 5 years) has been shown to reduce the risk of pneumococcal infections [16, 17]. Infections are the leading cause of mortality in pediatric sickle cell patients. Patients and families should be educated about the risk of serious infections and taught to seek medical care early in the disease course. Febrile patients with sickle cell disease should be evaluated, treated and monitored closely [1, 2].

Acute Chest Syndrome

Acute chest syndrome (ACS) is a disorder consisting of respiratory symptoms, pain, fever, and new infiltrate on chest X-ray. In some patients, especially pediatric ones, the symptoms can be vague and include extremity or abdominal pain [1]. Resembling pneumonia, but far more frequent in patients with sickle cell disease, ACS is a major cause of morbidity and mortality in this population, especially children [18]. It is thought to be due to either fat emboli or infection and leads to poor oxygenation from hypoventilation. This causes further sickling, pulmonary inflammation, and lung injury. ACS occurs frequently with an incidence second only to pain. Red blood cell transfusion, incentive spirometry, and macrolide antibiotics are the initial treatments. Treatment with bronchodilators is controversial. They are best used in patients with coexistent reactive airway disease. While many patients with ACS recover, the mortality is significant, especially in children [1, 2]. Hydroxyurea is recommended in patients with multiple or severe episodes of ACS to lessen the risk of additional events [16].

Acute Abdominal Pain

Acute abdominal pain is a frequent event in patients with sickle cell disease. While frequent causes of abdominal pain (such as constipation, gastroenteritis, or urinary tract infection) may be the culprit, other processes unique to sickle cell disease may be to blame [19].

Hepatic sickling can become so severe as to cause acute liver failure and progression to failure of multiple organ

systems. Immediate transfusion, simple or exchange, and plasma administration are required to decrease mortality [19].

In young children, acute abdominal pain may also be a sign of splenic sequestration. In this condition, massive red blood cell accumulation in the spleen results in acute and painful enlargement of the spleen and an associated drop in the blood volume/hemoglobin level that frequently leads to weakness and lethargy. This may cause hypovolemic shock and can be fatal. In patients under 10 years old, it is the second leading cause of death [19]. Intravenous fluid and transfusion must be given as soon as possible. After the patient's condition has stabilized, splenectomy may be considered due to the recurrent nature of this problem [1].

Cholelithiasis is common in patients with sickle cell disease. Half of patients will experience this by 18 years of age, and it is a frequent cause of acute and chronic abdominal pain. The history is often more vague in patients with sickle cell disease who do not necessarily report increased pain after meals. The timing of cholecystectomy is decided on a case by case basis [19].

Another cause of abdominal pain more frequently encountered in children with sickle cell disease is peptic ulcer disease. This is more common in children on Deferasirox and non-steroidal anti-inflammatory medications [19].

Of course vaso-occlusive disease may also be the cause of acute abdominal pain. It may be related to mesenteric sickling, bony change in the spine, or sickling in the liver or spleen. An infection causing an "acute abdomen" should be considered and radiographic studies obtained. Vaso-occlusive events of the abdomen often resolve with analgesics and hydration. However, care must be taken to rule out more ominous causes of acute abdominal pain [1, 19].

Stroke

If left untreated or unscreened, 11 % of children with HbSS or HbSβthal sickle cell disease will have a stroke by 20 years of age [20]. Ninety percent of first strokes are prevented by utilizing transcranial Doppler ultrasound screenings and chronic transfusion therapy [21]. Stroke, when it occurs, can have devastating neurological consequences leading to lifelong morbidity and cognitive delays. Following a first-time stroke, supportive therapy with chronic blood transfusions should be employed in an effort to reduce the risk of repeated events [1]. Moyamoya and other vascular abnormalities are frequently seen in children with sickle cell disease and increase the risk of cognitive delay and stroke [22]. In order to lessen the risk of stroke in patients with sickle cell disease, children from 2 to 16 years should have yearly transcranial Doppler ultrasound screenings. Transfusion should be performed if abnormal flow measurements are found [1, 16]. Other treatments such as hydroxyurea [1], bone marrow transplantation, and surgical revascularization may be indicated [22].

Priapism

Priapism occurs with greatly increased frequency in males with sickle cell disease. Approximately three-fourths of patients under 20 years old reported at least one such event. The first episode is usually when the patient is 12–15 years old [1, 23]. This is essentially a "compartment syndrome" of the penis due to vaso-occlusion from sickling. This can be mild and managed at home, recurrent, or severe. If severe and untreated, permanent structural damage [22] causing urinary retention and impotence can occur [1]. It is also associated with an increased risk of neurologic complications and increased morbidity. Treatment is aimed at relieving the vaso-occlusion of the venous drainage of the penis. Surgical drainage, alpha adrenergic agents administered orally or by injection, and transfusion have been advocated [1], but there are few large scale studies of efficacy [23].

Chronic End-Organ Damage

Chronic end-organ damage can be seen in the heart although myocardial infarction is rare. The lungs can have restrictive and/or obstructive damage as well as pulmonary hypertension [24]. The kidneys are commonly affected causing hyposthenuria and a higher incidence of renal medullary carcinoma and renal failure in adults. The liver, gall bladder and biliary system can also be adversely affected by long-term sickling with many patients requiring cholecystectomy. The skin can be involved leading to leg ulcers. Hearing loss is frequent owing to sickling in the vessels of the cochlea. The skeletal system may develop bony changes with the most severe occurring as osteonecrosis, especially of the hips and shoulders. The central nervous system can have frank stroke or "silent strokes" both of which can lead to cognitive delays and permanent impairment. Growth and development can also be adversely affected. There is increased mortality in patients with sickle cell disease, with life expectancy into the 40s and 50s [1]. Even sickle cell trait has been shown to be associated with chronic kidney disease, perhaps explaining the increased incidence of this in Americans with African ancestry [25].

Ophthalmic Manifestations

General

The eyes may be adversely affected by sickle cell disease. The vaso-occlusive events in patients with abnormal hemoglobin frequently happen in the eyes and periocular tissues.

While ocular complications tend to occur more frequently and worsen as the patient ages, they have been noted in children. We will examine these complications by location.

Orbit

Patients with sickle cell disease may infrequently present with eyelid edema, eye pain, and proptosis. While most of these cases are due to orbital bone infarction, orbital cellulitis should be considered because of the patient's increased risk of infection. Schündeln reported a case of orbital compression syndrome in an 8-year-old male with SS disease. This was due to bilateral orbital hematomas as a result of lateral orbital wall infarction during a sickle cell crisis. Hydration, transfusion, steroids, antibiotics, and analgesics were given. The hematomas resolved and vision remained intact [26]. Noble reported a similar event in a 20-year-old male with SS disease [27]. Ghafouri reported a 2-year-old boy with SS disease who had bilateral proptosis from orbital bone infarctions, The boy's proptosis fully resolved with IV prednisolone, hydration, and morphine, and IV ceftriaxone [28]. Ganesh reported the largest case series in the English literature of orbital involvement in sickle cell disease. He reported five cases: four had SS disease, and one had HbSβthal disease. All patients were 15 years or younger. They all responded to conservative treatment with hydration, transfusions (simple or exchange), analgesics, steroids, and antibiotics. No permanent vision loss was reported, although the final vision was not reported in one patient [29].

Even more infrequent causes of orbital involvement in sickle cell disease have been reported in adults. Adewoye described lacrimal gland enlargement in one woman thought to be due to sickling and the resultant inflammatory cascade in the lacrimal glands. The woman was treated with analgesics and antibiotics with resolution of symptoms and preservation of vision [30]. Renal cell carcinoma is associated with hemoglobin S (SS and AS). There is a report of an adult male patient with sickle cell trait that developed renal cell carcinoma metastatic to the orbit [31].

Conjunctiva

In patients with sickle cell disease, the conjunctiva can develop the so-called "comma" sign. When a thrombus forms in a conjunctival vessel, ballooning of the vessel wall occurs. The "comma" forms after such an event, with no blood on one side of the thrombus and a "tail of blood" on the other [32].

Serjeant was the first to devise a classification scheme for the severity of these conjunctival changes. There are five grades: 0 = normal; 1 = scant dilations of linear vessels that still appear attached to the surrounding vasculature; 2 = larger numbers of grade 1 vessels, with a few no longer connected to other vessels; 3 = small, straight, enlarged vessels with short, curved vessels that do not seem to connect to the surrounding ones; and 4 = many, dark, short vessels unconnected to other vessels. Serjeant also found that the stage of the conjunctival changes was positively correlated with an increased number of circulating irreversibly sickled cells [33]. Nagpal confirmed this and added that severity of these changes corresponded with the type of sickle cell disease. Sickle cell trait (or HbAS) was not found to exhibit conjunctival changes (0 of 10 patients) and SS was found to exhibit them more frequently (29 of 29 patients) than SC (15 of 26 patients) [34]. A nice photographic description of these changes as graded by Serjeant is included in both articles [33].

Clarkson studied 85 patients with sickle cell disease (SS, SC, HbSβthal) ranging from 28 to 123 months and found a prevalence of 59 %. The rate was higher at 70 % in SS disease, while it was only 34 % in SC and 17 % in HbSthal [35]. Friberg found the "comma sign" in 86 % in 110 patients. The vast majority of whom had SS disease (92 of 110, 84 %) [36]. Siqueira found that conjunctival changes increased in frequency with age and were worse in SS disease. Ninety-two percent of patients with SS disease had stage 3–4, compared to only 33 % with SC and 47 % with HbSβthal. All 39 patients with SS disease had grade 3–4 after they were older than 7 years, compared to only 11 of the 24 patients with SC and HbSβthal [37].

Cheung looked at 14 children and eight adult sickle cell patients' conjunctiva with computer-assisted intravital microscopy. They found fewer conjunctival vessels in patients with sickle cell disease. They also found differences in vessel caliber, tortuosity, shape, and distribution. Sludged flow, boxcar flow, abnormal RBC morphology, abnormal artery to vein ratio, and hemosiderin deposits were also seen. It is further stated that these abnormalities are worse in adults [38]. While these changes do not affect vision, they are an easily observable way to see and estimate the damage that sickle cell disease is inflicting on the entire vascular system.

Anterior Segment

Hyphema

A hyphema is defined as blood in the anterior chamber of the eye. While non-traumatic causes are responsible for a small number of hyphemas, most, especially in children, are due to blunt trauma. The force of impact causes compression of the eyeball, stretching the vessels of the iris and drainage angle. This can lead to bleeding into the anterior chamber. While most of these resolve uneventfully, re-bleeding, glaucoma (increased intraocular pressure), corneal bloodstaining, and optic nerve damage are possible. Patients with both sickle cell disease and sickle cell trait experience more complications than patients with normal hemoglobin. The reason for this is the abnormally shaped sickle cells have more difficulty exiting the anterior chamber through the drainage angle

of the eye [39]. This places these patients at higher risk for increased intraocular pressure (IOP). The increased IOP also leads to less oxygenation in the anterior chamber which creates more sickling and more stagnation of the RBCs. The increased IOP also causes less perfusion of ocular tissues, raising concern that there will be optic nerve damage from increased IOP or retinal artery occlusions [39–41].

Radius described an 18-year-old female with HbAS (sickle cell trait) who sustained ocular trauma. She presented with a hyphema, light perception vision, and IOP of 55 mmHg. IV Mannitol was administered to no avail and vision decreased to no light perception (NLP) after one hour. Anterior chamber paracentesis was used to restore her vision to light perception and acetazolamide was used to control her IOP. The young woman's final vision was 20/30, but her optic disc was pale. The authors conclude that she had a "reversible central retinal artery occlusion (CRAO)" [40].

Michelson reported two cases of CRAO after hyphema in patients with sickle cell trait. The first was a 9-year-old girl with IOP in the mid 30s (mmHg) for one week after vitreous hemorrhage from a blow to her right eye with a rock. She was managed conservatively and after one week the hemorrhage was gone and the IOP back to normal with 20/40 vision. Three weeks later she returned with NLP vision in her right eye and an IOP of 40 mmHg with angle recession, an afferent pupillary defect (APD), and a pale optic nerve. The second patient was a 17-year-old boy, hit in the right eye with a softball, who developed a 5 % hyphema and IOPs in the mid-30s to upper-40s (mmHg). He had a sudden loss of vision (his vision deteriorated to hand motions) and vitreous hemorrhage. Despite maximal medical management his IOP rose to 50 mmHg and his vision went to NLP. Emergent anterior chamber paracentesis returned his vision to 1/200 and IOP was thereafter maintained in the normal range with medicine. Six months later, his vision returned to 20/20. The authors attribute this to a CRAO that was caught in time to prevent permanent vision loss, save a small scotoma on formal visual field testing [42].

Sorr reports an 8-year-old male with HbAS (sickle cell trait) who sustained blunt trauma and lost vision. He presented with light perception (LP) vision, IOP of 34 mmHg and microhyphema. Twenty-four hours later, the disc was swollen and hyperemic with tortuous veins and a cherry red spot. Prednisone was started orally, but the patient lost all vision [41].

Nasrullah reported three patients with sickle cell trait who developed optic atrophy (presumably due to CRAO) after traumatic hyphema. Those patients had presenting IOPs of 39, 50, and 56 mmHg. Hence the recommendation that anterior chamber washout be preformed for sickle cell disease and sickle cell trait patients with IOPs above 30 mmHg [43].

Patients with sickle cell disease and sickle cell trait are thought to experience higher rates of rebleeding after hyphema than patients without the HbS mutation. This is likely due to abnormalities in clotting function. Lai found a similar risk of rebleeding in African American patients with and without SS or HbAS [44]. However, a larger study found that sickle cell trait (HbAS), not merely African American race, was a significant risk factor for secondary hemorrhage and increased IOP after traumatic hyphema [43]. Rebleeding after the initial injury increases the risk of increased IOP, optic nerve damage (from glaucomatous damage or CRAO), and corneal blood-staining.

Patients with hyphema should be screened for sickle cell disease (or trait) with a "sickleprep" or "sickle dex" test. If positive, the patient should be approached with even more caution than other patients with this injury. Patients with the HbS mutation should be followed daily with hospital admission seriously considered.

If a patient's IOP exceeds 24 mmHg, medical therapy should be initiated. Topical timolol is the first line of treatment. Oral carbonic anhydrase inhibitors (CAIs), especially acetazolamide, should be used with caution as these medications tend to create a metabolic acidosis contributing to further sickling. Methazolamide is likely a better choice, as it is less likely to create a metabolic acidosis [39]. While there are no studies regarding the safety of topical CAIs, there is a theoretical risk of decreasing pH in the anterior chamber and locally creating more sickling. Most agree that these should be avoided. The use of systemic osmotics is generally not recommended as they can lead to hemoconcentration and further sickling in the anterior chamber. IOP control of 24 mmHg or less within the first day is usually a positive sign that adequate IOP control is possible with medical management alone. If IOP is greater than 24 mmHg for greater than 24 h despite maximal medical management, surgical intervention should be considered. Also if IOP spikes to 30 mmHg or more on more than one occasion despite appropriate medical therapy, surgical evacuation of the blood should be undertaken [45].

Visual outcomes in patients after hyphema and surgical intervention are limited due to a lack of reports of long-term follow-up. However, visual outcomes tend to be good if no rebleeding occurs and any increased IOP is controlled medically. The results seem worse if rebleeding occurs or if surgery is necessary for increased IOP [43, 45].

Neovascular Glaucoma

Neovascular glaucoma is rare in patients with sickle cell disease or trait without other systemic conditions. Bergren reported a case of a 24-year-old male with SS disease and a history of retinopathy and vitreous hemorrhage in one eye whom, 4 years later, presented with neovascular glaucoma from retinal ischemia in the other eye. Laser photocoagulation and medical treatment of his glaucoma did not satisfactorily resolve the glaucoma and a Molteno glaucoma drainage device was implanted [46].

Iris

Iris atrophy was reported in one study to occur in 22 patients. Two of the patients had SS and 20 had SC disease. There was a high association with proliferative sickle retinopathy. The authors state that "many" of these patients had received laser treatment for their retinal disease so damage of the iris by the laser therapy could not be excluded. However, iris angiography did confirm avascularity in the areas of atrophy [47].

Choroid

Angioid Streaks

Angioid streaks are linear areas in the choroid (the vascular layer beneath the retina) where thickening and degeneration have occurred. They appear as "dark-brown, brownish-red or grayish lines or streaks suggestive of cracks in an old painting". They usually begin from a whitish or pinkish ring surrounding the optic disc and radiate outward [10]. As they extend peripherally from the disc, they taper down to an end point a few millimeters from their origin, therefore confining themselves to the posterior pole (see Fig. 11.1). They tend to occur in both eyes.

The pathogenesis of angioid streaks is poorly understood, especially in the setting of sickle cell disease. Clarkson [48] reports that along with sickle cell disease, the most common relationships are with pseudoxanthoma elasticum and Paget's disease. While they are associated with the hemoglobinopathies, they appear to be a rare feature, occurring in 1–2 % of patients with these diseases. They seem to increase with age and are not in and of themselves associated with vision loss. They have been noted to rarely cause visually significant complications, usually in the form of choroidal neovascular membranes [49]. Since there are breaks in Bruch's membrane, the vessels from the choriocapillaris are allowed, under certain circumstances, to grow unchecked under the retina leading to hemorrhage and serous retinal detachment. Angioid streaks also cause the eye to be more fragile leading to these eyes being called "egg-shell eyes". As a result, contact sports should be avoided by patients with angioid streaks [50].

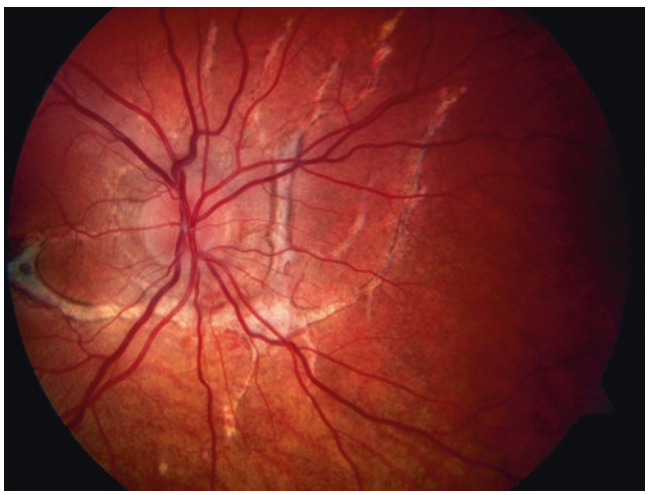

Fig. 11.1 Angioid streaks. Note the "star like" hypopigmented areas surrounding the optic nerve, courtesy of Edward Chaum, M.D. Ph.D.

Choroidal Infarctions and Ischemia

Choroidal infarctions and ischemia have been reported. Some believe that they cause the "black sunbursts" seen in the retina. Dizon documented a patient with SS disease who developed amaurosis and had angiographic and clinical evidence of choroidal infarction on two different occasions. She further noted that the incidence of this is not known as it can be asymptomatic leaving only non-specific retinal pigment epithelium (RPE) changes [51].

Retina

Macular complications of sickle cell disease can be acute macular occlusions and chronic macular changes. The macula is the area of the retina responsible for central vision. Acute changes include cotton wool spots (which represent vaso-occlusions of arterioles), "microaneurysm-like dots, dark and enlarged" arteriolar segments, and "hairpin-shaped venular loops". Many have reported macular infarctions in adult and pediatric patients with sickle cell disease [52–54]. Merritt reported a case of a 10-year-old girl with HbSS that developed bilateral infarctions of the macula with severe vision loss in the right eye (light perception) and mild loss (20/30) in the left. Hydration and transfusion improved left eye vision to 20/15, but her right eye only returned to counting fingers at 3 in. [55].

Chronic changes result from multiple vaso-occlusions of macular vessels leading to an enlarged foveal avascular zone (FAZ) [56]. Since most of these patients retain good vision, Lee studied this phenomenon with fluorescein angiography and Octopus visual field testing (of the central 30°). She found that for these patients the FAZ was indeed abnormal (enlarged) as were their Octopus visual field results [57]. Asdourin did not find corresponding visual field defects with the Goldman or Amsler grid despite angiographic evidence of severe macular changes [56]. Cusick reports a case of bilateral sickle cell macular disease in a patient with SC disease (he notes this is more common in SS disease). The presentation was unusual in that the patient's chief compliant was "dark spots" in his nasal field. Indeed he did have nasal visual field defects, which are usually considered to be optic nerve related. However, the use of ocular coherence tomography (OCT) and multifocal electroretinography (mfERG) allowed diagnosis of the retinal vascular pathology [58].

Epiretinal membranes (ERMs) are another rare complication of sickle cell disease. Moriarty [59] found a rate of 4 % in SS and SC patients that were under 60 and had not had previous laser surgery. He found the risks for ERM formation to be proliferative sickle cell retinopathy (PSR), the more extensive, the higher the risk; and vitreous hemor-

rhage. The risk for ERM formation was lowered by successful treatment of PSR [59]. Clarkson studied 85 patients with sickle cell disease (SS, SC, HbSβthal) ranging from 28 to 123 months and found a prevalence of 1.3 % for macular hole, 2 % for ERM, and 1.3 % for macular pucker [35]. Carney found a rate of ERM formation of 3.7 %, but that included patients with previous laser surgery, a known risk factor for ERM formation. Carney also reports a patient that developed a macular hole after ERM progression. Close observation of patients with ERMs from sickle cell disease is recommended [60].

New technology such as OCT can be especially useful in diagnosing macular pathology from sickle cell disease. Witkin reported a case of bilateral infarction of the branch retinal artery as documented on OCT [61]. Robert reports a 13-year-old female with HbSS disease that developed a central retinal artery occlusion in the left eye and thinning of the nerve fiber layer in the temporal median raphe of the right eye. The girl was asymptomatic and her vision was 20/20. She had stenosis of the internal carotid artery on the right side. The authors postulate that this retinal pathology was due to ocular ischemia [62]. Chow found retinal thinning with corresponding diminished sensitivities on microperimetry testing (measuring the patient's response to light stimuli at various retinal points followed by superimposing the data on a scanning laser ophthalmoscope (SLO) image). These patients all had good vision. While peripheral retinal pathology is more common, it is important to note that macular disease occurs in patients with abnormal hemoglobin [63].

Non-proliferative Retinal Disease

Venous Tortuosity

Clarkson studied 85 patients with sickle cell disease (SS, SC, HbSβthal) ranging from 28 to 123 months and found an incidence of 11 % for venuous tortuosity. The incidence was 14 % percent in patients with SS disease, 3.4 % in patients with SC, and 0 % in those with HbSβthal [35]. There does not appear to be a correlation with severity of tortuosity and the severity of the anemia. Others have found the rates of vascular tortuosity to vary between 10 and 50 % [64], with rates of 29 % in SS patients and 19 % in SC patients [36] (see Fig. 11.2).

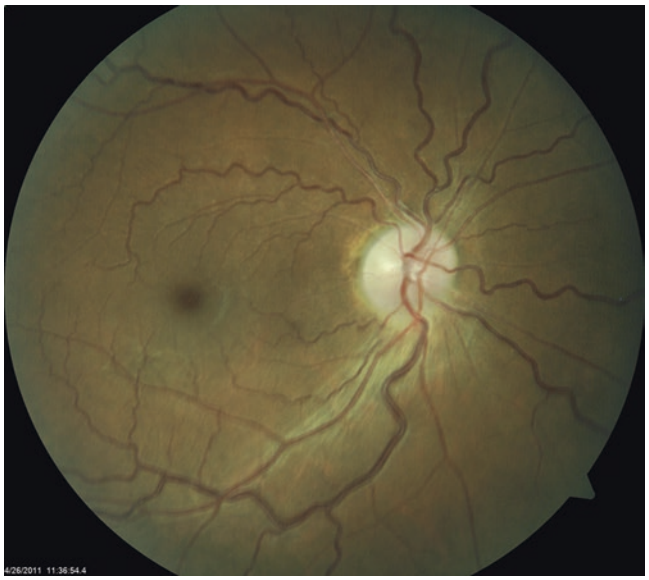

Fig. 11.2 Vascular tortuosity, courtesy of Edward Chaum, M.D. Ph.D.

Salmon Patches and Schisis Cavities

Occlusions of arteries within the retina will rupture the vessel's walls creating an intraretinal hemorrhage. Within several days, the red blood develops a "salmon" color, hence the name, "salmon patches". With continued resolution these may result in a schisis cavity with iridescent spots that represent macrophages containing hemosiderin. Welch and Goldberg, who first used the term, noted that the salmon patch could also become a "black sunburst" which represents migration of retinal pigment epithelial (RPE) cells into the retina after such an event. These misplaced RPE cells have undergone hypertrophy and hyperplasia to create the black retinal scar [12]. Gagliano later confirmed this photographically [65]. Others think the "black sunburst" is actually due to choroidal ischemia or choridal neovascular membranes that occur after choroidal infarction [66, 67]. Perhaps both can lead to these depending on the level of RPE disruption by vaso-occlusive events. In Clarkson's study of 85 patients (SS, SC, HbSβthal) ranging in age from 28 to 123 months he found a prevalence of 17 % for retinal hemorrhage (RH) and 28 % for schisis cavity/iridescent spots in patients with SC disease. The rates were 2.8 % for RH and 3.7 % for schisis cavity in patients with SS disease and 8.3 % for RH and 0 % for schisis cavity in patients with HbSβthal [35]. Friberg found black sunbursts in 46 % of 92 patients with SS disease, 63 % of eight patients with SC disease and 37 % of ten patients with HbSβthal [36].

Proliferative Retinal Disease

Goldberg was the first to devise a classification system for proliferative sickle cell retinopathy (PSR) based on clinical findings. The following is a brief description of each stage of PSR [68, 69].

Stage I: Peripheral arteriolar occlusions
Vaso-occlusive events in the small arterioles of the peripheral retina cause the normal terminus of the retinal vessels to end progressively closer to the macula and thus progressively farther from the ora serrata (the normal end point of retinal vessels).

Stage II: Peripheral arteriolar-venular anastomoses

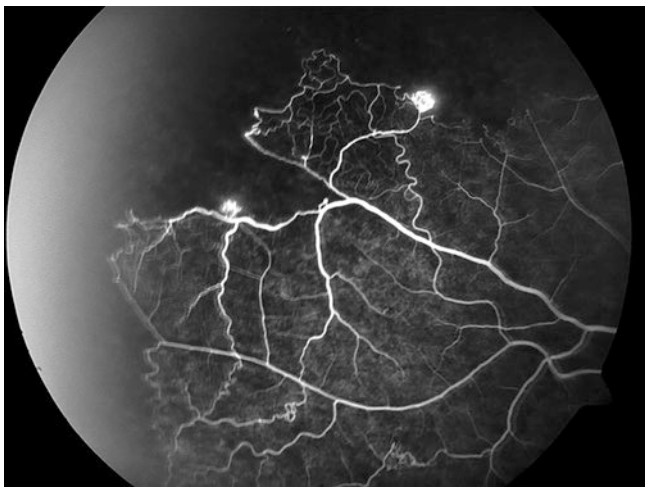

Fig. 11.3 Angiography of a patient with sickle cell retinopathy showing non-perfused retina with early neovascularization, courtesy of Edward Chaum, M.D. Ph.D.

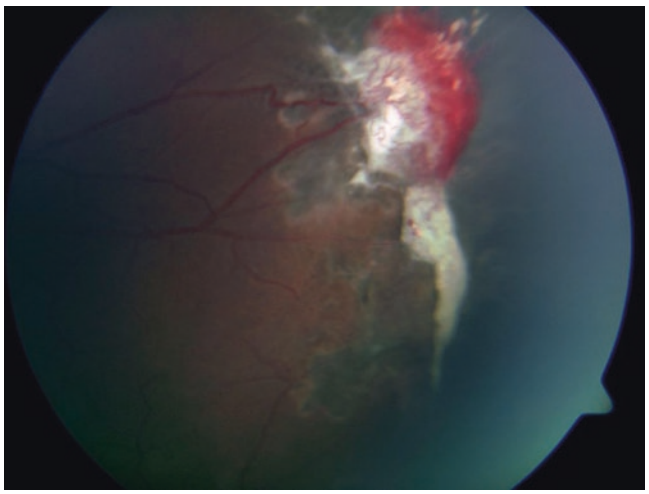

Fig. 11.5 Sea fan with hemorrhage, courtesy of Edward Chaum, M.D. Ph.D.

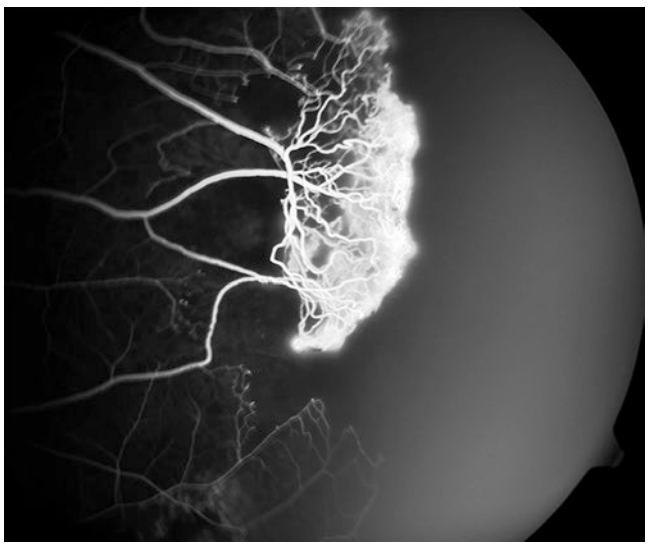

Fig. 11.4 Angiography of a sea fan, with avascular retina peripheral to the area of neovascularization. Courtesy of Edward Chaum, M.D. Ph.D.

The occluded arterioles fuse with pre-existing capillaries to form a connection with a venule. This forms loops at the terminus of the retinal vessels, which leaves avascular retina between this new endpoint of vascularization and the ora serrata [68]. McLeod found that the arteriovenous anastomoses formed "hair-pin loops" that were the result of new vessel formation between an occluded vessel and a patent one [66] (see Fig. 11.3).

Stage III: Neovascular proliferation
New vessels grow toward the area of ischemic retina and look like "sea fans" (Gorgonia flabellum). Fed by one or more arteriole and having one or more draining venule, these can coalesce and become larger (see Fig. 11.4). They often remain flat along the surface of the retina, but may grow into the vitreous causing traction, vitreous hemorrhage (see Fig. 11.5), or tractional retinal detachment. If the traction becomes sufficient, a rent may be created in the retina, causing a rhegmatogenous retinal detachment.

Stage IV: Vitreous hemorrhage

Stage V: Retinal detachment

Clinical and Angiographic Identification of Stages of PSR

While the above system is based on clinical examination alone, new technology such as non-contact wide-field angiography allows visualization and photography of the retina all the way to the ora serrata in one image. Cho described the use of non-contact wide-field angiography in the diagnosis of six patients (12 eyes) with significant peripheral retinal changes. These were not noticed clinically in 25 % of the eyes, they were only detected on wide-field angiography [70].

Management/Treatment

Untreated sickle cell retinopathy has been reported to cause vision loss (20/60 or worse) in 10 % of patients. Half of these were legally blind at 20/200 or worse. Almost all vision loss was attributable to proliferative disease. This was almost always caused by epiretinal membrane, traction retinal detachments (although one patient developed a rhegmatogenous detachment) or vitreous hemorrhage. Angioid streaks [leading to choroidal neovascular membrane (CNV)], sickling maculopathy and branch retinal artery occlusion (BRAO) were less frequent causes of vision loss in non-proliferative disease [71]. Proliferative retinopathy (and

retinopathy in general) is more common in SC disease and HbSβthal than SS disease [72].

Clarkson found the prevalence of proliferative retinopathy to be 18 % when all three groups (SS, SC, HbSβthal) were combined. If each group was examined independently, SS patients had a prevalence of 11 % and HbSβthal patients had a prevalence of 17 % [35]. He found a prevalence of vitreous hemorrhage of 21 % in patients with SC disease and 1.8 % in patients with SS disease. Retinal detachment was seen in 10 % of patient with SC disease. The incidence of PSR increased in patients over 40 years. While PSR is less common in children than in adults, it can occur and be vision threatening. Clarkson also reports an 11 year old that had Stage III disease in one eye and non-proliferative retinopathy in the other on initial exam. He eventually lost all vision in the more severely affected eye due to unsuccessful surgery to repair a retinal detachment.

Friberg found in patients with SS disease from 8 to 20 years old (34 patients) that the incidence of peripheral vascular occlusions was 9 %, arteriovenous anastomoses was 2 % and vitreous hemorrhage was 3 % [36]. However, Hayes did not find any proliferative retinopathy in patients with SS disease who were under 19 years old [73].

Penman looked at peripheral retinal changes angiographically in children with sickle cell disease in the hopes of stratifying risk for development of PSR. He classified type I as "fairly" normal peripheral retinal vasculature, with continuous arteriovenous loops. Type II did not have continuous loops and gave the appearance of "moth-eaten" vasculature. While few patients in his study developed PSR, all that did had Stage II disease prior to its development. He therefore concluded that this method of assessing angiography could be used for screening for the development of PSR [74]. Interestingly, all but one of the patients that developed PSR had SC disease [74].

Eruchalu looked at 37 patients under 13 years old who had severe systemic SS disease. "Severe" was defined as three or more vaso-occlusive events in 1 year. Thirty-two percent had retinopathy and three eyes of two patients had proliferative disease. All of these patients were 8 years old or older. After one year, one had received laser treatment and the other was stable. They recommend yearly screenings after age 8 in this high-risk group [75].

Goldberg found a tendency toward progression of PSR in 25 eyes of 16 patients with SC disease, although only one lost vision [76]. In Clarkson's study, only three patients had 20/30 or less vision on presentation and only five developed vision loss over the 6 years of follow-up [35]. Condon found that 61 % of PSR lesions autoinfarcted in his study of sickle cell patients followed over 8 years. He noted that the fastest progression of PSR lesions occurred in patients 15–29. Only, 12 % of eyes lost vision due to PSR. While many lesions autoinfarct, others go on to cause vitreous hemorrhage, retinal detachments, and vision loss [77].

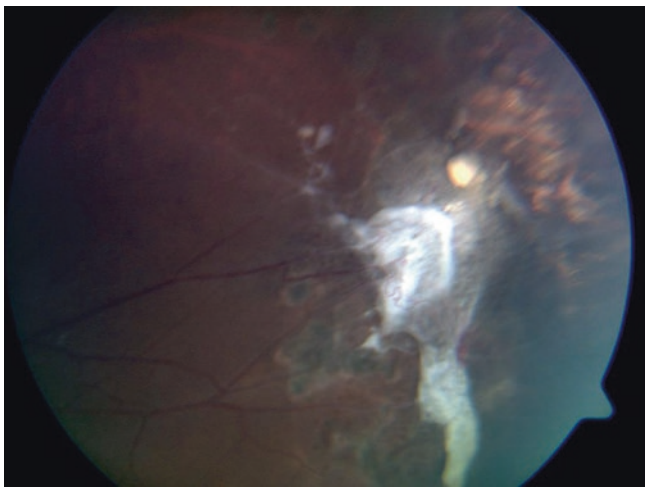

Fig. 11.6 Regressed sea fan after laser treatment (panretinal photocoagulation), courtesy of Edward Chaum, M.D. Ph.D.

Since a significant percentage of cases of PSR autoinfarct (20 % according to Nagpal) [77, 78], the treatment of PSR is somewhat controversial. Usually treatment is not indicated until active neovascular proliferation (Stage III) has occurred in both eyes, or rapid progression of PSR, or proliferative disease in patients with only one remaining eye [79]. Historically, laser occlusion of the feeder vessel to the proliferation was employed. However, this was fraught with complications, including breaks in Bruch's membrane, choroidal neovascular membrane development, choroidal ischemia, retinal detachments and vitreous hemorrhage [80, 81]. More recently panretinal photocoagulation, either sector or 360° treatments, has been utilized (see Fig. 11.6). Farber reported on 174 eyes in 116 patients randomized to either scatter photocoagulation (99 eyes) or observation (75 eyes). In the treatment group, 30 % achieved total resolution and 51 % partial resolution. In the observation group 22 % and 24 % achieved total and partial resolution, respectively. The treated eyes had slightly less visual loss (3 %) than did the control group (8 %) [82]. Fox reported a series of 88 patients with SC disease that were randomized to observation or sector laser photocoagulation. There was a higher rate of regression of neovascularization (NV) in the treatment group, although only a few in both groups had complete resolution of NV. If the patient was younger than 25 years old and NV was flat and small, there was a better chance that the lesion would infarct [81]. Sayag noted that Stage III was more common in SC disease and in the 20–31 year olds. Lesions in patients in their 40s tended to remain stable [83]. Condon reports that progression of PSR is more common in younger patients (15–29 years) and autoinfarction more common in older ones (29 and older) [77]. Fox also found progressive disease only in

patients under 40. He also noted higher rates of autoinfarction in patients over 40 and in patients with SS disease. This would suggest the need for more aggressive management of younger patients and a tendency to observe in patients 40 and over, especially in the setting of SS disease [84].

Sayag classified sea fans (Stage III PSR) in order to attempt to stratify risk of progression. He defined the following: Grade A: "sea fan with leakage less than 1 Macular Photocoagulation Study (MPS) disc area" on fluroscein angiography; Grade B: "elevated sea fan with hemorrhage"; Grade C: "elevated sea fan with partial fibrosis"; Grade D: "complete sea fan fibrosis without well demarcated vessels"; Grade E: "Complete sea fan fibrosis with well demarcated vessels". He identified 73 eyes of 101 patients with PSR and randomized them to scatter laser photocoagulations with argon green laser (38 eyes) or observation (35 eyes). He found that Grades A and C did not do statistically better with treatment while Grade B did. He further found that the only complications that occurred were in patients that were untreated and belonged to Grades B and E. Four developed vitreous hemorrhage and three developed rhegmatogenous retinal detachment [83].

While laser photocoagulation is the usual modality for the treatment of Stage III PSR, Seiberth reported a case of successful trans-scleral diode laser photocoagulation for the treatment of PSR. In this particular case, there was a vitreous hemorrhage, obscuring the view of the retina, so traditional laser treatment was not an option [85].

Vitreous hemorrhages usually remain localized over the site of neovascularization. They can, at times, spread over the macula and interfere with vision [69]. If vision is affected, the patient is usually followed for 6 months to see if the vitreous hemorrhage will clear. If it does not or a retinal detachment occurs, surgery is performed. However, both systemic and ocular complication rates are higher in patients with sickle cell disease. Therefore, careful consideration of the risks and benefits as well as proper pre-operative care of the patient are required [86].

The need for surgical treatment of Stage V sickle cell retinopathy (retinal detachment) is rare in children, however it is indicated at times. The techniques have improved over the years. Anterior segment ischemia was a dreaded complication of retinal buckling procedures. Ryan and Goldberg [87] reported six of ten eyes in patients with SC disease that developed anterior segment ischemia after scleral buckling for retinal detachments. Four eyes became phthisical or prephthiscial, while the other two regained 20/20 or 20/25 vision [87]. Some advocated transfusion prior to such surgeries and even then had significant post-operative complications. Newer vitrectomy and buckling techniques have been employed successfully, without anterior segment ischemia. Preoperative transfusion is no longer recommended routinely. Intraoperative attention to adequate hydration and oxygenation by the anesthesiologist and good control of intraocular pressure by the surgeon seem to limit the rates of this complication [88]. Chen looked at 15 eyes of 14 patients that underwent retinal surgery for sickle cell eye disease: six for vitreous hemorrhage, one for ERM, and eight for retinal detachment. All had local anesthesia. All had vitrectomy, and two additionally had retinal bands placed. While four patients in the retinal detachment group developed another detachment and required further surgery, none developed anterior segment ischemia. Visual results were good in the vitreous hemorrhage and ERM group (20/60 or better), and as expected in the retinal detachment group (20/400 or better) [88].

Williamson reported the results of 27 patients with PSR, ERM, or vitreous hemorrhage. For reasons not fully explained, 10 of them were observed. One had an inoperable retinal detachment. Some (no number given) were vitreous hemorrhages that cleared and some had traction retinal detachments that did not progress. Two resolved, one with a rhegmatogenous retinal detachment that spontaneously flattened and one with an ERM that resolved with posterior vitreous detachment development. None of the patients had pre-op laser surgery because the author believed it would increase the risk of anterior segment ischemia. There were no reports of this in any of the patients studied. Of the 18 eyes of 17 patients who had surgery, iatrogenic retinal tears developed in seven, vitreous hemorrhages in two (one requiring more surgery), and cataracts in three. Eighty-three percent had improved vision after surgery or surgeries [89].

Leen reported a case of anterior segment ischemia after vitrectomy. The patient had hypotension during surgery and intraoperative laser was employed, possibly contributing to the complication [90].

The role of bevacizumab in the treatment is still being elucidated. Several case reports have noted regression of neovascularization in patients with PSR [91, 92], but one noted a hyphema after injection [93].

Central retinal artery occlusion is a rare complication of sickle cell disease. Liem reports three cases in patients with SS disease. In his review of the literature, no other types of hemoglobinopathy have been reported to have CRAO. His patients, as well as most in his review, were treated with exchange transfusion resulting in 71 % recovering some or all of their vision [94]. Fine reported a case of spontaneous CRAO in a patient with sickle cell disease. This case was also remarkable because vision improved, without treatment, to 20/60 [95]. Brown reports one case of a 14-year-old patient with SS disease who developed a central retinal artery occlusion during an acute pain crisis. No further details are given [96].

Optic Disc

The phrase "disc sign of sickling hemoglobinopathies" refers to dark red spots or "curlicue" vessels on the optic nerve

head. They are transient occlusions of the small vessels of the disc, analogous to those seen in the conjunctiva. Like the conjunctival sign, the disc sign is more frequent in patients with SS disease. Goldbaum found a rate of 11 % in 80 patients studied. The group consisted mostly of patients with SS disease [97]. Clarkson found a prevalence of 12 % in patients with SS disease. No one in the SC or HbSβthal group was noted to have this [35]. Neither author reported visual sequela from these vascular changes. Neovascularization of the optic disc has been rarely reported in hemoglobinopathies [64].

Henry described three cases of idiopathic intracranial hypertension in three patients with sickle cell disease. One patient had SC disease and two had SS disease. They were all successfully treated with acetazolamide without any complications, either systemic or ocular [98].

Ophthalmic Complications of Sickle Cell Trait

While patients with sickle cell trait have been reported to develop ocular complications, it is usually in the setting of concomitant systemic disease or ocular trauma [69, 99–102]. Taban reported a case of frosted branch angiitis in a 4-year-old girl with sickle cell trait [103]. Lim reported an adult patient (58 years old) with sickle cell trait and hypertension who developed a superior ophthalmic vein thrombosis. The patient had orbital pain, diplopia, 4 mm of proptosis and 20/25 vision. Oral warfarin was given and the patient's condition was fully resolved with 20/20 vision 2 weeks later [104]. Wax and coworkers reported a case of a 14-year-old male with traumatic hyphema that developed IOPs from 28 to 43 mmHg. Nine days after injury his vision decreased to 6/60 and his IOP was 36 mmHg. There was acute cupping of the optic nerve and retinal whiting with a "cherry-red spot". Angiography and electroretinogram (ERG) confirmed an impending CRAO. An emergent paracentesis was performed and the patient's vision improved to 6/15 9 days afterward. The cupping resolved as well. The authors used acetazolamide and isosorbide in the initial management of the glaucoma. However, they advocate not using these modalities as they may have contributed to further sickling, increased IOP, and retinal occlusion [105]. Brown reported two patients with sickle cell trait who developed CRAO: one was a 9 year old who developed a CRAO after ocular trauma (no further details are discussed) and the other was a 24-year-old male with rheumatic heart disease in addition to sickle cell trait [96].

Hedreville reported a case of a 26-year-old cyclist with sickle cell trait who developed a central retinal vein occlusion (CRVO) shortly after a cycling race in a very hot environment. The patient had noted a sudden loss of vision a few months prior that resolved within 2 days. At the time of CRVO development, he also had four blood clots in the left atrium of his heart. This lead the authors to believe that the intense exercise, dehydration, and hot environment caused hemodynamic changes significant enough to cause clotting in this patient with "just sickle cell" trait. The patient developed neovascular glaucoma and despite aggressive treatment developed total retinal detachment and bare light perception vision [106].

Barry reported a case of a 3.5 year-old boy with sickle cell trait who presented with leukocoria and esotropia in the left eye due to vitreous hemorrhage. Ischemic changes were noted in the right eye. Vitrectomy and photocoagulation were performed on the left eye and vision returned to 20/32 [107]. Jackson reported three cases of retinopathy in patients with sickle cell trait: one was a 14-year-old boy who developed salmon patches and peripheral vascular occlusions after traumatic hyphema with increased IOP; and the other two patients were adults with glaucoma [108].

As mentioned in the anterior chamber/glaucoma section, patients with sickle cell trait are at increased risk of complications after traumatic hyphema. Please see that section for further details and treatment recommendations.

Diagnosis

A child with sickle cell disease will be asymptomatic at birth due the presence of fetal hemoglobin, which is protective; however, anemia and reticulocytosis develop during the first months of life due to the physiologic switch to adult hemoglobin. The classic blood smear occurs after 3 years when the majority of hemoglobin is the adult form [1]. In the United States, screening is performed in the "newborn screen" on all children born in a hospital. The majority of screening programs use isoelectric focusing (IEP) of an eluate from dried blood spots and some utilize high-performance liquid chromatography (HPLC) or cellulose acetate electrophoresis as the initial screening method. Confirmatory testing with complementary electrophoretic methods should be performed in abnormal initial tests. Solubility tests such as the "sickle prep" or "sickle dex" are inappropriate screening or confirmatory assays, in part because high levels of fetal hemoglobin (thus low levels of HbS) give false negative results in infants with sickle cell anemia.

Diagnosis of sickle cell retinopathy, before it becomes visually devastating, requires screening. Screening for sickle cell retinopathy in adults is yearly, sooner if complications arise. In children, the recommendations are a bit less clear. Gill recommends starting screening for sickle cell retinopathy at age 9 for patients with SC disease and 13 years for patients with SS or S β Thalassemia [109]. Others suggest beginning screening at age 10 for all these patients [110], while Eruchalu recommends screening yearly after 8 years old [75]. There is also disagreement about follow up exams. Gill recommends yearly exams [109], while others recommend yearly for SC disease and every 2 years for SS and S β Thalassemia.

Management

Hydroxyurea is a commonly used medication in sickle cell disease. It increases the proportion of fetal hemoglobin and decreases dense cells. It also increases mean corpuscular value and mean corpuscular hemoglobin [1]. These changes reduce complications normally associated with hemoglobinopathies. While guidelines exist, initiation and management of this medication should occur in consultation with a hematologist. Of note, ocular complications of hydroxyurea have rarely been reported. Limbal stem cell deficiency with eye pain, photophobia, corneal ulceration, opacification and loss of vision have been documented in patients receiving this medication [111, 112].

Anemia is a common complication of sickle cell disease. This and other indications create the need for chronic transfusions. In such patients, iron overload can lead to other complications, namely liver dysfunction. To avoid these complications, iron chelation therapy is often employed with deferoxamine (Desferral) and Deferasirox (Exjade). Desferoxamine has been reported to cause a myriad of ocular complications including optic neuropathy and retinopathy [113, 114]. Deferasirox is also thought to cause similar complications although there is scant evidence of such in the literature [115, 116].

Care of Pre-operative Patient

Patients with hemoglobinopathies are at higher risk of systemic and ophthalmic complications. Adequate pre-operative hydration, consideration of transfusion, and adequate oxygenation during the procedure are needed. An 11-year-old girl with SC disease died following evisceration after orbital trauma, proving adequate pre-operative and intra-operative care must be achieved even in the emergency setting [117]. Pre-operative consultation with hematology and anesthesiology is needed.

Prevention of Ophthalmic Disease

Hydroxyurea holds promise for decreasing the incidence of retinopathy in childhood. Estepp observed 123 children (under 19 years) with SS disease. Lower hemoglobin F levels were associated with an increased incidence of retinopathy. Additionally, 72 of the 123 children started hydrocarbamide (hydroxyurea) during the study. Of those, 8 % developed retinopathy while 14 % did so in the untreated group. While not a statistically significant difference, the treatment holds promise for preventing eye disease in children with sickle cell disease [15].

Leukemia

Definition

Ocular involvement by leukemia has long been recognized [118]. Leukemia is a neoplasm of the leukocytes (white blood cells). The prognosis for childhood leukemia has improved enormously since the 1970s [119] due to improved chemotherapy, new understanding of the natural history of the disease, bone marrow transplantation and better supportive care of the patient [120].

The leukemias are classified into acute and chronic forms as well as lymphoid and myeloid cell types. The classification is based on the cell type and maturation. In general, acute leukemias have more primitive appearing cells. The clinical course of the acute and chronic leukemias is also quite different, with acute leukemia having a relatively rapid and relentless deterioration unless treated aggressively.

The cells of acute lymphoblastic leukemia (ALL) are derived from the lymphocyte cell line. Acute and chronic myeloblastic leukemias (AML and CML, respectively) are derived from primitive myeloid cells [119]. There is increasing use of genetic evaluations to determine prognosis and subtypes of ALL and AML [121].

History

Leukemia was initially thought to be a suppurative disease of the blood [122]. With the advent of formal histopathology in the nineteenth century, leukemia was recognized to be a malignancy of leukocytes. Prior to the advent of bone marrow biopsy, Liebreich in the 1860s [123] recognized that the fundus examination was helpful in making the diagnosis of leukemia [118]. The study of Ridgway and coworkers was the first to review leukemic ophthalmopathy in children [124].

Epidemiology

The leukemias are the most common malignancies of childhood. It is estimated that approximately 3250 new cases are diagnosed each year in the United States in children less than 20 years old [119]. Of childhood leukemias, ALL makes up 75 %, AML accounts for 15–20 %, chronic myeloid leukemia makes up less than 5 %, and chronic lymphocytic leukemia is virtually never seen in children [120]. ALL occurs at a rate of 29.2/1 million while AML occurs at a rate of 7.6/1 million in children less than 20 years old [119].

Systemic Manifestations

Common presenting signs of ALL are fever, hemorrhage, bone pain, lymphadenopathy, hepatosplenomegaly, splenomegaly, mediastinal mass, and central nervous system (CNS) disease [120, 125]. Clinical features of childhood ALL at the time of presentation depend on the extent of disease. An elevated white blood cell count may cause cerebrovascular accident, renal failure, retinal cotton wool spots, or mild respiratory distress. Central nervous system involvement, while occurring in both AML and ALL is more common in ALL. Distinctive presentations of AML are granulocytic sarcomas or chloroma (tissue infiltration of leukemic cells) seen principally in the orbit, spinal cord or skin, which may precede the development of frank leukemia. Gum hyperplasia and disseminated intravascular coagulation may also be seen in AML [126]. Loss of weight is a common non-specific feature at the time of presentation [127].

Many of the systemic features of established leukemia are the consequences of therapy [121]. Infections (viral, bacterial, and fungal) are common and reflect the compromised state of the body's immune mechanisms. Doxorubicin (Adriamycin) is known to cause cardiac toxicity. High doses of intrathecal chemotherapy in association with cranial irradiation (as used for early CNS prophylaxis) may cause a late leukoencephalopathy. Graft-versus-host disease is a serious complication of bone marrow transplantation and has significant ocular, dermatological and gastrointestinal effects.

The prognosis for both ALL and AML has improved dramatically since the 1970s [119]. Five-year disease-free survival is reported to be approximately 80 % for ALL and 41 % for AML [119], although this is affected by age and other risk factors. Infection and the complications of hemorrhage are the usual cause of death.

Diagnosis

While blood counts are often abnormal, bone marrow aspiration is necessary for diagnosis of any leukemia. Blast cells must make up more than 20 % of the bone marrow for the diagnosis to be made. Cytogenetics and other diagnostic testing such as FISH, PCR, microarray, and spectral karyotyping are often used to further define the disease and tailor treatment [120].

Management

A detailed discussion of the treatment of leukemia is beyond the scope of this book. For such a discussion, the reader should consult a standard text such as the chapter by Margolin and coworkers in *Cancer: Principles and Practices of Oncology* [120].

The principles of treatment are the induction of disease remission and the maintenance of this disease free state. This involves multi-agent (combination) chemotherapy and CNS prophylaxis (both intrathecal chemotherapy and craniospinal irradiation) [121]. Supportive care involves the use of blood products to treat anemia and clotting disorders, the detection and treatment of infection, metabolic and nutritional support and psychosocial care of the patient and family [121]. Bone marrow transplantation (BMT) is an important treatment modality especially in the management of AML and high risk or refractory ALL [128].

With increasing overall cure rates for most children with ALL and AML, considerable research efforts have been expended to devise the most effective therapies with the least associated morbidity. Attention has been directed towards identifying high-risk subgroups and designing more aggressive treatment protocols for these groups in an attempt to improve overall survival.

Ocular Side Effects of Medications Used in the Treatment of Leukemia

Steroids are a mainstay in the treatment of leukemia. Oral, intravenous, and topical steroids have all been shown to cause increased intracranial [125] and intraocular [129] pressures in susceptible individuals. Blurry vision, headaches, nausea, and vomiting are common features of both conditions, but can also be side effects of many medications. A thorough ophthalmic exam is indicated if any of these complaints arise in a leukemic patient in active treatment in order to rule out these conditions. A more thorough discussion of increased intracranial pressure from steroid use is found in the optic nerve portion of this section. Ocular hypertension from steroid use can usually be controlled with anti-glaucoma drops while the patient is on high-dose steroids [129]. It is possible that surgical management may be needed.

Other medications commonly used in the treatment of leukemia are known to cause ocular complications. Vincristine is known to cause neuropathies, including those of CN II, III, IV, V, VI, and VII [130]. CN II would cause an optic neuropathy. CN III, IV, and VI would cause motility disorders and misalignments of the eye. CN V would cause decreased sensation of the cornea that can lead to break down and ulceration of the cornea. CN VII would cause inability to full close the eye as well as decreased facial tone. This could lead to compromise of the cornea depending on severity. These almost always resolve with cessation of the medication. Cyclosporine has been associated with idiopathic intracranial hypertension [131] and retinal toxicity [132]. Busulfan is implicated in the development of cataracts, especially posterior subcapsular cataracts [130]. Radiation and steroids are also known causes of cataracts [132]. Cytosine arabinoside (Ara-C) causes a toxic conjunc-

tivitis and keratitis [133] and warrants pre-treatment with topical artificial tears and steroid eye drops.

Bone Marrow Transplant

Bone marrow transplantation (BMT) has become a more common treatment for leukemia, especially for AML. Bone marrow transplantation leaves the patient severely immunocompromised causing them to be at increased risk of the infections described in the following retina section [134]. Bone marrow transplantation can cause mild to severe dry eye [135] and cataracts [136]. Graft-versus-host disease (GVHD) can develop after BMT and increases the chances of patients developing ocular GVHD. Ocular GVHD can cause very severe dry eye, conjunctival scarring, and possibly keratopathy and corneal scarring. Aggressive lubrication, topical and systemic steroids, topical and systemic immunosuppressants (cyclosporine and tacrolimus), autologous serum or albumin, punctual plugs, bandage or even scleral contact lenses have been employed in the treatment of this very difficult ocular disease process [136].

Central Nervous System Leukemia

Clinical Features

The symptoms and signs of CNS leukemia are the result of direct leukemic infiltration into the CNS leading to meningeal irritation and raised intracranial pressure [137]. The major symptoms of CNS leukemia in descending order of frequency are nausea and anorexia, lethargy, vomiting, headache, seizures, coma, visual blur or diplopia. The major signs (also in descending frequency) are papilledema, tendon reflex changes, facial nerve palsy, positive Babinski sign, nuchal rigidity, pupillary changes, and sixth nerve palsy [137].

Patients with CNS leukemia will rarely present directly to the ophthalmologist. However, ophthalmic opinion should be sought to elucidate the cause of visual symptoms and to confirm findings of papilledema, pupil abnormalities and CN VI palsy. There have been several reports of children presenting with CNS leukemia as their initial manifestation of leukemia [138–141]. Two presented with sudden development of strabismus. One also had ataxia and papilledema [138] the other had bilateral ptosis, sluggish pupils, and upgaze paresis [139].

Diagnosis

In any child with CNS abnormalities and a history of leukemia, CNS involvement should be considered. The diagnosis is confirmed by the finding of blast cells in the cerebrospinal fluid (CSF) [120].

Differential Diagnosis

Meningitis (bacterial or viral) may present with similar ocular symptoms and signs as those of CNS leukemia. Various antileukemic medications have side effects that may be confused with CNS leukemia. Chief amongst these are corticosteroids, methotrexate and vincristine. Pseudotumor cerebri or idiopathic intracranial hypertension syndrome secondary to corticosteroid use is well recognized [142]. Intrathecal methotrexate has been noted to cause optic neuropathy and internuclear ophthalmoloplegia [142]. This effect is potentiated by concurrent cranial irradiation. Vincristine has been noted to cause cranial nerve palsies, optic neuropathy (and subsequent optic atrophy), night blindness, and transient choroidal blindness [142].

A temporal relationship of the onset of symptoms and signs to the use of a specific therapy may implicate medication as a cause. CSF studies are very helpful in differentiating the various causes of newly acquired neurologic dysfunction in leukemic patients.

Incidence

Prior to the development of antileukemic chemotherapy in 1948, meningeal or CNS leukemia was rarely diagnosed. Shaw and coworkers reviewed the literature in 1960 and found that only 31 cases were reported prior to 1948 while over 100 cases were reported in the 10-year period from 1949 to 1959 [137]. Later CNS prophylaxis resulted in a reduction of the number of cases of CNS leukemia. Currently less than 10 % of children with leukemia develop CNS leukemia [143].

Natural History

Untreated, the natural history of CNS leukemia is one of continued neurologic dysfunction, coma, and death. Early reports of treatment reported little success and the prognosis for survival was considered poor [137]. Recently the rate of CNS relapse has been reported to be between 2 and 10 % [144]. The long-term prognosis is still guarded; though in more than 90 % of patients, remission for 1–2 years is obtained [143]. Long-term event-free survival has been reported to be 70–80 % with the more recent strategy of delaying radiation for 6–12 months while intensive chemotherapy is administered [144].

Treatment

There have been numerous randomized trials undertaken in an attempt to determine the optimal treatment obtained for overt CNS leukemia [143]. In most cases remission can be obtained with either intrathecal chemotherapy and/or craniospinal irradiation. Without some form of maintenance therapy, however, this remission is generally short-lived.

Ophthalmic Manifestations of Leukemia

The effects of leukemia on any tissue may be primary or secondary. Leukemic infiltration is an example of a primary effect while hemorrhage secondary to thrombocytopenia is a secondary effect. This distinction becomes readily apparent when considering the ophthalmic manifestations of leukemia.

The incidence of various sites of leukemic ocular involvement depends upon the method of ascertainment and the stage of the disease in which the examination is made. Pathological studies consistently show higher incidence of eye involvement than clinical series. This is almost certainly because these are autopsies with a large number of patients dying of disseminated disease. Pathological examination often detects leukemic involvement that is clinically silent. Choroidal leukemic involvement, which is generally cited as the most common site of ocular involvement in autopsy series, is a good example of this phenomenon [145, 146].

Ocular involvement is detected in approximately 30–80 % of autopsy eyes [145–148]. In a prospective study of 120 patients examined at the time of initial diagnosis, only 3 % were found to have primary ocular involvement (retinal infiltrates). Thirty-nine percent had secondary manifestations (hemorrhage, cotton wool spots and central retinal vein occulsions secondary to hyperviscosity). The authors of this study acknowledge that choroidal infiltration may easily have been missed [149]. Reddy and Menon examined 82 children with acute leukemia within two days of diagnosis and found that three had ocular symptoms, while 14 (17 %) had ocular signs related to leukemia [150].

There have been several excellent reviews of the ocular manifestations of leukemia [124, 145, 146, 148, 151]. The most recent series of ophthalmic manifestations of leukemia have focused on ocular involvement of leukemia within two days of diagnosis. Reddy and co-workers found that 17 % of newly diagnosed children with acute leukemia had ocular changes related to their disease [150]. Ohkoshi reported that of 28 patients found to have ophthalmic manifestations of acute childhood leukemia, 27 died within 28 months of the diagnosis of eye abnormalities [152]. All 28 patients had either CNS or bone marrow relapse at the time of diagnosis of ocular involvement. They further reported that the 5-year survival was reduced by half (from 45.7 to 21.4 %) if there was ocular pathology [152]. However, Somervaille and colleagues reported 17 cases of ocular relapse (as a first relapse) in ALL. Eight of them had a relapse in the CNS or bone marrow at the time or ocular relapse. All were treated with chemotherapy and radiation. Eleven of those were still alive and in remission over 4 years after diagnosis of relapse. These authors note that more aggressive treatment at the time or relapse seems to improve survival. All of the 11 survivors were treated with intense relapse protocol chemotherapy with radiation to the involved eye(s). If treated less intensely, all but one expired and the one survivor was in chronic relapse at the time of publication of the study. This suggests that aggressive treatment is warranted in the setting of ocular involvement at the time of relapse [153].

Orbit

Clinical Features

Clinically significant orbital infiltration with leukemia usually presents with proptosis, lid edema, chemosis and pain [146]. ALL and AML may infiltrate the orbit although AML does so more often [154–158]. The orbital mass seen in myeloid leukemia (AML) is known as a granulocytic sarcoma (GS or chloroma). These were so named because of a greenish color due to myeloperoxidase seen in two-thirds of specimens [159]. AML may present with orbital or spinal cord "chloromas".

The proptosis caused by orbital infiltration may cause displacement of the eyeball in any direction. Retinal striae may be observed if there is compression of the globe. Specific orbital structures, such as the lacrimal gland or extraocular muscles, may be infrequently infiltrated by leukemic cells [130, 160]. Compression of the optic nerve at the orbital apex may result in sudden loss of vision.

Diagnosis

A clinical diagnosis may be made readily with MRI imaging in a child know to have leukemia. The homogenous mass molds to bony walls of the orbit without destruction. It is isointense to brain and muscle on computed tomography (CT, unenhanced), isointense to gray matter and muscle on T1-weighted MR and isointense to muscle and white matter on T2-weighted MR [158]. If it is not possible to reach a diagnosis on the basis of clinical findings, imaging studies and systemic assessment followed by orbital biopsy is required [130].

The histopathological interpretation of granulocytic sarcoma can be difficult in a patient not known to have a hematologic disorder [161]. Frequently, special histochemical stains are required to differentiate the cells as being myeloid in origin [159, 161, 162].

Differential Diagnosis

The differential diagnosis includes the causes of rapidly expanding orbital masses. Entities that should be considered are orbital inflammatory conditions [such as orbital cellulitis (bacterial or fungal) and pseudotumors] and tumors [such as lymphoma (including Burkitt's lymphoma), rhabdomyosarcoma, and neuroblastoma] [163].

Orbital and preseptal cellulitides are the most common cause of orbital inflammation in childhood. Leukemic patients are more prone to such infection because of the effects of their disease and systemic chemotherapy on their immunocompetence. Sinus disease either due to direct leu-

kemic infiltration [130] or infection may also give rise to signs and symptoms of orbital inflammation. Infection with unusual organisms, such as Aspergillus and Phycomycetes (including Mucormycosis), needs to be considered in immunocompromised patients [164]. McCarty et al., reported seven cases of fungal cellulitis in pediatric cancer patients, all of whom presented with fever and neutropenia. Four patients had upper eyelid edema, one complained of headache, and one noted facial pain. One additional patient was discovered to have fungal orbital cellulitis incidentally on CT imaging. Despite aggressive medical and surgical management, five of the seven patients died. The authors advocate that even subtle signs of preseptal cellulitis in the immunocompromised patient should be treated with antifungal therapy in addition to antibiotics. This should be done while work up is initiated. Since the immunocompromised patient cannot mount a normal inflammatory response, even subtle signs of infection should be fully investigated and treated empirically [165].

Orbital lymphoma is rare in children. Before this diagnosis is made granulocytic sarcoma should be excluded using the appropriate histochemical stains [163]. Neuroblastoma may present with rapidly growing orbital metastases, with or without the characteristic "raccoon-eye" periorbital hemorrhage and involvement of the lateral orbital wall.

Incidence

Kincaid and coworkers reported a 7.3 % incidence of orbital involvement in acute leukemia in an autopsy series of 233 cases [130]. The majority of these cases were diffuse infiltrations of orbital tissue and not clinically significant.

Granulocytic sarcomas of the orbit were thought to be rare in Caucasian children. In a group of 257 children with proptosis reported by Crawford, 2 % were due to granulocytic sarcoma [166]. Porterfield reported a series of 214 children with orbital tumors in which 3 % had GS [167]. In contrast Cavdar reported a 27 % incidence of granulocytic sarcoma in a series of 121 with AML from Turkey [157]. However, more recently, Bidar reported 17 of 27 children with GS who were white [158]. Most series document a higher incidence in males than females [157, 158, 163, 168].

Natural History

Granulocytic sarcoma may present at the same time as the hematological malignancy though some studies show that it precedes the onset of the leukemia [169]. Zimmerman and Font reported 33 patients with GS [163]. Four of these patients developed GS late in the course of established AML, while 29 presented with GS and went on to develop leukemia. Most develop AML less than 1 year after diagnosis of GS [163], although longer intervals have been reported [170]. Bidar reports on 23 of 27 children that were diagnosed with orbital disease after their leukemia diagnosis [158].

Cavdar and Zimmerman both reported orbital leukemic involvement as a poor prognostic indicator. However, Bidar's survival rates were considerably higher and were approximately that of the underlying disease. The majority of their patients were already diagnosed with leukemia so the diagnosis of orbital leukemic involvement was made earlier. They also state that since their report was on more recently treated patients, advances in leukemic treatments likely played a strong role in the higher survival rates in their patients [158].

Treatment

Orbital leukemic infiltrates respond well to systemic chemotherapy. If there is massive infiltration or compression of the optic nerve secondary to mass effect, local irradiation is indicated [157, 158, 171]. Radiation may also be indicated if systemic chemotherapy is ineffective in treating the orbital disease [158].

Lacrimal Apparatus and Lids

Leukemic infiltration of the lacrimal gland is occasionally noted [130, 172]. Leukemia rarely may present with lacrimal gland enlargement [130]. Reports of such have been limited to adults, most with the chronic forms of leukemia.

Leukemic dacryocystitis has been reported in adults with chronic lymphocytic leukemia [130, 172–174]. Dacryocystectomy [174] and dacryocystorhinostomy [130] have been undertaken to confirm the diagnosis and treat the symptoms.

Reddy reported a 15-year-old male whose presenting sign was an abscess of the left upper eyelid. Dilated retinal examination revealed dilated and tortous venules in both eyes as well as cotton-wool spots of the left retina [175].

The lids may be swollen and occasionally infiltrated by leukemic cells in association with orbital infiltration. Rarely, isolated leukemic involvement of the skin (leukemia cutis) is noted and occurs on the lids [130].

Conjunctiva

Clinical Features

Subconjunctival hemorrhage is seen in acute leukemia due to hematologic abnormalities [175, 176]. Conjunctival infiltration by leukemia is more commonly identified post-mortem than ante-mortem. Allen and Straatsma noted conjunctival involvement in 18 % of their series [145] and Kincaid and Green reported a 4 % incidence [130]. Ante-mortem recognition of leukemic infiltration of the conjunctiva is a rarity and most cases have been in adults with either AML or CML [177–180], although Lo Curto reports one child who presented with conjunctival infiltration that on biopsy proved to be leukemia [181].

Leukemic infiltration of the conjunctiva may appear as giant papillae of the palpebral conjunctiva [179] or apparent chemosis. The conjunctiva with leukemic infiltration has been noted to be firm rather than soft and boggy as in chemosis [177].

Diagnosis

Biopsy is required to make a definitive diagnosis, as there are no distinctive clinical features of leukemic infiltration of the conjunctiva [179]. The differential diagnosis includes: allergic/vernal conjunctivitis, sarcoidosis, and other causes of papillary conjunctivitis.

Treatment

The reported literature gives little guide as to the most appropriate treatment for conjunctival infiltration by leukemia. In one report the conjunctival changes responded to systemic chemotherapy alone [177]. While in another, radiotherapy was also required. Local measures may be required to prevent corneal and conjunctival drying and ulceration in cases of massive involvement with conjunctival prolapse [179].

Corneal and Sclera

Clinical Features

Corneal and scleral involvement in leukemia is rare. There have been reports of limbal infiltration [145], corneal infiltration [182–184] and ring ulceration [182, 183]. However, these have been mostly in adults. Russo noted five pediatric patients that developed keratitis, but no further details were given [176]. These cases may have been due to infection secondary to immunosuppression, epithelial changes from chemotherapy, or dry eye secondary to graft-versus-host disease [185]. Scleral involvement is rarely noted clinically. Allen and Stratsma noted scleral involvement in 22 of 76 autopsy cases [145]. There have been no ante-mortem reports of leukemic infiltration of the cornea or sclera in children.

Diagnosis

The diagnosis of corneal or scleral infiltration can be confirmed by biopsy.

Differential Diagnosis

The corneal ulceration induced by leukemic infiltration may mimic an infectious keratitis or chronic ulceration. Episcleral involvement, if recognized clinically, may simulate episcleritis.

Treatment

In cases of corneal ulceration, infective causes have to be excluded with scrapings for microscopy and culture. In the single reported case in which resolution of corneal involvement occurred, treatment consisted of topical antibiotic and steroid in conjunction with systemic chemotherapy [183].

Anterior Segment and Glaucoma

Clinical Features

Leukemic iritis generally presents with minimal symptoms and is more common with relapse of disease. It is also more common with ALL, but may be seen in AML [186, 187]. Patients may notice photophobia, tearing, ocular pain, and headache; but these symptoms are usually mild. Pain may be a more significant symptom if secondary glaucoma develops [188]. Older children may complain of blurring of vision. Anisocoroia has been described as a feature prompting ophthalmic evaluation [189, 190].

Ciliary injection of a variable degree is commonly apparent at presentation. Leukemic involvement of the anterior segment has been mis-diagnosed as conjunctivitis [124, 190–192]. Hypopyon is commonly present [186, 187, 190, 193–202]. On occasion the leukemic infiltrate in the anterior chamber may present as a solid mass, rather than a fluid level [190]. Heterochromia iridis and hyphema are less frequently seen [124, 189, 203]. Involvement is generally unilateral; bilateral cases make up less than 20% of those reported [187, 189–191, 194, 201, 202, 204–206].

Examination reveals a variable uveitis. Keratic precipitates, if present, are usually fine and white [124]. The iris frequently appears diffusely thickened with a smooth, velvety surface. This is secondary to infiltration of the iris stroma with resultant loss of definition of the iris stromal trabeculae and crypts [124, 207]. This infiltration is also responsible for the alteration of iris color. The iris involvement is less commonly nodular [186, 190, 204, 206, 208].

Iris infiltration may be associated with stromal hemorrhages [209]. The involved eye may appear lighter [202, 210] or darker [204, 206] than the normal eye. The hypopyon may vary from white to grey and on occasion may be admixed with hyphema [203].

Posterior synechiae have rarely been described in patients with leukemic iritis [211]. Ectropion uveae has been noted in one case of anterior segment relapse [188]. Anisocoria has been reported [189, 190], but rubeosis iridis has not been noted in the literature. Anterior segment involvement may mask posterior segment disease [195].

Elevated intraocular pressures are found in about 20% of children with leukemic infiltration of the anterior segment [186, 187, 189–192, 194, 195, 201, 202, 204, 205, 211]. All these cases had marked involvement of the anterior chamber with hypopyon, hyphema, and/or nodular infiltration of the iris. Pain was noted in some, but not all. Secondary glaucoma is, in most cases, believed to be due to leukemic infiltration of the trabecular meshwork [124, 188]. Corneal haze is often noted in children with secondary glaucoma [188, 190]. Rarely, cases of open angle glaucoma with minimal or no anterior chamber involvement have been reported [100, 212, 213]. Acute angle closure glaucoma has also been reported in the setting of spontaneous choroidal hemorrhage in leukemic patients [214, 215].

Diagnosis

The diagnosis is generally made clinically on the basis of a combination of clinical findings described above in a patient already known to have leukemia. Iritis refractory to treat-

ment is very common in leukemic iritis and should be high on the differential in such a patient. Also any mass or thickening of the iris should alert the clinician to such a possibility. Clinical misdiagnosis most often occurs in the rare setting of an ophthalmic presentation of leukemia [191, 204].

Most authorities recommend that the clinical diagnosis be confirmed by biopsy as accurate diagnosis is vital in planning further therapy for such patients [124, 130, 190]. This can be by needle aspiration of aqueous from the anterior chamber or by open biopsy of the iris. It is recommended that a pathologist be on hand for the immediate delivery of the specimen as the leukemic cells are extremely fragile and prompt examination is needed for accurate diagnosis.

Glaucoma should be suspected in all patients with leukemic infiltration of the anterior segment. Measurements of intraocular pressure should be part of the standard assessment of such patients.

Differential Diagnosis

Leukemic involvement of the anterior segment has been misdiagnosed as idiopathic iritis [187], endophthalmitis [191, 199] and juvenile xanthogranuloma [204]. Leukemic patients are also immunocompromised as a result of their primary disease and secondarily by their treatment. Endogenous endophthalmitis is generally seen in the setting of a very ill patient and presents with a chorioretinitis and vitritis more commonly than with an anterior uvitis [216].

There are only two reports of infectious or inflammatory anterior segment uveitis in the literature, one due to mumps [217] and the other idiopathic [190].

Juvenile xanthogranuloma (JXG) can present as a mass in the anterior chamber of a child and may cause a spontaneous hyphema [218]. It is rare to develop a hypopyon in the setting of JXG [204].

Incidence

Leukemic iritis is not common [124, 181, 188–197, 199, 202, 204–207, 209, 211, 219, 220]. Two large series of anterior chamber relapses have been reported [124, 194]. Bunin showed 0.5 % anterior segment relapse while Ridgway reported 1.7 % [124]. A more recent study by Somerville reports a rate of 1.43 % of relapse in the anterior chamber [153].

Natural History

The natural history of untreated leukemic iritis has not been described. Glaucoma, if not already present at the time of diagnosis, appears to supervene in a matter of days to weeks if treatment is not commenced immediately [204]. In general the raised intraocular pressure responds rapidly to treatment of the leukemic infiltrate. The leukemic infiltration appears to cause no gross permanent structural damage to the iris or angle. When the patient survives long enough to respond to treatment, the eye clinically appears to return to normal [124, 190, 194]. Lens opacities are frequently noted after ocular irradiation for anterior segment leukemia. Only one case of visually significant cataract requiring lensectomy has been reported. The patient's vision improved markedly afterwards [201].

Second relapse in an eye has been reported on numerous occasions [153, 181, 192–194, 196, 201, 207, 211]. Jankovic and coworkers described a child who had at least four episodes of leukemic iritis in one eye over a 6-year period [193].

As with any leukemic relapse, ocular relapse carries a grave prognosis for ultimate survival [121, 194]. However, Somervaille proposes aggressive systemic chemotherapy and radiation to improve survival. The survival rate in his series was 65 % for patients with initial relapse occurring in the eye [153], while other older studies have had poorer outcomes [181, 193, 194].

Treatment

Both local and systemic therapies are employed. The local ocular treatment includes topical or subconjunctival corticosteroids, antiglaucoma medication as needed and often ocular irradiation. Chemotherapy, both systemic and possibly intrathecal, is needed if long-term remission is to be obtained [153, 181, 194].

Irradiation is used to destroy any residual leukemic cells within the eye. The whole eye is irradiated via lateral and anterior ports with no attempt to protect the lens. Doses of radiation needed vary in the literature [153]. The radiation is fractionated to minimize the risk of cataract formation. Iris stromal hemorrhages may persist for some time after irradiation for leukemic infiltration [209].

Reports of local chemotherapy have been described in the treatment of anterior segment leukemia [201, 220].

Vitreous

Clinical Features

Leukemic infiltration of the vitreous rarely occurs in isolation. It is usually seen in association with vitreous hemorrhage [145] or with leukemic retinal infiltrates that "spill" into the vitreous [185]. There is one case report in the literature of bilateral vitreous infiltration in a child with ALL. He was not responding to chemotherapy and first developed vitreous infiltration in the right eye and then 3 months later in the left. His disease was refractory to treatment and he died shortly thereafter [221].

Diagnosis

The diagnosis of leukemic infiltration of the vitreous can be suspected on clinical grounds using slit lamp examination

and indirect ophthalmoscopy. However, it can be confirmed by vitreous biopsy.

Differential Diagnosis

Vitreous hemorrhage and endophthalmitis are the two principle differential diagnoses of leukemic infiltration of the vitreous. If the vitreous hemorrhage is sufficiently dense to preclude an adequate fundus examination for evidence of frank retinal or optic nerve infiltration then diagnostic vitrectomy is recommended. This will allow a clear fundus view and provide material for cytological examination and culture.

Endophthalmitis generally occurs in association with evidence of fungal or bacterial septicemia [222]. Exclusion of these predisposing factors makes the diagnosis of infective endophthalmitis extremely unlikely. If endophthalmitis cannot be excluded on clinical grounds then urgent vitreous biopsy maybe required to provide diagnostic material.

Incidence

The published literature suggests that clinically significant leukemic involvement of the vitreous is a rarity [185].

Natural History

Both the natural history and the prognostic significance of leukemic involvement of the vitreous are uncertain. In the few reports in which the patient survived, the visual outcome was excellent [185, 223].

Treatment

No firm treatment recommendations can be made. In keeping with other forms of ocular involvement, a thorough general reassessment of the patient, including CSF studies and bone marrow aspiration, is mandatory. Systemic chemotherapy and local irradiation could be expected to control the ocular component of such relapses, but systemic chemotherapy alone may be sufficient.

Retina

Clinical Features

The fundus features of childhood leukemia are numerous and common. Duke-Elder estimates that up to 90 % of patients with leukemia demonstrate retinal abnormalities at some stage of their illness [224]. The following list outlines the fundus changes that may be seen in leukemia.

- Fundus Changes in Childhood Leukemia
  - Altered vessel caliber, color and tortuosity
  - Retinal hemorrhages (flame, blot, subretinal, subhyaloid, vitreous extension, with and without white centers)
  - Cotton wool spots
  - Central retinal vein occlusion
  - Leukemic infiltrates:
    perivascular sheathing
    leukemic nodules in retina
    optic nerve head
    vitreous
  - Optic disc swelling and papilledema
  - Peripheral neovascularization
  - Central serous retinal detachments
  - Retinal pigment epithelial abnormalities
  - Macular holes
  - Cystoid macular edema
  - Retinal detachment

Alteration in the vessel caliber and tortuosity are probably the earliest fundus changes in leukemia [130, 225]. Venous dilation and tortuosity are noted first. Arteriolar tortuosity is generally less marked. The blood column in the vessels may appear a different color. Gibson describes the venules as appearing darker [118] while others have noted yellowish discoloration of the retinal vessels [130, 225]. It is assumed that these changes are due to associated anemia, high white cell counts and hyperviscosity.

The retinal hemorrhages seen in leukemic patients demonstrate considerable variation in their physical appearance and temporal pattern with regard to the general disease state of the patient. The hemorrhages vary from flame to blot to extensive pre-retinal and subhyaloid hemorrhages that on occasion may break through into the vitreous. A prospective study by Schachat found that of 120 acute leukemia patients 24 % had intraretinal hemorrhages at presentation. Of those, 11 % were associated with white centers and 4 % with varying degrees of central retinal vein occlusion [149]. A study by Reddy and coworkers found that 44 % of adults and children with acute leukemia had retinal hemorrhages on exam within 2 days of diagnosis. Seventeen percent of those had white centers [175]. In a prospective evaluation of patients with AML at presentation, 53 % were found to have retinopathy (cotton-wool spots and/or hemorrhages) [226]. White-centered hemorrhages are commonly seen in leukemic patients [130, 149–151, 175]. For many years it was assumed that these white centers represented leukemic infiltrates [145, 227]. More recent pathological evidence has been produced that shows in some instances these white centers are fibrin and platelet plugs [228], leukemic cells or septic emboli [185].

There have been several studies that have tried to determine if there is a correlation between the hematological status of the patient and the presence of retinal hemorrhages [118, 148, 227, 229, 230]. The results have been conflicting. The factors that have been most commonly implicated are thrombocytopenia, anemia, and leukocytosis [230]. These authors found a correlation between retinopathy (defined as

hemorrhages and/or cotton-wool spots) and thrombocytopenia but not with any other hematological parameters.

Cotton-wool spots are frequently noted in adults with leukemia [130, 225, 227, 230]. Guyer and coworkers believe these cotton-wool spots are the result of local vascular occlusion by abnormally large leukemic cells or small aggregations of leukemic cells [230]. Cotton wool spots have also been reported in children with acute leukemia [150, 152, 175].

Central retinal vein occlusions (CRVO) have been reported in patients with acute leukemia, although it is not clear if any of these were children [149]. All patients with CRVO were adults in Reddy's study [175]. CRVO secondary to hyperviscosity states may have associated disc edema [231]. In such cases, neuroimaging and lumbar puncture are indicated to exclude the possibility of concurrent CNS or optic nerve involvement.

Leukemic infiltrates of various types have been noted in the fundus. The infiltrate may be perivascular, nodular, on the optic nerve, or in the vitreous. Schachat and coworkers noted a 3 % incidence of retinal infiltration at presentation in their series of 120 patients [149].

Perivascular and nodular retinal infiltrates are said to be more common in patients with CML though both may be seen in children with acute leukemia [232, 233]. Cases of massive retinal infiltration with gross destruction of retinal architecture have been described [130, 234]. Primack reported the case of a 3 year old with retinal infiltration by leukemia causing retinal necrosis and retinal detachment [234]. In general the internal limiting membrane appears to act as a barrier preventing the spread of intraretinal leukemia into the vitreous [233]. Although that phenomenon has been seen by one of the authors.

Retinal neovascularization and microaneurysms have not been described in childhood leukemia. There have been a few reports of peripheral neovascularization [235–237] and microaneurysms [238] in adults with CML.

Central serous retinal detachments have been reported with acute and chronic leukemias [146, 239–245]. These patients present with sudden deterioration in vision and may be unilateral or bilateral. Four cases have been reported in which the development of the serous retinal detachment was the initial presenting feature of leukemia [146, 243–245]. Fundus examination reveals elevation of the retina in the region of the macula and fluorescein angiography reveals typical subretinal leakage and pooling of fluorescein in the area of the detachment [146, 242, 244]. Ultrasonography will demonstrate choroidal thickening in some cases [242, 246]. In most cases, which have been studied pathologically, there has been considerable choroidal infiltration and focal disruption of the retinal pigment epithelium beneath the detachment [146, 239, 241]. All of the reported cases of serous retinal detachment in patients with leukemia involve the macula. This may be due to the fact that only cases involving the macula present because of visual loss or because of the apparent predilection of leukemic cells to involve the posterior pole choroid. There have been several cases of childhood leukemia presenting with central serous detachment. In all of these there was no evidence of CNS leukemia [243–245]. Serous detachments have also been noted after the diagnosis of acute leukemia [247].

Retinal pigment epithelium (RPE) disturbances may occur in leukemic patients without associated central serous retinopathy [248–251]. These cases of RPE disturbance all showed marked leukemic infiltration of the choroid on histopathological examination [248, 250]. It has been suggested that the RPE changes are most likely a direct effect of leukemic infiltration of the choroid, however, toxic effect of chemotherapy cannot be excluded as a contributing factor [248–251].

Cystoid macular edema, macular hole formation, and retinal detachment (other than central serous retinal detachment) have rarely been noted in association with leukemia [130, 250, 252].

Diagnosis

The diagnosis of leukemic retinopathy is made clinically and generally presents no difficulty as the majority of cases have known leukemia. Diagnostic difficulty may be encountered when a patient presents to the ophthalmologist without a prior diagnosis of leukemia. Any child presenting with retinal hemorrhages in the absence of an obvious ocular explanation should have a blood count to rule out the possibility of hematologic malignancy. Central serous retinopathy may be the presenting feature of leukemia [243–245]. To make the correct diagnosis in such a case requires a high index of suspicion. In a child such findings are very unusual and demand a more general assessment. Investigations such as fluorescein angiography, ultrasonography, and optical coherence tomography (OCT) may help further delineate the extent of RPE disturbances and central serous retinal detachment. However, they will not help make a definitive diagnosis. A thorough fundus examination with indirect ophthalmoscopy is essential. A thorough pediatric examination with complete blood count should also be considered.

Leukemic retinopathy may appear similar to infective retinitis such as caused by cytomegalovirus (CMV), herpes simplex (HSV), varicella zoster (VZV) and paramyxovirus (measles virus). The retinal involvement in infective retinitis tends to be more extensive and there are areas of retinal edema and destruction as well as extensive retinal hemorrhage. Infective retinitis is progressive while leukemic retinopathy is less so. Retinitis is commonly seen in leukemic patients, and, if suspected, systemic investigation for the causative agent should be undertaken. This is particularly

important now as there are effective treatments for several of these viruses. In selected cases, chorioretinal biopsy may be used to differentiate leukemic infiltration from viral retinitis [253]. Other systemic infections in leukemic patients may involve the retina. The most common are fungal infections, with Candida and Aspergillus species being the main organisms responsible. Clinically it may not be possible to differentiate these entities. In children fungal endophthalmitis rarely occurs in the absence of fungal septicemia or locally invasive fungal disease [222]. Thus in such cases the diagnosis of endogenous endophthalmitis rests in the finding of systemic evidence of infection and retinal lesions which are consistent with such an infection [254]. Care should be taken in dismissing retinal infection in absence of vitritis as Graham reported an immunosuppressed patient with Aspergillus that did not have clinically apparent vitiritis [255].

Incidence

The incidence of retinal involvement in childhood leukemia is difficult to estimate. Autopsy series suggest that 25–45 % [130, 148] of cases have retinal hemorrhages and 13 % have retinal infiltrates [148, 256]. Other retinal involvement is much less frequent. There have been three prospective studies of the ocular manifestations of leukemia at presentation [149, 175, 226]. The first revealed retinal infiltrates in 3 % and intraretinal hemorrhages in 24 %, cotton-wool spots in 16 % and white centered hemorrhages in 11 % [149]. The second reported an incidence of retinopathy of 53 % (cotton-wool spots and retinal hemorrhages 36 %, retinal hemorrhages alone 13 % and cotton-wool spots alone 4 %) [226]. Nine percent suffered from visual loss secondary to macular hemorrhage [226]. Reddy found a rate of 34 % of retinal involvement in children with leukemia examined within 2 days of diagnosis [175].

Natural History

There have been few studies that have attempted to address whether the presence of retinal hemorrhages (with or without white centers), cotton-wool spots and retinal infiltrates at presentation have prognostic significance for patient survival [148, 226]. Ohkoshi did find that ophthalmic involvement portended a poor prognosis, retinal involvement included [152].

The visual prognosis is directly dependent on the part of the retina involved. Subfoveal hemorrhage or infiltration or intraretinal hemorrhage at the fovea has the potential to adversely affect vision. Some recovery in such cases can be expected but the visual prognosis should be guarded. However, the visual prognosis for central serous retinal detachments appears to be quite good [243–245].

Treatment

In general no specific ocular treatment is indicated for leukemic retinopathy. The retinal hemorrhages usually resolve spontaneously once the anemia and thrombocytopenia are normalized with transfusions and chemotherapy [229]. Chemotherapy is often sufficient to treat retinal infiltration. Irradiation may be indicated in cases of massive leukemic infiltration of the retina. However such cases are rare in children. Local irradiation was applied in a single case report [257]. The place of such treatment is not clear and more experience is required before its value can be determined. One eye with total retinal detachment and glaucoma at presentation was enucleated due to failure to respond to therapy and uncontrolled pain [234].

Retinal infiltration indicates the need for reassessment of CNS and bone marrow status. One autopsy series has shown a correlation between retinal infiltration and meningeal leukemia [148]. Ohkoshi also found high rates of either CNS or bone marrow relapse in patients with retinal findings [152].

Thrombocytopenia in the presence of retinal hemorrhage that threatens the macula is an indication for platelet transfusion to lessen the risk of extension of the hemorrhage and subsequent visual loss [226].

Infective retinitis requires specific treatment that depends on the etiology. This is discussed further in the chapter dealing with infectious disease.

Choroid

Clinical Features

Leukemic involvement of the choroid is rarely detected clinically. Several pathologic studies have revealed that the choroid is the most common site of leukemic involvement of the eye [130, 145, 148]. The ante-mortem diagnosis of choroidal involvement has only been confirmed by biopsy in one case [252] and considered likely in several other cases studied by ultrasound [242, 246] and OCT [258]. Choroidal leukemic infiltration is generally diffuse and thin and hence is not apparent on routine fundus examination [246].

Diagnosis

The diagnosis can be suspected on the basis of choroidal thickening on ultrasound or OCT but only confirmed by biopsy [246, 252, 253]. Trans-scleral biopsy or transvitreal biopsy with retinotomy to gain access to the choroid, have been employed. Such procedures are only justified when the diagnosis must be put beyond doubt, as in the case of isolated choroidal relapse [252].

Differential Diagnosis

The differential diagnosis includes causes of choroidal thickening and serous retinal detachment. In the former group entities such as choroidal melanoma [259] and intraocular pseudotumor [260] should be considered. Serous retinal detachment may be seen in association with diseases such as Vogt-Koyanagi-Harada disease, posterior scleritis, and ciliochoroidal effusion syndrome [146]. All of these diagnoses are exceedingly rare in the pediatric age

group. Practically speaking any choroidal thickening or serous retinal detachment in a patient with leukemia is evidence of leukemic infiltration of the choroid until proven otherwise.

Incidence

Autopsy series indicate that the incidence of infiltration of the choroid is as high as 46–50 % [145, 148]. Clinical evidence of choroidal involvement is seen in less than 1 % of cases. The high incidence of choroidal infiltration in the autopsy series may reflect the era in which they were undertaken. The study of Allen and Straatsma was certainly undertaken in the pre-modern era of leukemia treatment [145]. However the study of Kincaid and co-workers revealed little alteration in the incidence of ocular involvement in a series that spanned the years 1923–1980 [130]. As survival improves the importance of choroidal involvement as a sanctuary site for leukemia may increase.

Natural History

The natural history and prognostic significance of choroidal involvement in leukemia is poorly understood as it is infrequently detected during life. In cases in which it is recognized ante-mortem it appears to respond to local irradiation and chemotherapy in a manner analogous to anterior segment involvement. The only well documented case of choroidal relapse was associated with a concurrent bone marrow relapse [252].

Treatment

Systemic chemotherapy and local irradiation form the basis of treatment for choroidal infiltration. Local treatment is indicated when the choroidal involvement results in decreased vision.

Optic Nerve

Clinical Features

Optic nerve involvement in leukemia can take several forms [261]. The optic nerve abnormalities seen may reflect CNS involvement, a rheological effect of leukemia, leukemic infiltration (Fig. 11.7a, b), or a side effect of treatment.

Acute papilledema due to CNS leukemia is well recognized [137]. Prior to the discovery of antileukemic drugs CNS leukemia was a rarity [137] and its incidence has decreased again following the introduction of CNS prophylaxis as part of the treatment of childhood leukemia [121]. The clinical features of CNS leukemia are nausea and vomiting, lethargy, headaches, convulsions, papilledema, cranial nerve palsies, and non-specific neurological signs [137]. Rarely papilledema secondary to CNS leukemia may be part of the presentation of childhood leukemia [138–141, 261]. There are no distinctive clinical features of papilledema secondary to CNS leukemia. Chronic papilledema is seldom seen in association with CNS leukemia as the patient either succumbs or is treated and the papilledema resolved. The visual acuity with papilledema is usually normal.

Papilledema due to pseudotumor cerebri (or idiopathic intracranial hypertenstion, IIH) secondary to steroid use may cause diagnostic difficulty. IIH can occur in children while they are taking corticosteroids or when the dosage is altered or the medication withdrawn [125]. As corticosteroids are almost always a component of the treatment protocol for acute leukemia, occasional cases of IIH may be expected. Careful examination of the CSF is the key to differentiating the two syndromes. The intracranial pressure is generally elevated in both. In CNS leukemia the white cell count will be elevated, but not in IIH. CSF protein may be elevated in both entities.

Disc edema may result from hyperviscosity with or without frank central retinal vein occlusion. The retinal venules are dilated and tortuous. Typically the visual acuity is normal or near normal. It is seen early in the course of the disease when the cell counts are grossly elevated. Such disc edema resolves with induction of remission and resultant decreased blood viscosity. Lumbar puncture is vital to differentiate disc edema secondary to CNS leukemia and IIH from the hyperviscosity syndrome. Frank central retinal vein occlusion occurs in up to 5 % of leukemic patients at presentation [149]. These patients tend to be adults [175]. Hyperviscosity and CNS leukemia may co-exist and have an additive effect in causation of papilledema [261].

Ischemic papilledema from either intrinsic or extrinsic compression of the optic nerve results in sudden and profound loss of vision. The disc appears pale and swollen and there may be associated peripapillary hemorrhages. It is generally unilateral and not associated with other symptoms of CNS leukemia (nausea, vomiting, headache, seizure) helping distinguish it from papilledema from CNS leukemia.

Diagnosis

Accurate differentiation of the various causes of optic nerve involvement in leukemia is important as the treatments vary greatly. This differentiation can usually be made on the basis of clinical examination (Table 11.1). The appearance of the optic nerve head, the visual acuity, the presence or absence of a relative afferent pupillary defect and visual field examination will generally differentiate between the major types of optic nerve involvement described above.

In cases of bilateral disc edema, lumbar puncture with measurement of intracranial pressure and cytological examination of the CSF is required to differentiate between CNS leukemia, pseudotumor cerebri and hyperviscosity syndrome.

Orbital imaging is required to further delineate the nature and cause of extrinsic and intrinsic compression of the optic nerve [246]. Fluoroscein angiography will document delayed retinal circulation time in the hyperviscosity syndrome and central retinal vein occlusion. Similarly, leakage

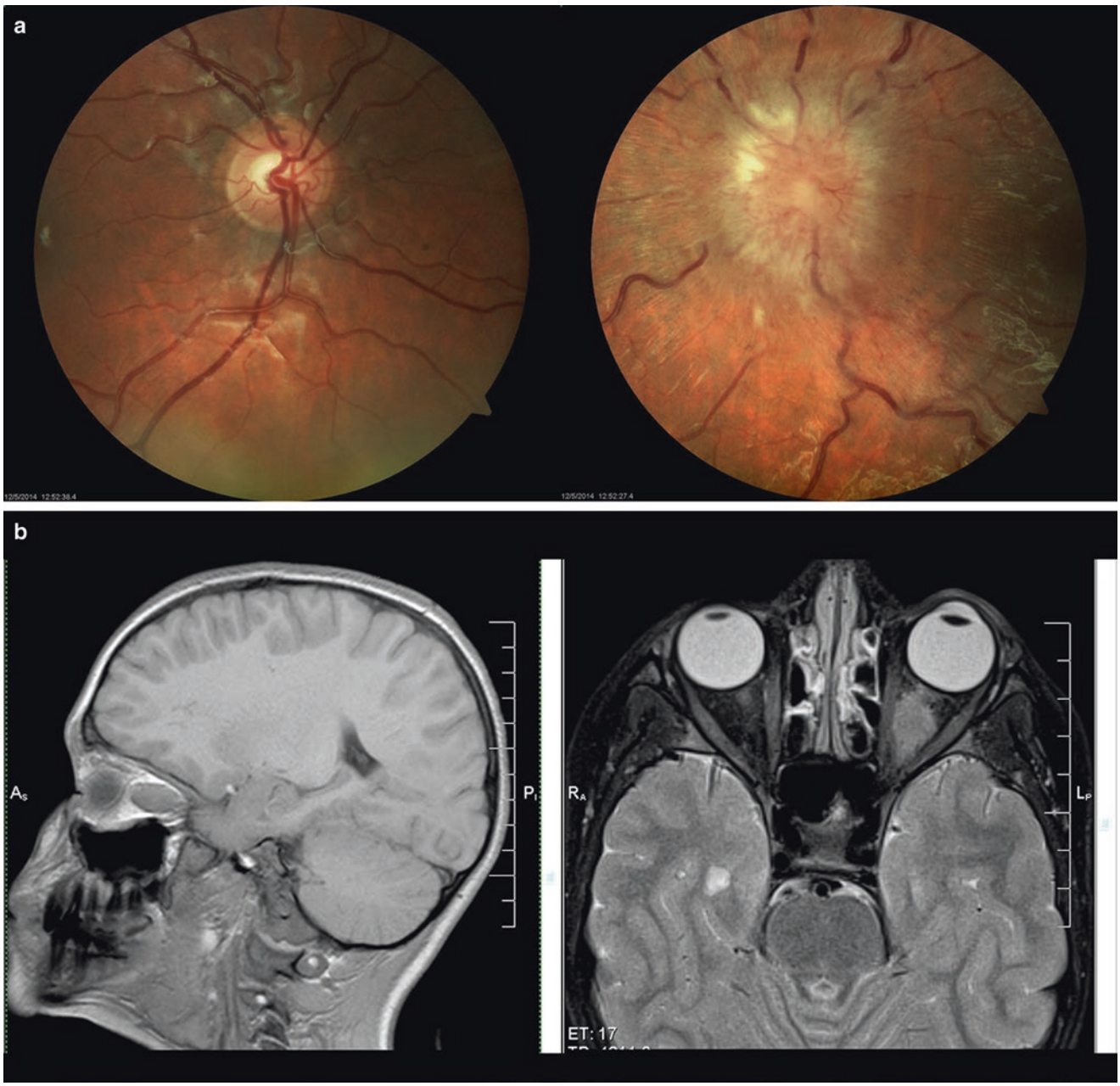

Fig. 11.7 (**a**) Normal optic nerve on the left (*right eye*) and leukemic infiltration of the optic nerve on the right (*left eye*). (**b**) Magnetic resonance image of optic nerve. Note enlarged optic nerve and sheath on the left due to leukemic infiltration

Table 11.1 Clinical features of different types of optic nerve involvement in childhood leukemia

Optic nerve involvement	Systemic features	Vision	Stage of disease	Laterality	Visual field
Papilledema	Headache, nausea, vomiting	Normal	Late	Bilateral	Full
Disc Edema	Nil	Normal	Early	Bilateral	Full
Ischemic Papillitis	Nil	Normal	Early	Unilateral	Altit defect
Leukemic	Nil	Prelaminar normal	Late	Unilateral	Full
		Retolaminar decreased	Late	Unilateral	Altit defect
Optic Atrophy	Nil	Decreased	Late	Unilateral or bilateral	Constr

from optic disc vessels will be seen in case of papilledema. MRI shows enhancement and tubular enlargement in leukemic infiltration (Fig. 11.7b), as long as an orbital protocol is followed [262].

Differential Diagnosis

The major differential diagnoses are congenital anomalies of the optic nerve that simulate disc edema or infiltrative mass, buried drusen and myelinated nerve fibers. Pseudopapilledema or a hypermetropic eye may be mistaken for papilledema in the setting of a child with leukemia. Autofluorescence and presence of calcium on CT or ultrasound of the optic nerve may help in the detection of buried drusen. In some cases it may be necessary to perform lumbar puncture with CSF cytology if papilledema secondary to CNS leukemia or pseudtumor cerebri cannot be satisfactorily excluded. Such diagnostic confusion can be reduced if careful ophthalmic examination is undertaken at the time of initial presentation in all children with leukemia. Such an examination would allow documentation of congenital anomalies of the optic nerve head.

Incidence

The incidence of optic nerve involvement in children with leukemia is not well documented. Prospective studies of adults with AML found a 6 % incidence of optic disc edema at presentation [226] and another found 1.7 % [175]. The experience at the Hospital for Sick Children would suggest an incidence of less than 1 % [166]. Autopsy series have documented leukemic infiltration of the optic nerve in 6–12 % of patients [145, 148]. In keeping with other ocular manifestations of leukemia, the incidence of clinically detected leukemic infiltration of the optic nerve is considerably less than that found at autopsy. The incidence of papilledema varies with the incidence of CNS leukemia and since the introduction of CNS prophylaxis this cause of papilledema has become less common. In 1976, Ridgway reported an incidence of 1.5 %. All these patients had concurrent or subsequently diagnosed CNS leukemia. This association reflects the lack of CNS prophylaxis in this population of patients.

Natural History

The natural history of optic nerve involvement in childhood leukemia depends on the underlying pathology. The visual prognosis and the prognosis for ultimate survival after optic nerve involvement are considered separately.

Visual loss is rare in papilledema and the hyperviscosity syndrome associated with leukemia. The papilledema seen in leukemic patients seldom becomes chronic as the patients either respond to treatment or succumb to their disease. Varying degrees of optic atrophy are common after any but the most transient of episodes of papilledema, however visual loss in terms of reduced visual acuity is infrequent. Disc edema secondary to hyperviscosity usually resolves without visual sequelae as systemic remission is induced.

Optic atrophy and permanent visual loss frequently follow ischemic papillitis due to any cause. Altitudinal visual field defects are common. In some cases early and aggressive treatment of compressive lesions of the optic nerve can be followed by considerable visual recovery.

The visual outcome in leukemic infiltration is largely dependent on the position of the infiltrate. Pre-laminar infiltration has a good visual prognosis, while retro-laminar infiltration has a poorer prognosis. Untreated pre-laminar infiltration may spread into the retro-laminar optic nerve and cause visual loss [263, 264].

The chance of survival after leukemic infiltration is unclear. Early reports suggested that involvement of the optic nerve was associated with systemic [265] or CNS relapse [124, 148] in a high proportion of cases and the prognosis for long-term survival was poor. More recent reports have emphasized the occurrence of isolated optic nerve infiltration in patients off chemotherapy [266] or in remission on maintenance chemotherapy [267]. Isolated infiltration of the optic nerve is good evidence for this site being a pharmacological sanctuary for leukemic cells [268]. With early, aggressive treatment long-term survival is possible for such patients [266, 267].

Treatment

A specific diagnosis is necessary before treatment can be commenced. In all cases of leukemic relapse, whether it is isolated to the optic nerve or involves the CNS more generally, a thorough reassessment for other evidence of systemic disease is required.

In cases of papilledema in children with leukemia the treatment is directed at relieving the cause of papilledema. CNS leukemia requires intrathecal and systemic chemotherapy and in most instances craniospinal irradiation. Pseudotumor cerebri may necessitate treatment with acetazolamide.

The treatment of optic nerve infiltration requires systemic corticosteroid, intrathecal and systemic chemotherapy and irradiation [269]. Once optic nerve infiltration is suspected immediate high dose steroids should be commenced. The corticosteroid has a direct lymphocidal effect and will also decrease inflammation about the site of a lesion and thus lessen the compressive effect. Systemic and intrathecal chemotherapy will have an effect on the infiltration, though this is not as rapid as corticosteroids. Irradiation is effective in shrinking the leukemic infiltration and should be commenced on an urgent basis within 24 h of diagnosis [263, 264].

Opportunistic Infections

Patients with leukemia are at higher risk of infection due to their immunocompromised state, from leukemia and from its

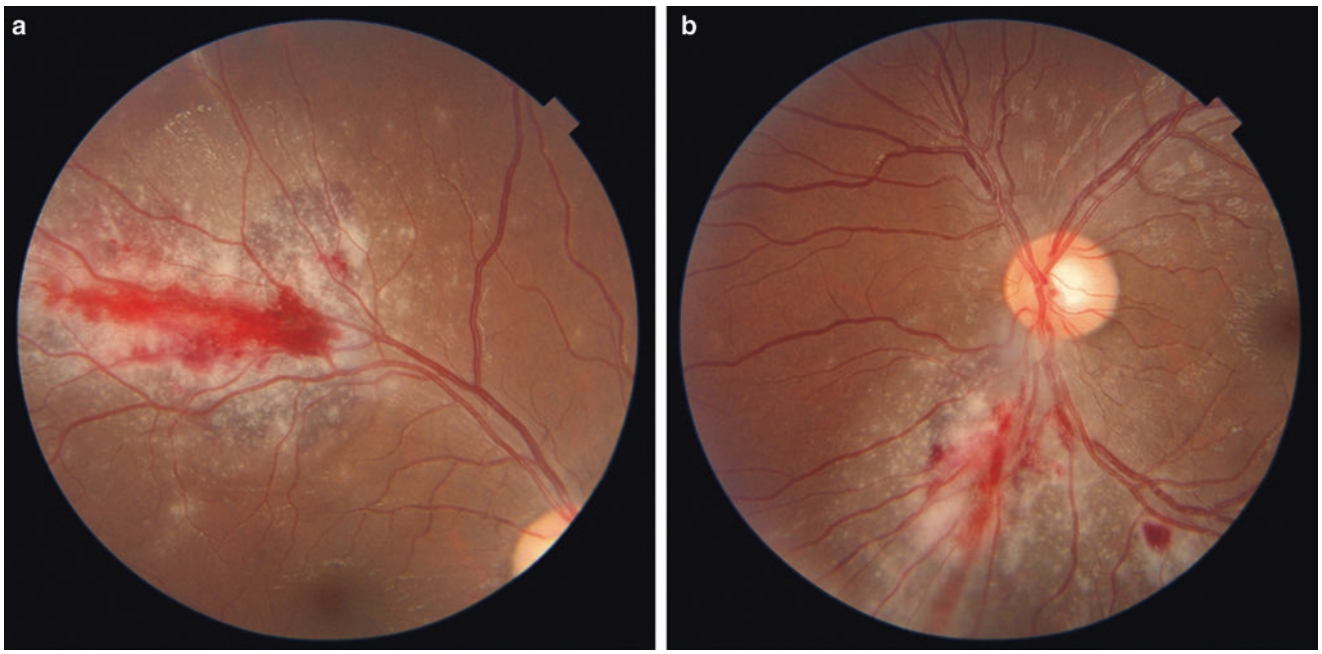

Fig. 11.8 Cytomegalovirus (CMV) retinitis is an opportunistic infection seen in the immunocompromised host. (**a**) right eye; (**b**) left eye of the same patient

treatments. Patients may develop bacterial, viral, or fungal infections that may not appear as they do in an immunocompetent host. Indeed, immunocompromised patients are susceptible to numerous infections that healthy patients are not. Cytomegalovirus (CMV) (see Fig. 11.8a, b), *Herpes simplex* (HSV), *Herpes zoster* (HZV), mumps, measles, candida, mucor, Cryptococcus, aspergillus and toxoplasma are a few of these. Most of these cause a retinitis and/or vitritis, although HSV, HZV and mumps may cause anterior segment involvement [146, 185]. Other rarer infections such as Pseudallescheria boydii [254], Scedosporium prolificans [270], Strongyloides stercoralis [245], and Nocardia [271] have been reported in adults with leukemic immunosuppression. Broad spectrum antibiotic and anti-fungal coverage is recommended for the febrile, neutropenic patient while the infectious agent is sought [165].

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Ocular Manifestations of Infectious Diseases

12

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Introduction

Many systemic infectious diseases have ophthalmic complications or associated eye findings. The goal of this chapter is to discuss the ophthalmic manifestations in infectious disease. Due to the exhaustive list of infections that affect the eye, there are some noteworthy omissions to this chapter. This chapter does not cover the plethora of infections that can cause preseptal or orbital cellulitis or diseases that alter the immune system and increase risk of infections, such as human immunodeficiency virus (HIV). Additionally, many of the pathogens known to cause endophthalmitis and conjunctivitis are not covered. Here we discuss the most common systemic diseases in which ocular complications can arise so that the pediatric ophthalmologist and treating pediatrician can provide the proper surveillance and treatment.

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Bacterial Diseases

Bartonella Henselae

Definition

Bartonella henselae is a gram-negative bacteria that causes a systemic infection, often referred to as Cat Scratch Disease. Antecedent scratch or bite, generally from a cat and occasionally from a dog, is reported in most patients and often recalled as a result of mild trauma occurring a week or two before illness begins [1].

Epidemiology

Exact incidence of Cat Scratch Disease is unknown. Serologic prevalence of *Bartonella henselae* in cats in the US ranges widely from 13 to 90 % [5]. The rate of pediatric hospitalizations from cat scratch disease has remained stable in the last 20 years [6]. Cat scratch disease is not transmitted from person to person [5] and is more common in children than adults [2].

Systemic Manifestations

Most patients with Cat Scratch Disease develop local lymphadenopathy and about one third develop a febrile illness, which is usually mild. Patients may also describe a papule or pustule at the scratch or bite site 1–2 weeks preceding the lymphadenopathy. Atypical manifestations of Cat Scratch Disease include prolonged fever, vertebral osteomyelitis, new onset status epilepticus, encephalopathy or encephalitis, osteolytic bone lesions, and granulomatous hepatitis. Immunocompromised individuals may present with a rare vasoproliferative disordered names bacillary angiomatosis, characterized by numerous vascular tumors of the skin and subcutaneous tissue. Another vasoproliferative disorder that can developed in immunocompromised patients is bacillary peliosis, which involves solid organs with reticuloendothelial elements, such as the liver or spleen [1].

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Cat-scratch disease is a common disease for pediatricians, although the actual incidence is unclear. CSD commonly presents with regional lymphadenopathy. Affected children can be quite ill with fever and malaise, or have minimal complaints. The enlarged lymph nodes drain the site of inoculation, both from scratches and bites. The lymphadenopathy generally occurs 1–3 weeks after bacterial inoculation, and may involve axillary, cervical, or inguinal nodes. Most patients have some systemic symptoms such as myalgias, arthralgias, malaise, chills and fever. The vast majority of cases are self-limited with a benign clinical course, but the enlarged lymphadenopathy may persist for several months. CSD generally resolved spontaneously, with or without treatment, in 1–2 months. However, on rare occasions, CSD can result in serious neurologic complications such as meningoencephalitis, encephalopathy and seizures or cardiac complications, specifically lethal endocarditis [1].

Ophthalmic Manifestations

Eye involvement with systemic *Bartonella henselae* infection is reported to be 3–10 % [2, 3] with a minority of those patients presenting with the classic neuroretinitis (2–3 %) [4]. Most patients who have eye involvement due to *Bartonella henselae* infection come to the attention of the ophthalmologist due to decreased vision in one or both eyes or complaints of eye pain. Some other symptoms include photopsias and floaters. Visual acuity can range from normal to very poor (counting fingers or worse) depending on the severity of the eye involvement. In the largest series of patients with cat scratch optic neuropathy, flu-like symptoms was most common complaint followed by headache, eye pain, and pain with eye movement [2].

Patients who have eye involvement complain of blurred vision usually in one eye though up to 17 % of cases have bilateral involvement [2]. Patients usually have had known contact with cats or kittens but often will just recall the scratch or bite in retrospect.

The most common ocular manifestation of a systemic Bartonella Henselae infection is optic neuropathy (63–90 %) [2, 7] followed by neuro retinitis (nerve edema with a macular star) [2]. Vitritis can occur in cat scratch disease, and other more rare complications include branch retinal vein occlusion and macular hole [2, 7].

The combination of optic nerve edema and macular edema are often described as neuro retinitis, and an also be seen in other disorders such as Lyme disease, sarcoidosis, Rocky Mountain spotted fever, malignant hypertension, and toxoplasmosis. Some patients do not develop the full neuro retinitis, but have isolated nerve edema, retinal whitening, vitritis, choroiditis, or focal retinitis [2]. The neuroretinitis in bartonella infection has been reported to be bilateral in about 17 % of cases [2]. The mechanism of the macular star is not known but thought to be secondary to an immune response [8].

Most (67[2]–74[7]%) patients who have cat scratch disease with ocular involvement have an excellent visual outcome yet it is unclear how much of a role, if any, antibiotic or steroid treatment has in the final vision.

Diagnosis

Culture is rarely useful for the diagnosis of *Bartonella henselae* due to its fastidious nature. Bartonella serology, IgG and IgM and/or polymerase chain reaction (PCR) may be used for diagnosis depending on the clinical scenario and specimen. Additionally histology from lymph biopsies can be helpful if epitheliod granuloma formation is present [5].

Management

For typical cat scratch disease without severe vision loss or lymphadenopathy in an immune competent patient, treatment may not be needed [9]. Management of neuro retinitis is controversial with many ophthalmologists in favor of treatment of all cases and some physicians feeling comfortable with observation since an immune competent patient should be able to heal without intervention [8].

For patients without eye involvement and without significant systemic illness or immunodeficiency, for whom the decision to treat is made, the current recommended treatment is azithromycin 10 mg/kg orally on day 1 and then 5 mg/kg orally from days 2 to 5. The standard treatment for adults with retinal involvement is doxycycline (100 mg PO bid) and rifampin (300 mg PO) for 4–6 weeks with the consideration of topical steroids [9]. There is no consensus on the treatment of children with retinal involvement of *Bartonella henselae* infection. Azithromycin, clarithromycin, trimethoprim-solfamethoxazole, doxycycline, fluroquinolones, gentamicin and rifamim all have activity against bartonella and can be used in certain clinical situations. Generally combination therapy is used for neurologic disease.

Lyme Disease

Definition

Lyme disease is a tick-born infection caused by the spirochete *Borrelia burgdorferi*. It is transmitted to humans from the bite of the *Ixodes* tick, also known as the deer tick or blacklegged tick [10]. Lyme infection in the eye is often referred to as a masquerade disease due to its variable presentation.

Epidemiology

Lyme disease is the most common vector-born disease in the U.S. [12]. In 2011, there were over 24,000 confirmed cases of Lyme disease in the U.S. It is most commonly seen in children between the ages 5 and 15, with a secondary peak in adults aged 45 and 55. Most cases present between

May and September [10]. It is endemic in multiple regions of the U.S., particularly the Northeast, upper Midwest, and Northwest [12].

Systemic Manifestations

Patients do not always have a known history of a tick bite or the typical erythema migrans rash in which case travel and activity history are useful. Systemic manifestations and travel history are what guide the clinician toward diagnosing Lyme disease as the cause of ocular disease. Ocular symptoms often include periocular or intraocular pain, photophobia, blurred vision, and floaters [11].

Systemic features include the characteristic "bulls-eye" rash that spreads slowly from the site of the tick bite, known as erythema migrans (EM). The rash is seen in about 90 % of patients and is often accompanied by a flu-like illness with headache, malaise, fever, and regional lymphadenopathy [13]. Disseminated disease presents with musculoskeletal and neurologic signs, including arthralgias, myalgias, cranial nerve palsies (most commonly facial nerve palsy), and meningitis. Carditis, causing heart block, is seen in <1 % of children [10]. In late disease, the most frequent manifestation is a chronic, episodic arthritis [14].

The CDC recognizes three stages of Lyme disease an early stage that occurs 3–30 days after the tick bite and is associated with the EM rash as well as fatigue, swollen lymph nodes, and generalized aches. In the days to weeks after the tick bite, the patient enters the early disseminated stage where additional areas of EM appear on the body, facial nerve palsies appear, and other symptoms such as severe headaches and neck pain due to meningitis, large joint pain and swelling, and heart palpitations may occur. The late disseminated phase occurs months to years after the tick bite and the patient experiences intermittent arthritis and chronic neurologic complaints such as short term memory problems and tingling in extremities [15].

Ophthalmic Manifestations

Ophthalmic findings can be seen in early or late disease [11]. A nonspecific follicular conjunctivitis is seen in approximately 11 % of patients with early disease and occurs within a few weeks of infection, and is the most common ocular finding in Lyme disease [11, 14, 16]. Stromal keratitis and episcleritis have been reported in late disease [13].

Intraocular inflammation can occur in both early and late disease [11, 16]. It can present with anterior uveitis, vitritis, choroiditis, and retinal vasculitis. Optic neuritis and neuroretinitis have also been described [14].

Seventh nerve palsies associated with Lyme can lead to an exposure/neutropic keratopathy. Other cranial nerve palsies (cranial nerve III, IV, and VI) will cause abnormalities in extraocular motility and diplopia [14].

Uncommonly, children with Lyme meningitis can develop a pseudotumor-cerebri-like syndrome causing elevated intracranial pressure and vision-threatening papilledema [10, 14].

Diagnosis of Lyme Disease

The CDC recommends a 2-step protocol for serologic diagnosis of active or previous infection: ELISA for IgM and IgG followed by Western immunoblot testing [15]. The clinician should keep in mind that an antibody response can take weeks to develop and may be transient, so a negative antibody test does not rule out disease. False positive testing can occur with infectious mononucleosis and autoimmune disease [10].

Direct DNA testing by PCR is of limited value in diagnosis because of lack of target DNA in clinical samples of blood or CSF [10].

Management

Children with localized erythema migrans or early disseminated disease without neurologic manifestations or without third-degree heart block should be treated with oral doxycycline (1–2 mg/kg BID) or amoxicillin (50 mg/kg/day divided in 3 doses) for 14–21 days [12]. Doxycycline is contraindicated in children <8 years of age. Patients with facial nerve palsy or first/second-degree heart block can also be treated with oral antibiotics as above.

Recommendations for the management of Lyme disease from the Infectious Disease Society of America do not include specific management based on eye findings and the route and duration of treatment has not been established for ocular disease. However, ocular involvement should be considered a central nervous system manifestation and treated with IV ceftriaxone (75–100 mg/kg/day in single dose) or cefotaxime (150–200 mg/kg/day in 3 or 4 doses) for 14–28 days in children [12].

Topical corticosteroids or mydriatics may be used to treat ocular inflammation and keratitis [13].

Syphilis

Definition

Syphilis is a systemic, bacterial diseased caused by the spirochete *Treponema pallidum.* It is transmitted by sexual contact or transplacentally from mother to fetus after the 10th week of pregnancy [17].

Epidemiology

Primary and secondary acquired syphilis account for 31 % of all cases, with the rest being either congenital or latent. The rate of primary and secondary syphilis more than doubled

between 2000 and 2013 from 2.1 per 100,000 to 5.3 per 100,000 people, with men accounting for 91 % of early cases in 2013 [19]. Ocular involvement occurs in about 10 % of secondary disease [17]. The rate of syphilis in men who have sex with men increased from 2000 to 2010 [20].

Congenital syphilis in the U.S. is related to late or no testing for syphilis during pregnancy.

Systemic Manifestations

Mothers of patients with suspected congenital syphilis and patients with suspected acquired syphilis may have a high-risk sexual history or a partner with high risk sexual behaviors. Ophthalmic symptoms are generally nonspecific and include pain, redness, photophobia, floaters, and visual impairment [18].

Syphilis can affect almost any organ or system in the body.

Untreated acquired syphilis is categorized into four stages: [17].

- Primary: Incubation period of 10–90 days. Characterized by non-tender, indurated, non-purulent chancre at the site of inoculation. Resolves spontaneously in 4 weeks.
- Secondary: 4–10 weeks following appearance of the chancre. Hematogenous dissemination of the spirochete causing neurologic, ophthalmic, gastrointestinal, and hepatic disease. A diffuse, maculopapular rash, prominent on the palms and soles is characteristic. Symptoms resolve without treatment.
- Latent: Asymptomatic period after resolution of secondary symptoms. Can last from months to a lifetime.
- Tertiary syphilis: 1/3 of patients progress to this stage. An obliterative endarteritis that can affect any organ in the body, most prominently cardiovascular and neurologic involvement (aortitis, neurosyphilis)

Systemic findings in early congenital syphilis (less than 2 years old) include: hepatosplenomeglay, changes in long bones on radiographic imagined, abdominal distension, desquamative rash, low birth weight, and pneumonia. Late manifestations (older than 3) include Hutchinson teeth, mulberry molars, abnormal facies, CNVIII deafness, saber shins, hard palate perforations, cutaneous lesions, and neuro syphilis [18].

Ophthalmic Manifestations

Ocular findings in syphilis are extremely variable. Anterior findings can include a papillary or granulomatous conjunctivitis, interstitial keratitis, episcleritis, or scleritis [17]. Corneal inflammation results in an immune-mediated, nonulcerative, stromal keratitis. Untreated, this keratitis can cause corneal neovascularization or scarring with ghost vessels. In the pre-antibiotic era most interstitial keratitis was associated with syphilis, 90 % with congenital syphilis [17]. Interstitial keratitis is the most common inflammatory finding in untreated late congenital syphilis. Interstitial keratitis, cranial nerve VIII deafness, and Hutchinson teeth is called the *Hutchinson triad* [18].

Syphilis can present as a nonspecific granulomatous or nongranulomatous anterior, intermediate, posterior, or pan uveitis. Posterior findings can include vitritis, chorioretinitis, retinal vasculitis, branch retinal vein occlusion, and serous retinal detachment. Optic nerve involvement includes disc edema, neuroretinitis, pallor, or an optic nerve gumma [19].

There are some clinical patterns that can allow rapid diagnosis on ophthalmic examination. In syphilitic panuveitis, patients may have preretinal, white opacities that migrate over the retina during the disease course and treatment. Another distinctive presentation is an acute, placoid chorioretinitis.

The Argyll Robertson pupil (miotic pupil with light-near dissociation) is mostly associated with late disease [17].

In congenital syphilis, ocular inflammatory disease can be present at birth or can present decades later. A multifocal choroiditis and retinal vasculitis are the most frequent uveitis manifestations. Patients can also have a pseudoretinitis pigmentosa picture caused by secondary degeneration of the RPE [18]. Congenital glaucoma and cataracts are also associated with congenital syphilis [17].

Diagnosis

Treponomal serologic testing is valuable for diagnosis. The CDC currently recommends enzyme immunoassays (EIAs) and chemiluminescent immunoassays (CIAs) to detect antibodies to treponemal antigens as the best screening tests for syphilis followed by reflex testing of positive specimens with the nontreponemal test, rapid plasma reagin (RPR). Syphilitic uveitis can also be directly diagnosed by PCR of aqueous humor [19].

Positive serologic testing in a patient with ophthalmic disease warrants CSF testing [19].

Management

Ocular syphilis is treated as neurosyphilis, with parenteral penicillin G being the treatment of choice. Ocular inflammation usually subsides with penicillin treatment [19].

Steroids have an adjuvant role in treating ocular inflammation. Topical steroids can be used to treat interstitial keratitis and anterior uveitis. Systemic steroids can be used in posterior uveitis, optic neuritis, and scleritis [19].

Chlamydia Trachomatis

Definition

Chlamydia trachomatis is a gram-negative, obligate intracellular bacterium. Urogenital infection is typically caused by serotypes D-K whereas serotypes A-C cause trachoma; an eye disease transmitted by direct exposure to the bacteria

often secondary to poor hygiene in developing countries. Urogenital serotypes of C. *trachomatis* can be passed to infants via perinatal exposure to the mother's infected cervix during birth [21, 22].

Epidemiology

Sexually active women <25 years of age are at high risk for chlamydial infection from C. *trachomatis* serotypes D-K [21]. The risk of transmission to infants of infected mothers is estimated to be between 50 and 75 %. Neonatal conjunctivitis is the most common clinical manifestation and is seen in 20–50 % of infected infants [23].

Trachoma is a blinding condition caused by repeated infection with *C. trachomatis* (serotype A–C) principally in resource-poor areas in developing countries. Transmission is through direct exposure to the bacterium in contaminated water and houseflies. It is the most common cause of infectious blindness worldwide. Trachoma is endemic in some of the poorest areas of Africa, Asia, Australia, and the Middle East, with 21 million people affected and 2.2 million blind or severely visually impaired worldwide. Active trachoma is most common in children <5 years of age [22].

Systemic Manifestations

Patients with Chlamydial infections of the eye caused by serotypes D-K usually present with unilateral, but occasionally bilateral irritated and red eye. Patients sometimes complain of blurred vision and usually complain of watery discharge. Genital infection is often asymptomatic.

Serotypes A-C cause an indolent infection usually beginning with foreign body sensation and tearing, sometimes with eye pain when patients have associated entropion, subsequent corneal scarring, and finally resulting in decreased vision, which can be very poor.

In addition to ocular findings, chlamydial infection from serotypes D-K in infants can cause a subacute, afebrile pneumonia around 1–3 months of age if left untreated. Characteristic presentation of chlamydial pneumonia includes a staccato cough with tachypnea, hyperinflation and bilateral infiltrates on chest X-ray. Chlamydia can also infect the urogenital or rectal mucosa, although infection is often asymptomatic in these locations [21].

Ophthalmic Manifestations

Ophthalmia neonatorum is conjunctivitis in newborns with onset <30 days after birth. *Chlamydia trachomatis* is the most frequently identified cause of ophthalmia neonatorum, which typically presents between 5 and 12 days of age as an acute, mucopurulent, papillary, conjunctivitis which may have pseudomembranes [21].

Chlamydia conjunctivitis can also present at older ages, often in sexually active teenagers and adults. In these cases, patients present with a chronic follicular conjunctivitis.

As noted earlier, trachoma is a blinding eye disease caused by repetitive ocular infection by *C. trachomatous* in developing countries. Active trachoma is characterized by a severe follicular conjunctivitis. Once active inflammation wanes, patients develop significant conjunctival scarring, eyelid distortion, entropion with trichiasis causing corneal damage that can progress to blindness. Classic manifestations of trachoma include Arlt's line, a thick horizontal line of scar tissue seen on the palpebral conjunctiva, and Herbert's pits, cicatrized limbal follicles seen on the cornea [22].

Diagnosis

In infants, diagnosis is confirmed by culture and nonculture tests, such as direct fluorescent antibody testing from specimens from conjunctival swabs. Conjunctival cells should be obtained from the everted eyelid using a Dacron tipped swab. The specimen must contain conjunctival cells, not just exudate. The specimen should also be tested for *Neiserria gonorrhea* co-infection [21].

Trachoma is principally a clinical diagnosis and laboratory confirmation is not necessary [22].

Management

Prenatal screening of pregnant women and treatment with azithromycin prior to delivery prevents the vertical transmission of Chlamydia serotypes D-K to infants. Neonatal ocular prophylaxis with silver nitrate or erythromycin ointment does not prevent ophthalmia neonatom caused by *C. trachomatis*, but should still be given as it prevents gonorrheal conjunctivitis [21].

In cases of neonatal conjunctivitis secondary to Chlamydia, treatment is warranted in both the child and the mother. Topical treatment alone in infants is not sufficient due to the risk of developing pneumonia. Infants are systemically treated with oral erythromycin 50 mg/kg/day divided into 4 doses daily for 14 days. Patients require close follow-up as treatment initial treatment with erythromycin approximately 80 % effective and a second course of antibiotic treatment may be required [21].

Patients with sexually transmitted Chlamydia also need to be treated systemically, and in these cases a single dose of oral azithromycin is recommended [21].

For trachoma, the World Health Organization recommends mass drug treatment in areas where the prevalence of follicular conjunctivitis is >10 %. The treatment of choice is a single oral dose of azithromycin (20 mg/kg). Topical tetracycline is given for 6 weeks. Surgical intervention is also recommended to correct clinically significant entropion and trichiasis. Along with antibiotic and surgical intervention, facial cleanliness and environmental improvements are also stressed to address the root cause of repeated infection [22, 24].

Gonococcal Infections

Definition

Gonococcal disease is caused by *Neisseria gonorrhea*, a gram negative diplococcus. Gonorrhea is primarily a sexually transmitted disease. It is transmitted vertically to infants by exposure to the mother's infected cervix.

Epidemiology

Humans are the only reservoir of gonorrhea [25]. In the U.S., approximately 700,000 new cases of gonococcal infection are reported each year. It is the second most common sexually transmitted disease, behind chlamydial infection [26].

Systemic Manifestations

The infected neonate can present with meningitis, sepsis, scalp abscesses, septic arthritis, and wound infections. Less commonly they may develop a vulvovaginitis, proctatis, rhinitis, and urethritis. Blood and CSF cultures should be obtained in infants with ocular infection due to the risk for sepsis and meningitis [25].

Ophthalmic Manifestations

Neonates will present with a purulent conjunctivitis at 2–4 days of life. Often eyelid edema is present. A history of gonorrhea in one or both parents can often be elicited.

The most common manifestation of gonococcal infection in infants is ophthalmia neonatorum. It can range from a mild to a severe, rapidly destructive conjunctivitis causing corneal scarring and blindness. It can occur earlier with premature rupture of membranes. Infants will present with bilateral, mucopurulent, and sometimes bloody discharge with eyelid edema and chemosis. Severe cases can lead to corneal ulcers, corneal perforation, and panophthalmitis [25]. Sexually active adolescents can also get a severe mucopurulent conjunctivitis from direct contact with infected secretions (Fig. 12.1).

Diagnosis

For ocular disease, culture from conjunctival exudates is the gold standard for diagnosis of gonoccal infections. Colonies grow within 24–48 h of inoculation but generally gonorrhea tends to be difficult to culture. It is important to plate the secretions immediately onto chocolate agar for best results [5]. Gram stain as has good sensitivity for gonococcal infection, but does not confirm diagnosis. Nucleic acid amplification tests (NAATs) are useful for urogenital infection [5].

Management

A single IM dose of ceftriaxone is the treatment of choice for gonococcal ophthalmia neonatorum, along with eye irrigation with saline solution at frequent intervals until the discharge has resolved. Topical antibiotic treatment is unnecessary when systemic treatment is given [25].

Fig. 12.1 Purulent conjunctivitis due to gonorrhea infection

In the United States, prophylaxis for gonococcal ophthalmia neonatorum is recommend in all infants and required by law in many states. Medication is applied topically within 1 h after birth. Prophylactic medications include 1 % silver nitrate solution, 1 % tetracycline ointment, or 0.5 % erythromycin ointment, however topical silver nitrate and tetracycline are no longer manufactured in the U.S. [25, 26]. Infants born to mothers with known gonococcal infection should be treated with a single parenteral dose of a 3rd generation cephalosporin due to the potential for failure of prophylaxis [25].

Leprosy

Definition

Leprosy, also known as Hansen's disease, is a chronic, granulomatous infectious disease caused by the acid-fast bacillus *Mycobacterium leprae.* The bacterium is transmitted from person-to-person through droplet exposure. It is a slowly replicating bacterium, with an incubation period of about 5 years. It can take up to 20 years for symptoms of the disease to actually appear. Leprosy is disease of the skin, peripheral nerves, and mucus membranes caused by infiltration of the bacterium in these locations [27].

Epidemiology

Worldwide, 200,000–300,000 patients are blind from leprosy [28]. At the end of 2012, official figures from 115 countries reported a registered global prevalence of leprosy at 189,018 with 232,857 new cases reported during the same year. Leprosy is exceedingly rare in the United States, but is highly endemic in the following countries: Angola, Bangladesh, Brazil, China, Democratic Republic of Congo, Ethiopia, India,

Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Nigeria, Philippines, South Sudan, Sri Lanka, Sudan and the United Republic of Tanzania [27]. Even in highly endemic areas, the bacterium has low pathogenicity. Only 5 % of people exposed to the bacterium eventually develop disease. The remaining 95 % show resistance to the disease [29].

Systemic Manifestations

Clinical manifestations of leprosy depend on the patient's immune response. There are two clinical forms of leprosy, lepromatous and tuberculoid, however patients can also have overlap between these two types. In tuberculoid leprosy, patients have a vigorous cellular immune response that limits the disease to a few, defined skin patches or nerve trunks. In lepromatous disease there is an absence of a specific cellular immune response to the bacterium, thus allowing for uncontrolled proliferation of the bacterium resulting in many lesions and extensive infiltration of the skin and nerves [30].

Skin lesions most commonly manifest as hypopigmented, and sometimes erythematous, macules or plaques with a raised edge, often with reduced sensation. Nerve infiltration and damage occurs in the peripheral nerve trunks and the small dermal nerves. Involvement of nerves causes nerve enlargement, with or without tenderness, and regional patterns of sensory or motor loss. Small dermal and autonomic nerve involvement causes hypoaestheisa, anhidrosis, and can cause a stocking-glove sensory loss [30].

Ophthalmic Manifestations

Along with systemic findings, patients with leprosy involving the eye will present with reduced visual acuity or even blindness [27].

Leprosy affects the eye through direct infection of the bacterium in the skin of the eyelids, tear ducts, and lacrimal glands, facial nerve, ophthalmic division of the trigeminal nerve, or direct invasion of the anterior segment [28].

Adnexal manifestation includes madarosis of the eyelashes and eyebrows, lagophthalmos (due to facial nerve infiltration), entropion, ectropion, trichiasis, and low lacrimal secretion. Anterior segment findings include conjunctivitis, decreased corneal sensation (due to trigeminal nerve involvement), exposure keratitis, corneal opacities, iris nodules, iris atrophy, anterior uveitis, episcleritis, and scleritis [28, 29]. Thickening and beading of corneal nerves is detected on slit lamp exam and is a common and characteristic finding in early leprosy [31]. The posterior segment involvement, very rare in leprosy, manifests as minute, white, "pearl-like" choroidal nodules, similar to those seen in the iris [29, 31].

Diagnosis

Diagnosis of leprosy is principally based on clinical signs and symptoms. Smears of affected skin can be performed to detect the presence of acid-fast bacilli. In endemic regions, a patient is regarded as having leprosy if he or she has the following:

1. Hypopigmented or reddish skin lesions with loss of sensation
2. Involvement of the peripheral nerves, indicated by loss of sensation and weakness in the muscles of the hands, feet, or face
3. Skin smear positive for acid-fast bacilli [27]

Management

For treatment purposes, leprosy is classified as multibacillary (more than 5 lesions), puacibacillary (2–5 lesions), or a single-lesion disease [30].

The World Health Organization recommends a multidrug antibiotic regimen for the treatment of leprosy, which includes a combination of rifampin, clofazamin, and dapsone for 12 months in patients with multibacillary leprosy or a combination of rifampin and dapsone for 6 months in patients with paucibacillary leprosy. Patients with single lesion leprosy can be treated with a one-time dose of rifampin, ofloxacin, and minocycline taken together [27].

Facial nerve paralysis causing lagophthalmos with onset within 6 months can be treated with oral corticosteroids. The patient should be instructed to tape the eyelids closed, lubricate corneal and consider an eye patch/shield to protect the eye for exposure. Uveitis should be treated with topical corticosteroids and mydriatics. Corneal abrasions, keratitis, or ulcers caused by exposure should be treated as usual with lubrication and topical antibiotics [27].

Tuberculosis

Definition

Tuberculosis (Tb) is a chronic, granulomatous infection caused by the acid-fast bacillus *Mycobacterium tuberculosis* [32]. The bacterium is most commonly transmitted by aerosolized droplets [33].

Epidemiology

The World Health Organization estimates approximately one-third of the world population is latently infected with Tb, with >9 million cases of active tuberculosis yearly [33]. China, India, and the African continent account for the largest number of new and recurrent cases. The incidence of tuberculosis in the United States in 2011 was 3.4 cases per 100,000 people, with immigrants and ethnic minorities being disproportionately affected. The highest incidence in the U.S. is among Asians. Approximately 79 % of foreign-born people with Tb were diagnosed after being in the U.S. more than 2 years, consistent with reactivation of latent disease. In the U.S., tuberculosis has

reemerged as a public health problem due to the AIDS epidemic [32]. Eighty-one percent of those diagnosed in 2011 were HIV-positive [34].

Uveitis due to systemic Tb infection varies around the world. Eye involvement in patients with systemic Tb ranges from 0.14 to 10 % of patients with Tb in India, 1 % in the United States, 4 % in China, 6 % in Italy, 7 % in Japan, and 16 % of patients in Saudi Arabia [33].

Systemic Manifestations

Systemic disease can occur after primary exposure, but in 90 % of cases it occurs secondarily after reactivation of the disease. The great majority of patients mount an immune response upon initial infection leading to the formation of pulmonary caseous granulomas that contain, but do not eliminate, the infection. A small proportion of the bacteria live in a dormant state within these granulomas and can be reactivated later in life. In an immunocompetent individual, the risk of reactivation is 10 % over the course of a lifetime. The risk of reactivation is even higher, 10 % yearly, in a patient with HIV [33].

The most common manifestation of reactivated tuberculosis infection is granulomatous lung disease, seen in 80 % of patients with reactivation. Extra-pulmonary tuberculosis can manifest in the gastrointestinal tract, cardiovascular system, musculoskeletal system, genitourinary system, central nervous system, as well as the eyes [32]. Miliary Tb most commonly occurs in immunocompromised patients, and represents unchecked hematogenous dissemination of the infection in primary or secondary disease.

Ophthalmic Manifestations

Ocular manifestations of Tb can result from active infection or from an immunologic reaction to the organism [32]. Tuberculosis can affect the anterior and posterior segment of the eye, as well as the orbit. Presentation of Tb is extremely varied and it can present as an acute anterior uveitis, chronic granulomatous anterior uveitis with mutton fat keratic precipitates, an intermediate uveitis, vitritis, macular edema, retinal vasculitis, neuroretinitis, multifocal choroiditis, subretinal abscess, endophthalmitis, and panophthalmitis [32]. Tb has also been associated with necrotizing and non-necrotizing diffuse or nodular scleritis, epscleritis, and peripheral ulcerative keratitis. Rarely, Tb associated inflammation presents as an interstitial keratitis, phylyctenulosis, iris or ciliary body granulomas, and dacroadenitis [34]. Among these manifestations, the most common clinical finding is posterior uveitis [32, 34]. Eales disease, classically thought to be an idiopathic retinal vasculitis, is now considered to represent a hypersensitivity reaction to tuberculous antigens. It is characterized by a peripheral ischemic vasculitis with neovascularization and recurrent vitreous hemorrhage without other signs of inflammation, and is typically seen in young men where tuberculosis is endemic [33].

Tuberculous choroidal granulomas (tuberculomas) occur in association with pulmonary and non-pulmonary systemic disease. They are usually white, cream, or yellow in appearance and can be unifocal or multifocal. Visual symptoms depend on location and extent of the tuberculomas. Systemic symptoms such as fever, malaise, cough, hemoptysis, and weight loss are helpful in alerting the clinician toward TB as the cause [34].

Diagnosis

A tuberculin skin test (TST) or serum quantiFERON-TB Gold testing can help aid in the diagnosis of ocular tuberculosis. However, neither of these tests is diagnostic for tuberculosis eye disease and the clinician must rule out other potential infectious or inflammatory causes of uveitis (such as sarcoidosis) on the differential before designating a diagnosis of ocular Tb. The gold standard for diagnosis of ocular Tb is a positive culture from ocular tissue or fluid, although this may be difficult to obtain in many cases. PCR testing on ocular tissue or fluid for Tb has low sensitivity, possibly due to a low bacterial load in ocular fluids and a thick cell wall of *M. tuberculosis* [34]. Chest X-ray or chest computed tomography can help in the cases of suspected ocular TB as it can reveal pulmonary lesions and lymphadenopathy [32].

Fluorescein angiography has an important role in the evaluation of a patient with suspected ocular tuberculosis. It is very sensitive in picking up evidence of retinal vasculitis, and often shows that vasculitis is more extensive than indicated by clinical examination. Macular edema, optic disc edema, and choroiditis are other potential angiographic findings [32].

Management

Treatment for ocular Tb is directed at both the inflammatory and infectious components of the disease. Multi-drug therapy with isoniazide, rifampin, ethambutol, and pyrazinamide initially for 2 months, followed by rifampin isoniazide for an additional 4–7 months is recommended. Systemic corticosteroid therapy (oral prednisone at 1 mg/kg/day) and topical steroids and cycloplegics are used in conjunction with antimicrobial therapy to treat the inflammatory response [32].

Group B Streptococcal Infections

Definition

Group B streptococcus, also known as *Streptococcus agalactiae,* is a gram positive cocci that is a major infectious cause of neonatal obidity and mortality. In the U.S., universal screening guidelines have been in place by the CDC since 2002 to identify mothers to receive intrapartum antibiotics in

order to reduce the transmission of the bacteria to neonates and reduce the neonatal infection [35]. Pregnant women are routinely screened for GBS colonization between 35 and 37 weeks of gestation. If testing is positive, they are treated with intravenous antibiotics during delivery [36].

History Related to Eye Findings

Ocular infection with GBS is extremely rare in neonates. Neonates with ocular involvement of GBS will have mothers who tested positive on screening prenatally. Most cases present with coincident sepsis or meningitis. Patients may present with conjunctival injection, periorbital edema/erythema, corneal edema or opacity, elevated intraocular pressure, iris neovascularization, or leukocoria mimicking retinoblastoma [36].

Epidemiology

Prior to perinatal preventative strategies, the incidence of early-onset neonatal infection with group B strep was 0.47/1000 live births (between 1991 and 2001). It has since declined to about 0.3/1000 live births in the following years. Despite this reduction, neonatal GBS is still the leading cause of serious neonatal infection resulting in significant morbidity and mortality [35].

The GBS colonization rate in pregnant women varies from 15 to 35 %. Risk factors for neonatal infection include positive vaginal cultures in the mother, bacteriuria during pregnancy, low-birth weight, preterm gestation, rupture of membranes >18 h, intrapartum fever, chorioamnionitis, previous infant with GBS disease, intrauterine fetal monitoring, and low levels of maternal anticapsular antibody [35].

Systemic Manifestations

Group B strep is a major cause of neonatal infection. It can present as an early-onset sepsis in the first days of life as well as a late-onset sepsis, which is into the first month or two of life. Presenting features of infants with GBS sepsis include respiratory distress or apnea, lethargy, refusal to feed, temperature instability, poor perfusion, hyperbilirubinemia, skin rash, pneumonia, or meningitis [35].

Ophthalmic Manifestations

Most patients with ocular tuberculosis have no manifestation of systemic or pulmonary disease [32]. Ocular symptoms are varied and depend on the part of the eye that is involved. Patients can present with visual changes, pain, photophobia, and tearing [33].

GBS ocular infection presents as endogenous endophthalmitis. As of 2010, there were only 6 reported cases of GBS endogenous endophthalmitis in neonates reported in the literature. In 4 of these reported cases, the infant was also diagnosed with GBS meningitis [36].

Diagnosis

Diagnosis of GBS endophthalmitis can be confirmed through vitreal culture. It most reported cases, it was presumed as these patients either had confirmed GBS sepsis or meningitis through blood and CSF cultures, respectively [36].

Management

As GBS endophthalmatis in neonates is very rare, there is no defined protocol for treatment. The few reported cases infants have been treated in varying ways. Nearly all infants were treated with systemic, intravenous antibiotics, which included a broad-spectrum penicillin and an aminoglycoside. Many also received intravitreal injection with vancomycin and ceftazidime. In cases where retinoblastoma could not be ruled out or the patient had a blind, painful eye, the eye was enucleated [36].

Parasites

Baylisascaris Infections

Definition

Baylisascariasis is caused by infection by the nematode parasite *Baylisascaris procyonis.* The definite host for this parasite is the American raccoon. Infection occurs in humans after consumption of the parasite egg, which hatches in the intestine. Hatched larvae penetrate the gut wall and migrate to other organs after entering the blood stream through the portal system [37].

Epidemiology

Baylisascaris is indigenous in North American raccoons, but occurs in raccoons all across the world. In North America, the prevalence of *Baylisascaris* in raccoons is highest in the Midwest, northeast, and West Coast raccoon populations [37].

The most important risk factors for infection include pica or geophagia, and exposure to raccoons or environments contaminated with raccoon feces, which contain the parasite eggs [37].

Baylisascaris is the most common cause of diffuse unilateral subacute neuroretinitis (DUSN) though other nematodes have been described to cause DUSN including *Toxocara* spp. or *Ancylostoma* spp. [37, 39].

Systemic Manifestations

Infection of organs other than the eye and heart is known as visceral larva migrans (VLM), and is caused by migration of hatched larva to various organs of the human body. Infection causes granuloma formation, which have histologically been found in the heart, mediastinal soft tissues, pleura and lungs,

small and large bowel walls, and mesentery and mesenteric lymph nodes. Presentation includes nonspecific clinical findings such as a macular rash most commonly on the face and trunk, hepatomegaly, and pneumonitis with dyspnea and tachypnea [37].

In its most severe form, *B. procyonis* is a rare cause of fatal or neurologically devastating neural larva migrans (NLM) in infants and young children, characteristically presenting as an acute, fulminant eosinophilic meningoencephalitis [37].

Ophthalmic Manifestations

Patients infected with *Baylisacaris* will present with diffuse unilateral subacute neuroretinitis (DUSN) and complain of progressive visual impairment, often unilateral. In those with isolated ocular disease, there is commonly no known exposure to raccoons or raccoon feces, indicating that disease occurs after ingestion of a small number of eggs followed by chance migration of a single larva to the eye [37].

DUSN can have an insidious onset. Early symptoms may include a unilateral paracentral or central scotoma, pain, discomfort, or transient visual obscurations. Patients usually have good general health [38].

Ocular disease (Ocular larva migrans, OLM) occurs in both adults and children. It can be an isolated finding or associated with NLM and VLM [37].

Most infants and children with NLM or VLM can develop visual impairment or blindness from invasion of larva into the visual cortex or into the eye itself [37].

Patients with DUSN have a variety of findings that can cause visual loss including vitritis, choroidioretinitis, optic neuritis or atrophy, papillitis, and crops of multiple evanescent, gray-white outer retinal lesions. In the late stages, optic atrophy, retinal artery narrowing, diffuse pigment epithelial degeneration, and an abnormal electroretinogram can be seen [40]. Late features of DUSN can include retinal narrowing, optic nerve atrophy, and focal or diffuse retinal pigment epithelium atrophy [38]. Ophthalmic exam can sometimes reveal a migrating larvae within the retina (Fig. 12.2). Visible *Baylisascaris* in the retina is larger in size than *Toxocara*, another common cause of OLM (1000–2000 × 60–70 μm vs. 350–445 × 20 μm, respectively).

Eighty percent of patients with late stage DUSN have profoundly decreased vision at 20/200 or worse [40].

Diagnosis

Diagnosis is mainly clinical, based on signs/symptoms, along with evidence of eosinophilia. Serologic testing showing the presence of anti-Baylisascaris antibodies in the CSF or serum is supportive of the diagnosis [37].

Management

OLM and DUSN have both been successfully treated with laser photocoagulation of the intraretinal larvae, however the worm is only visualized in 25–40 % of cases [41]. Systemic steroids are used to reduce any sequential intraocular inflammation. There is no one drug proven to be effective in treating Baylisascariasis [5]. The role of anti-helminthics in ocular disease has not been established [37].

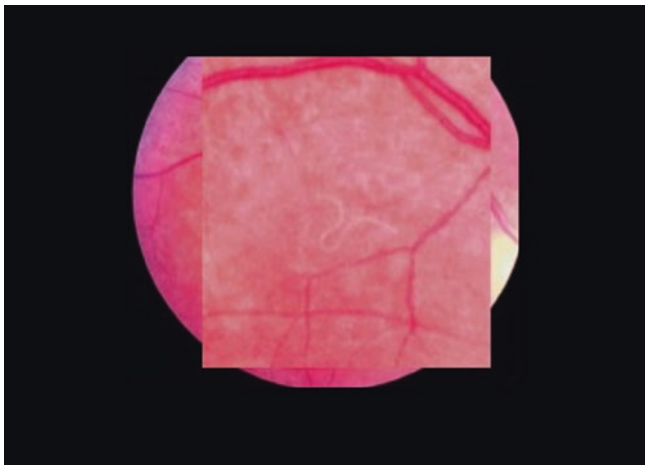

Fig. 12.2 Subretinal larvae seen in DUSN (photo courtesy of Scott Oliver, MD)

Toxocariasis

Definition

Toxocariasis is a parasitic infection caused by the roundworm species *Toxocara.* The definitive host of this species is the common house cat (*Toxocara cati*) and dogs (*Toxocara cani)*. Infection in humans occurs after ingestion of material contaminated with parasite eggs. The eggs hatch in the intestines then migrate to tissues throughout the body [42].

Epidemiology

Ocular *Toxocara* primarily affects children, with geophagia and dog-ownership being significant risk factors. Most children present in late childhood or in adolescence [42].

Systemic Manifestations

As with *Baylisascaris* infection, systemic infection with *Toxocara* is also termed visceral larva migrans (VLM). Systemic disease is characterized by fever, malaise, hepatomegaly, rash, and leukocytosis [42].

Ophthalmic Manifestations

Patients usually present with monocular visual loss. Visual acuity can be severe, as low as 20/200 or less in many cases. Toxocariasis is an important diagnosis to consider in patients who present with leukocoria and can have presentation similar to retinoblastoma. The most common clinical findings include diminished vision, leukocoria, vitritis, ocular injection, and strabismus [42].

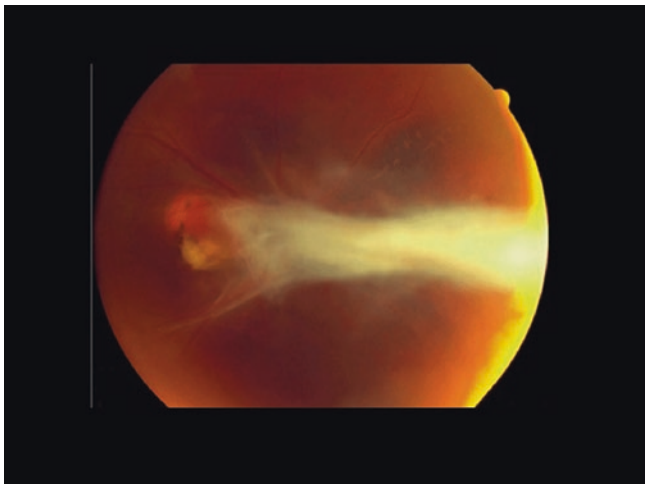

Fig. 12.3 White, posterior pole granuloma in patient with toxocariasis (photo courtesy of Scott Oliver, MD)

Toxocara is another parasitic infection that causes ocular larva migrans (OLM), which occurs when the parasite infiltrates the eye and causes and inflammatory reaction. It occurs unilaterally in 90 % of cases.

Clinical presentation can be classified into four forms: a posterior pole granuloma, peripheral granuloma, nematode endophthalmitis, or an atypical presentation. The posterior pole granuloma is the most common form of presentation (Fig. 12.3), and is characterized by a focal, whitish subretinal or intraretinal inflammatory mass in the posterior pole, with or without signs of acute inflammation. Peripheral granulomas appear as focal, white, elevated nodules in the periphery, which may have surrounding inflammatory membranes or pigmentary changes.

Toxocara endophthalmitis is a panuveitis and involves a prolonged course of inflammation caused by the intraocular nematode. It manifests as a red, painful eye with diffuse inflammation, and retinal exam may reveal a granuloma and tractional inflammatory membranes.

Atypical presentations include papillitis, optic nerve head edema, motile subretinal larvae, diffuse chorioretinitis, conjunctivitis, keratitis, iridocyclitis, focal iris nodules, and cataract [43].

Diagnosis

Serologic testing with ELISA for the *Toxocara* excretory secretory IgG has a reported 90 % sensitivity and specificity for systemic infection. ELISA studies can be performed on aqueous or vitreous samples as well. However, ocular toxocariasis is primarily a clinical diagnosis, and only histopathologic evaluation of an enucleated eye will reveal larvae [42].

Management

Ocular inflammation is routinely managed with topical, periocular, or systemic corticosteroids. Cycloplegics may be used if anterior segment inflammation is present. The need for systemic antihelmenthics is unclear. However, the use of antihelminthic drugs, such as albendazole, in combination with corticosteroids has shown favorable outcomes in some studies [43]. Vitreoretinal surgery is indicated in patients with retinal detachments caused by tractional membranes [42].

Toxoplasmosis

Definition

Toxoplasmosis is infection caused by the protozoan *Toxoplasma gondii*. Felines are the primary host of *T. gondii*. The organism is transmitted to humans orally after handling or eating raw meat that harbors tissue cysts or by drinking water or contaminated food with parasite oocysts. Congenital infection occurs through vertical transmission from an acutely infected mother transplacentally to the fetus. The risk of congenital toxoplasmosis is highest in the third trimester, whereas clinical manifestations are more severe if acquired during the first trimester [44].

Epidemiology

In 2004, it was estimated that that up to one-third of the world's population was infected with *Toxoplasma gondii*; however, there is significant geographic variation in seroprevalance. Prevelance of *T. gondii* IgG positivity among U.S. born subjects between 1999 and 2004 was estimated to be about 9 %. Multiple studies performed in various countries have identified toxoplasmosis as the most common cause of posterior uveitis [44].

The incidence of congenital toxoplasmosis varies geographically. In the U.S., it is estimated to occur in 1 in 10,000 live births, with the incidence ocular disease being reported to be as high as 75–94 % of these cases. Ocular disease is the most common manifestation of congenital toxoplasmosis [44].

Systemic Manifestations

Immunocompetent people who acquire toxoplasmosis usually do not have any other systemic findings other than asymptomatic cervical lymphadenopathy. Roughly 10 % of otherwise healthy people who are infected with toxoplasmosis will report non-specific symptoms such as myalgias, fevers, and fatigue. Infection in immunocompromised individuals most commonly presents as a fatal encephalitis, but may also manifest as a pneumonitis or septic shock [45].

Congenital toxoplasmosis can cause spontaneous abortion, or the child may be born with hydrocephalus, microcephaly, intracranial calcifications, epilepsy, psychomotor retardation, and leukopenia [45] (Fig. 12.4).

Ophthalmic Manifestations

The most common clinical presentation of toxoplasmosis is eye involvement, presenting as a retinochoroiditis [44]. The classic finding ocular finding is a fluffy, white area of

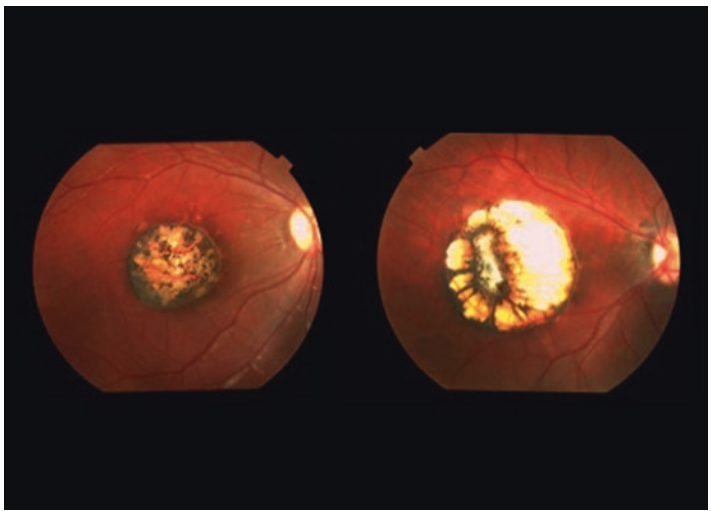

Fig. 12.4 Macular scarring seen in congenital toxoplasmosis (photo courtesy of Scott Oliver, MD)

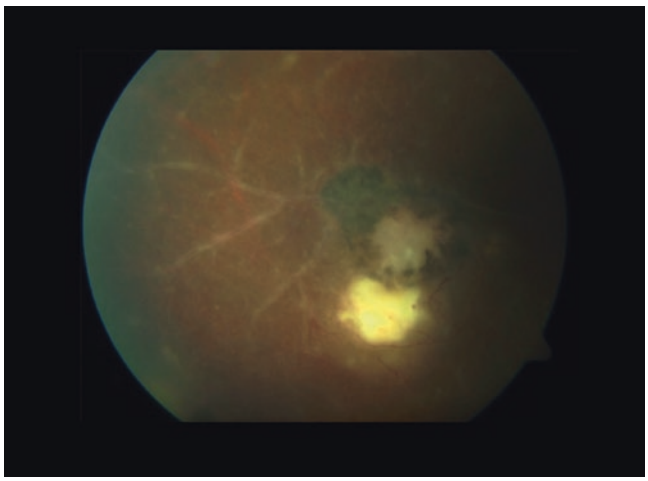

Fig. 12.5 Classic white area of retinitis adjacent to chorioretinal scar in reactivated toxoplasmosis (photo courtesy of Scott Oliver, MD)

retinochoroiditis or necrotizing retinitis adjacent to a chorioretinal scar (Fig. 12.5). Patients will typically also have a vitritis, causing a "headlight in the fog" appearance. Atypical presentations can manifest as retinal vasculitis, granulomatous or nongranulomatous anterior uveitis, or papillitis [45]. Ocular disease may be asymptomatic in young children. Verbal children may note decreased vision or eye pain, while parents may notice leukocoria or strabismus [45].

Diagnosis

In the majority of cases, the diagnosis of ocular toxoplasmosis is made by observation of the classic clinical findings described above. PCR or antibody testing can be performed on ocular fluid in atypical or unclear cases. Serologic testing for *T. gondii* antibodies has little role in the diagnosis of ocular toxoplasmosis due to high rate of seropositivity in the general population [45].

Management

With or without treatment, the active retinochoroiditis caused by toxoplasmosis resolves within 1–2 months in immunocompetent individuals. There is currently no drug available that is known to completely cure infection in humans. Thus, the goal of antimicrobial therapy is to limit parasite replication in active retinochoroiditis. Most ophthalmologists will treat patients with reduced vision, a lesion located within the arcades or near the optic disc, or those with significant vitreous haze. Infection in immunocompromised patients and atypical presentations also warrant treatment. The classic treatment includes pyrimethamine orally, sulfadiazine, and systemic corticosteroid. Folinic acid should be used to avoid toxicity related to pyrimethamine. An alternative treatment option is trimethoprim-sulfamethoxazole and systemic corticosteroid. Corticosteroids should be omitted in immunocompromised patients, and these patients should remain on prophylactic therapy (often with trimethoprim-sulfamethoxazole) while in an immunocompromised state [45].

Cysticercosis

Definition

Cysticercosis is a parasitic infection caused by the pork tapeworm, *Taenia solium.* The parasite exists as a cyst in pig, the intermediate host, and as worm in humans, the definitive host. Humans become infected after eating raw pork or consuming water or food contaminated with fecal matter [46]. Ingested eggs hatch in the intestines, migrate across the intestinal wall into the blood stream or lymphatic system. The parasite travels

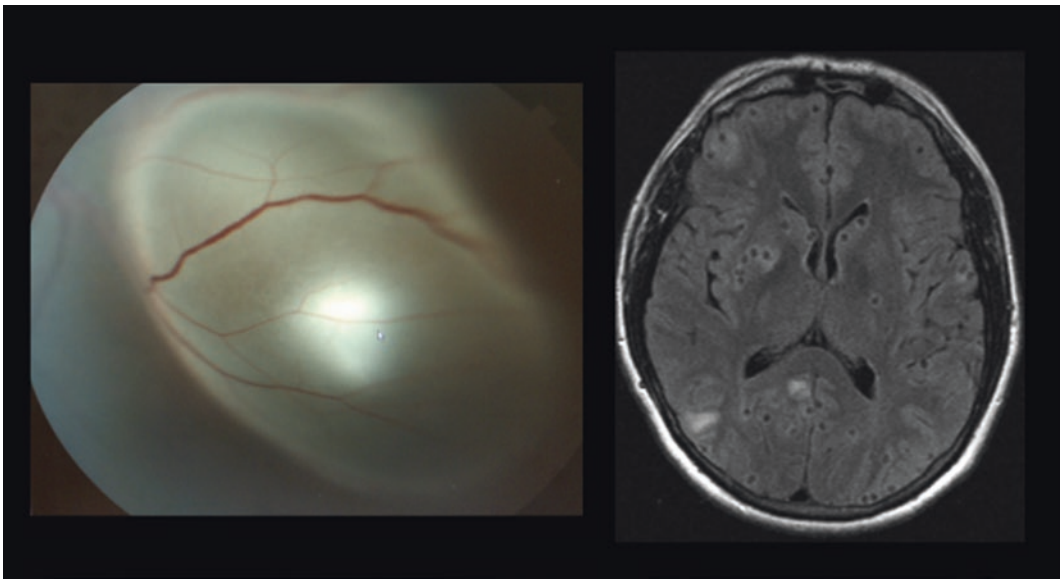

Fig. 12.6 *Left*: Fundus photo demonstrating subretinal cyst from cystercercosis with white scolex centrally. *Right*: axial FLAIR MRI sequence demonstrating multiple cystic lesions in the brain due to neurocystercercosis

throughout the body, infecting the central nervous system, eyes, and/or muscles and cysts within these tissues [47].

Epidemiology

The prevalence of cysticercosis is highest in areas with poor sanitation, where pigs roam freely and consume human feces [47]. Cysticercosis is endemic in Andean South America, Brazil, Central America and Mexico, China, the Indian subcontinent and South East Asia, and sub-Saharan Africa [47].

Systemic Manifestations

There are two clinical forms of cysticercosis. In focal cysticercosis, the parasite invades the muscles or perimuscular tissue only. The other form is systemic or central nervous system disease [47].

Cysts within the brain and spinal cord cause the most severe form of the disease, called neurocysticercosis. This may be asymptomatic, or cause seizures, headaches, confusion, difficulty with balance, cerebral edema, hydrocephalus, stroke, or death. Cysts in the muscles are usually asymptomatic, but can cause tender lumps under the skin [47].

Ophthalmic Manifestations

Intraocular cysticercosis is a manifestation of systemic disease, while orbital/adnexal cysticercosis is a manifestation of focal disease. *T. solium* reaches the eye via the posterior ciliary vessels and nerves [47].

Patients with intraocular disease may present with loss of visual acuity, scotoma, or eye pain. Many will also have coincident central nervous system disease. In orbital or adnexal disease, symptoms depend on the size and location of the cyst [46].

The most common form seen in children is orbital/adnexal cysticercosis. The most common site of cyst formation include the extraocular muscles, subconjunctival space, eyelid, optic nerve, retro-orbital space, and lacrimal gland [47] (Fig. 12.6).

Intraocular cysticercosis is characterized by cysts floating in the anterior chamber or vitreous, or posteriorly lodged in the subretinal space. Visual loss occurs if there is macular involvement. Death of the encysted parasites incites a severe inflammatory response and scarring, leading to scarring and possible visual loss [47]. Often, fundus examination is difficult due to the presence of significant vitritis and vitreous opacities. B-scan is routinely warranted and allows visualization of the cyst wall and the parasite within the cyst. Stimulation of parasite with light can elicit movement [46].

Diagnosis

Diagnosis is made by direct visualization of the cyst on tissue biopsy or inside the eye, or with cyst movement on B-scan. It can also be confirmed by serum antibodies or by parasite detection in the stool, either by direct visualization or by antigen testing [47].

Stool is not a sensitive way to diagnose cysticsercosis, so a negative result will not rule out cysticercosis infection of the eye.

Management

For orbital or adnexal disease, surgical removal of the cyst is the treatment of choice for accessible lesions. Lesions that cannot be surgically removed are treated systemically with Praziquantel (50 mg/kg/day) along with corticosteroids to reduce inflammation [47].

Antihelminthic therapy is not recommended for patients with intraocular disease, as it can precipitate severe inflammation, causing inflammatory phthisis or severe visual loss. The treatment of choice is surgical removal of the encysted parasite [47].

If patients present with intraocular and systemic disease, which is often the case, the surgical removal of the parasite should be performed before systemic treatment. Thus a thorough eye exam is recommended prior to the initiation of antihelminthic treatment in patients with neuro-cysticercosis.

Onchocerciasis (River Blindness, Filariasis)

Definition

Onchocerciasis, also known as river blindness and Robles disease, is caused by the nematode *Onchocerca volvulus*. The parasite is transmitted to humans by the bite of *Simulium exiguum,* also known as the black fly. Adult female worms are transmitted from the bite into the subcutaneous tissue, where the worm lays eggs. The eggs hatch into microfilaria [46].

Epidemiology

The World Health Organization estimates that onchocerciasis is the second leading cause of infectious blindness worldwide, with 17 million people infected, 270,000 of whom are blind and 500,000 of whom are visually impaired. 123 million people are at risk for becoming infected with the parasite [46, 49]. The disease is most prevalent in Africa, where 99 % of cases are seen and people in 28 countries are affected [50]. It is also found in Yemen and Central and South America [46].

Systemic Manifestations

Other than ocular involvement, onchocerciasis primarily affects the skin. Skin manifestations include acute and chronic papular dermatitis, scratch marks, lichenification, and pigmentary changes known as "leopard skin" [48].

Ophthalmic Manifestations

Individuals with ocular involvement will invariably have dermatologic involvement [48]. Ocular symptoms include visual impairment, including visual field loss and blindness, eye pain, irritation, and itching skin lesions [48, 49].

When deposited near the eye, the parasite migrates through the skin or bulbar conjunctiva into the cornea, anterior chamber, and iris. They enter the posterior chamber via the ciliary vessels and nerves. Dead or degenerating worms incite a severe inflammatory reaction leading to scarring and local inflammation, which can cause significant visual morbidity [46].

Ocular disease is classified into two types: savannah and rainforest. Blindness is more common in the savannah type, and is mainly caused by a punctate or sclerosing keratitis, snowflake corneal opacities, and iridocyclitis with a characteristic pear-shaped iris deformity (torpid iritis). In rainforest onchocerciasis, blindness is less common and is caused by posterior segment involvement, including peripheral chorioretinal lesions, vascular sheathing, and optic neuritis leading to optic atrophy. In addition to these ocular findings, microfilaria may be visualized in the cornea or anterior chamber on examination [46, 48].

Diagnosis

The diagnosis of onchocerciasis is confirmed by observation of live microfilaria in biopsy specimens of symptomatic skin nodules [46].

Management

Ivermectin, 150 mg/kg annually is the treatment of choice. Suramin may be used in cases that are resistant to ivermectin [46].

Phthiriasis Palpebrarum

Definition

Phithriasis palpebrarum is a rare parasitic infection of the eyelashes and eyelids caused by the pubic louse, *Phthiriasis pubis,* and its ova. Humans are the only host, and transmission is by direct human-to-human contact, although fomites, such as bedding and clothing may also play a role [51]. Because of its mode of transmission, a diagnosis of *phithriasis palpebrarum* in children should always raise concern for child abuse and involvement of child protective services may be warranted [52].

Epidemiology

Phithiriasis pubis infestation is found worldwide and occurs in all races and ethnic groups and all levels of society. Infestation of eyelashes or eyelids, however, is very rare. As noted above, when seen in children, it raises concern for sexual exposure or abuse [53].

Systemic Manifestations

Ophthalmic disease may be isolated, but individuals can also present with signs and symptoms of pubic involvement. The most common symptom is pruritis of the pubic and groin area [53].

Ophthalmic Manifestations

Presentation of ocular disease includes pruritus and irritation of the skin around the eye, including the lid margins and conjunctiva [52].

Ocular findings can include secondary blepharitis, follicular conjunctivitis, periauricular lymphadenopathy, and marginal keratitis. Examination may reveal conjunctival injection, eyelid erythema and swelling. Adult lice, nits (ova), and their excretions can be visualized at the base of the eyelashes [52].

Diagnosis

Diagnosis is based on clinical examination through observation of adult lice and nits on the eyelashes under magnification [52].

Management

There is no single treatment plan that has been determined to be optimal for the treatment of *Phithriasis palpebrarum*. Treatment should include mechanical removal of the lice and nits with jewelers forceps or plucking/trimming of the eyelashes. Additional treatment should include a topical pediculocidal agent, such as fluorescein 20 %, physostigmine, 0.25 %, mercuric oxide 1 % ophthalmic ointment and ammoniated mercury 3 % ophthalmic ointment, 1 % malathion drops or shampoo, and pilocarpine gel 4 %. Any ointment, including petroleum jelly or water-based gels, can be used to smother the lice. Treatment is recommended for 2 weeks, which corresponds to the life cycle of the louse [52]. Any items of close contact including bed sheets and clothing should be washed and dried at 50 °C or higher [52].

Viruses

Herpes Simplex Virus

Definition

Herpes simplex virus (HSV) is a double-stranded DNA virus. There are two types, HSV-1 and HSV-2. In general, infections with HSV-1 are above the waist and HSV-2 occur below the waist in sexually active individuals, however that is not an absolute and either virus can present in any location. All human herpes viruses establish latency and can reactivate. Reactivitation of HSV-1 and HSV-2 manifests as disease, typically vesicles in the oral or genital areas, or can be asymptomatic, typically shedding in the same areas. Additionally, HSV-1 and 2 can cause disseminated disease [5].

Epidemiology

HSV infections are ubiquitous with seropositivity of HSV-1 estimated to be over 25 % by the age of 7 [5] and between 50 and 90 % by adulthood [54, 55]. HSV is transmitted by direct contact from virus shed by HSV lesions or oral or genital secretions that harbor the virus. Thus, sexual abuse should be suspected in cases of HSV-2 infection in pre pubertal children.

It is estimated that 0.15 % of the US population experiences recurrent ocular infection due to the HSV virus [54]. Children have a worse visual prognosis due to corneal HSV infections than their adult counterparts due to a higher rate of late or missed diagnosis (up to 30 %) leading to more corneal scarring and amblyopia [56]. Additionally, children are more likely to have HSV recurrence, bilateral disease, and are more likely to have stromal keratitis than adults [56].

Intrauterine infections are rare, but can cause significant risk to sight due bilateral congenital cataracts, keratitis, conjunctivitis, and chorioretinitis. Neonatal infections are generally due to transmission of HSV-2 during birth and about 15–20 % of infants who have a neonatal HSV infection have some eye involvement [54].

Systemic Manifestations

Primary HSV-1 infection in an immunocompentent host is generally asymptomatic, but can sometimes cause pharyngitis, submandibular lymphadenopathy, and the classic gingivostomatitis. There is an incubation period of 2–14 days and then vesicles and fever develop. Symptoms resolve over the next 2 weeks. Recurrent HSV-1 infection is generally more mild and begins with paresthesias in the affected areas followed by vesicles and pain. It takes 3–10 days for the vesicles to crust and completely heal.

Primary HSV-2 infections incubate for about a week and are often asymptomatic. Similar to HSV-1, symptoms of a HSV-2 infection can include fever, lymphadenopathy and vesicle formation. Generally vesicles are in the genital area. Recurrent HSV-2 infections are also milder than primary infection.

Patients with neonatal HSV infection will present with symptoms between birth and 6 weeks of age. Twenty-five percent of patients with a neonatal infection have disseminated disease that can include liver, lung and central nervous system involvement. Less than half of patients with disseminated disease have only skin, eye and or mouth disease (SEM disease) and about 30 % of cases have CNS only disease [5]. Many of these patients who have disseminated HSV disease will present without the skin vesicles, making the initial diagnosis more difficult.

HSV encephalitis (HSE) can occur with primary or recurrent HSV-1 infection and can cause fever, altered mental status, and focual seizures. HSE tends to affect the temporal lobe and carries a very poor prognosis [5]. HSV can also cause meningitis or meningoencephalitis.

Ophthalmic Manifestations

Patients most commonly present with recurrent unilateral red eye associated with pain and photophobia. Patients can have a history of fever blisters/cold sores and many have a known diagnosis of HSV.

Primary eye infections usually present with a unilateral blepharoconjunctivitis with vesicles on the eyelid. Many children also have a follicular conjunctivitis. Epithelial keratitis presents in many patients with primary HSV-1 infection, often with a primary ocular infection. This is sometimes the typical dendrite, but can also be a superficial punctate keratitis, or geographic keratitis.

In recurrent ocular herpes, patient can have the epithelial keratitis as described above, but can also have a disciform keratitis, iridiocyclitis, increased IOP, or endotheliitis. Retinitis can also occur and cause acute retinal necrosis, but

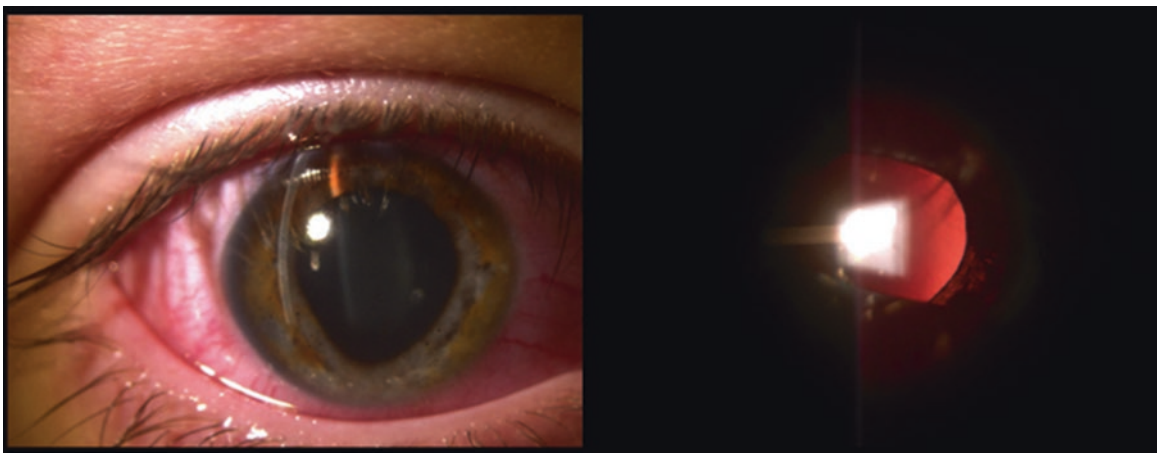

Fig. 12.7 *Left*: external photo demonstrating synechiae and pigmented keratic precipitates in patient with HSV uveitis. *Right* shows transillumination defects in same patient

this is generally rare and generally present in the immunocompromised individual.

The edges of a herpetic corneal lesion tend to have heaped up edges with swollen epithelial cells that stain with Rose Bengal or Lissamine Green. Central ulcerated portion of the HSV lesion stains with fluorescein. It is important to check for decreased corneal sensation because this can predispose the patient to secondary bacterial infections and neurotrophic ulcers.

Interstitial keratitis is an uncommon complication and can occur in the presence of iritis or glaucoma. These patients have multiple or diffuse stromal infiltrates and may not have an overlying epithelial defect [57].

The uveitis associated with HSV infection typically is associated with an increased intraocular pressure, granulomatous keratic precipitates, and iris atrophy (Fig. 12.7).

Diagnosis

Ocular HSV is usually diagnosed clinically, but cell culture, immunofluorescence, PCR, and the Tzanck smear can also be useful in the diagnosis. Serologic tests should be interpreted with caution as patients can be IgM positive with reactivitation disease and a high percentage of the population is positive serologically. Corneal or conjunctival scraping can be sent for viral culture [57].

Polymerase chain reaction (PCR) can detect HSV DNA in the CSF of neonates and older children with concerns for HSV meningoencephalitis. PCR of aqueous or vitreous fluid can be useful in certain cases.

Management

Congenital and neonatal herpes infections should be managed as an inpatient and treatment consists of intravenous acyclovir followed by long-term suppressive therapy. The duration of treatment depends on the type of infection (disseminated, skin-eye-mucous membrane, or CNS) and the long term suppressive therapy is typically a minimum of 6 months.

For eyelid and skin involvement, cool compresses as needed and topical antibiotic ointments to lesions can help with comfort. For any eyelid margin or conjunctival involvement, trifluridine or vidarabine ointment should be added.

HSV keratitis in a child can be treated with systemic acyclovir, topical trifluridine, or vidarabine ointment. Debridement of HSV epithelial lesions can promote healing, but may not be tolerated in the pediatric age group. In patients with stromal keratitis or uveitis, topical corticosteroids are indicated, but in patients with isolated epithelial disease, topical steroids are contraindicated.

Cycloplegics are indicated in patients with uveitis and can be helpful in patients with keratitis and photophobia [57].

The Herpetic Eye Disease Study Group was not designed to study the pediatric patient under 12 years old, but the results suggest that oral acyclovir helps prevent recurrent herpetic eye disease [58]. A period of acyclovir prophylaxis should be considered in children after serious disease and in recurrent disease, especially when it puts the child at risk for amblyopia or longer term vision problems.

Corneal scarring caused by herpes virus infection causes both deprivation and refractive amblyopia due to induced astigmatism, and the treatment of this amblyopia is important in restoring vision.

Varicella Zoster Virus

Definition

Varicella Zoster Virus (VZV) is also known as *Human herpes virus type 3*. Primary infection with VZV causes varicella (also known as chicken pox). After primary infection or immunization, the virus remains dormant in the dorsal root ganglion. Reactivation infection is called shingles or zoster. When the reactivation infection occurs in the V1 distribution of the trigeminal nerve, it is called herpes zoster ophthalmicus

(HZO). This usually occurs along the frontal nerve when associated with HZO [5, 59].

Epidemiology

Humans are the only host of VZV. The typical incubation period before vesicles appears 0–14 days and the host is contagious for approximately 1–2 days before the vesicular rash begins. The virus is transmitted when virus particles are aerosolized from vesicles and also by respiratory secretions. The virus does not survive on fomites.

Prior to implementation of the VZV vaccine in the United States, varicella infection occurred mostly in children under the age of 10 and often in the late winter to early spring. The incidence of VZV was so high it was almost equal to the birth rate [59]. A single vaccination was recommended in 1995 and decreased the incidence of varicella in the United States decreased by 90 % between 1995 and 2005. The recommendation for a second dose of the vaccine in 2006 has further decreased the incidence of VZV in this country [5].

The incidence of Herpes Zoster is estimated to be about 1 million cases/year in the United States. Of those cases, about 10–20 % are cases of HZO [59]. The main risk factor for HZ is increased age. While immunosuppression is a risk factor, most (92 %) of patients who get HZ are immunocompetent [60]. Treatment of HZ can reduce HZO by 50 % [59]. It is still unclear how vaccination will affect the rates of HZ over a lifetime, and many other factors will also play into HZ incidence including increasing numbers of immunocompromised individuals, people living longer, and vaccines targeted at preventing herpes zoster.

Systemic Manifestations

Primary infection with VZV causes a diffuse pruritic, vesicular rash. Systemic symptoms such as low grade fever can also occur. Occasionally patients with VZV infection can develop complications such as encephalitis, thrombocytopenia, pneumonia, hepatitis, and glomerulonephritis among others. Young children tend to be mildly symptomatic while infants, adolescents, and adults with a primary VZV infection are most affected [5].

Reactivation of VZV, also known as shingles, presents with groups of vesicles usually along 1–3 dermatomes often associated with pain and itching. In adults it is common to have a post herpetic neuralgia that can last for months [5]. The risk of post herpetic neuralgia increases with age and is rare in children.

Ophthalmic Manifestations

Patients with primary VZV infection may have mild conjunctivitis or episcleritis. Rarely, dendritic keratitis, iritis or sclerokeratitis have been reported [41].

HZO can also cause periocular pain, eye pain or foreign body sensation, blurred vision, or photophobia.

HZO presents with a varied and long list of eye problems with some patients being severely affected and others with mild or no eye involvement. The rash in HZO is similar to other cases of shingles and often starts with red painful skin progressing to macules and vesicles. This can be associated with ptosis and periorbital edema and sometimes can result in cicatricial eyelid changes as a late complication.

Cranial nerve palsies are frequent and result in double vision, though most cases are transient and self-resolving. They are thought to be secondary to associated vasculitis.

The ocular surface can be involved and patients can have scleritis, episcleritis, sclerokeratitis and even a posterior scleritis, which is quite painful. Conjunctival hyperemia and follicular reaction of the conjunctiva are relatively common.

Corneal involvement is concerning in this population. Pseudodendrites are the most classic corneal change in HZO. They are often transient, and along with punctuate epithelial keratitis usually present early in disease. Nummular anterior stromal keratitis, keratouvitis, endotheliitis, disciform stromal keratitis, interstitial keratitis, and neurotrophic keratopathy are all complications of HZO.

Posterior segment complications are rare but can be devastating. Retinal vasculitis, ischemic optic neuritis and retinal necrosis have all been reported [59]. Cases of congenital VZV, while rare, can present with cataracts, chorioretiitis, microphthalmia, or nystagmus.

Diagnosis

Herpes zoster is most usually made as a clinical diagnosis. For any diagnostic dilemmas, PCR of the fluid from a vesicle or from a scab can be diagnostic. Cell culture and direct fluorescent antibody assay (DFA) may be helpful but are less sensitive [5].

Management

In patients with a primary HZO infection, cool compresses and erythromycin ointment can help with conjunctival involvement and foreign body sensation. For patients with keratitis, topical steroid and cycloplegics can be used, but this is an uncommon presentation in patients with primary disease. Systemic antivirals are not recommended in children with primary and uncomplicated varicella infections [5, 57].

Systemic treatment with antivirals should be started in patients with HZO and in immunocompetent patients systemic steroids should also be considered. Children who are immunocompromised and or have systemic disease often need hospitalization and IV acyclovir due to poor bioavailability of oral acyclovir.

Conjunctival involvement and corneal pseudodendrites should be treated supportively with cool compresses, frequent artificial tears and lubricating ointment. Patients with immune stromal keratitis need long term steroid treatment,

tapered over months and sometimes years. Uveitis associated with VZV infection should be treated with standard topical steroids and cycloplegics with care to watch for intraocular pressure (IOP) rise and also treat ocular hypertension aggressively with aqueous suppressants. Neurotrophic keratitis is difficult to treat and long term management often includes bandage contact lenses, aggressive lubrication, tarsorrhaphy and sometimes ambiotic membrane grafting. Complications of neurotrophic cornea, specifically corneal ulcerations, need to be managed aggressively and take a long time to heal. In children, amblyopia frequently occurs secondary to these complications and also requires treatment [57].

Patients with HZ infection and eye involvement need to be followed frequently during the first week of infection to ensure that they are healing appropriately and that there is no corneal melt or secondary infection.

Measles (Rubeola)

Definition

Measles, also known as rubeola, is caused by a single-stranded RNA virus of the genus Morbillivirus in the Paramyxoviridae family [61–63]. Humans are the only natural host and transmission is via direct person-to-person contact or airborne droplets. The virus can remain infectious for up to 2 h in the air. It is considered one of the most contagious of all infectious diseases by the Center for Disease Control and Prevention (CDC) as reportedly 9 out of 10 susceptible individuals who come into contact with the virus will develop clinical symptoms [61]. Infectivity is greatest in the 3 days before appearance of the rash.

Epidemiology

In cases of congenital measles infections, a history of measles infection during pregnancy can be elicited [62, 63].

Before development of the measles vaccines over 40 years ago, the measles virus affected 95–98 % of children by age 18 years [64]. Prior to the institution of vaccination programs, approximately 48,000 people were hospitalized and 1000 people were plagued with chronic disability from measles-related acute encephalitis in the United States each year. The measles containing vaccine is administered as a combination vaccine, called the measles-mumps-rubella (MMR) vaccine which is 93 % effective in preventing measles after just one dose [61]. However, despite the existence of this vaccine, measles still remains the fifth leading cause of infectious mortality among children younger than 5 worldwide [62, 63]. The CDC estimates that 20 million people worldwide are infected with measles annually of which over 100,000 die. While still prevalent worldwide, in the year 2000, measles was declared eliminated from the United States. Still, because of high rates of worldwide travel and variable compliance with vaccination programs, measles cases and outbreaks still occur in the U.S. with numbers ranging from 37 reported cases in 2004 to 668 in 2014 [61].

Those are highest risk for severe illness and complication include children under the age of 5 years, adults over the age of 20 years, pregnant women, and immunocompromised individuals [61].

Systemic Manifestations

Measles is an acute respiratory illness characterized by a prodrome of high fever (up to 105 °F) followed by a maculopapular rash and the "three C's"; cough, coryza and conjunctivitis. The virus has an incubation time of 7–21 days, however the pathognomonic maculopapular rash typically appears 14 days after exposure [61, 64]. The rash begins on the face and neck as discrete erythematous lesions which then spreads to the trunk and lastly to the extremities. Koplik spots, bluish-white lesions on an erythematous base, can be found on the buccal mucosa, soft palate, conjunctiva, and vaginal mucosa in 60–70 % of patients with measles.

The most common complications related to measles are otitis media, bronchopneumonia, laryngotracheobronchitis (also known as "measles croup") and diarrhea. Bronchopneumonia and otitis media are theorized to be due to secondary viral or bacterial infections rather than directly related to the measles virus. Other serious complications include febrile seizures, post-infectious encephalomyelitis and acute encephalitis. One out of every 1000 people with measles will develop acute encephalitis which can unfortunately often leads to permanent neurologic complications.

A rare but serious complication, subacute sclerosing panencephalitis (SSPE) occurs in one out of every 8.5 million people infected with measles. This fatal slowly progressive demyelinating disease typically presents with behavioral and other neurologic changes 7–10 years after initial infection. It is caused by the persistence of the measles virus within the central nervous system. At this time, it is unknown what factors predispose an individual to this complication, but it is theorized that infection prior to the age of 2 years may increase risk [61, 63, 65].

Ophthalmic Manifestations

In addition to the typical systemic complaints, patients may present with non-purulent conjunctivitis or eye irritation and blurry vision [62–64].

The most common ophthalmologic complication in persons with measles is a nonpurulent, papillary conjunctivitis; reported in up to 65.6 % of patients. Koplik spots may also be present on the conjunctiva, but are rare. Keratitis has been reported to occur in as high as 57 % of people affected. Typically the corneal and conjunctival changes resolve without permanent sequelae. However, worldwide, in patients with vitamin A deficiency, the keratitis is often

more severe and can lead to blindness [62–65]. Acute acquired measles retinopathy has been described as well. This typically presents with profound vision loss, attenuated arterioles, retinal and optic nerve edema with or without macular star, and retinal hemorrhages. Electroretinogram (ERG) testing is typically extinguished during the acute phase but may return to normal with resolution of inflammation. Acquired measles retinopathy resolves over weeks to months. Most patients retain some useful vision but prognosis is still guarded [62, 63].

Ocular manifestations of congenital measles include congenital cataracts, optic nerve head drusen and bilateral pigmentary retinopathy. Congenital measles retinopathy, less common than the acquired type, typically involves pigmentary changes in both the posterior pole and peripheral retina. Other findings such as attenuated vessels, retinal edema or macular star may also be present. In contrast to acquired cases, the ERG in congenital cases is typically normal [62, 63, 66].

Diagnosis

Diagnosis was traditionally made clinically. However, Laboratory confirmation is now used for sporadic cases and outbreaks. Presence of measles specific IgM and measles RNA by PCR testing is diagnostic. Testing requires both serum samples and nasopharyngeal swabs from suspected patients and urine samples can also aid in the diagnosis [61]. Other forms of serologic testing is available including complement fixation and ELISA testing [62, 63]. Healthcare providers in the U.S. are required to report suspected cases to their local health department within 24 h [61].

Management

Treatment for measles consists of supportive care and symptomatic relief. Those who develop secondary bacterial infections or complications are treated accordingly. Vitamin A is now recommended for severe, hospitalized cases in children and is administered based on guidelines developed by the World Health Organization. Post-exposure prophylaxis (PEP) is available for any persons exposed to measles who have not previously been immunized. In such cases, the MMR vaccine should be administered within 72 h of exposure. For immunocompromised individuals including infants younger than 1 year or unimmunized pregnant women who were exposed to the virus, intramuscular or intravenous immunoglobulin can be administered within 6 days of exposure [61].

Rubella

Definition

Rubella, also known as the German Measles, is a caused by the rubella virus, an RNA virus of the *Togaviridae* family and *Rubivirus* genus which is spread by nasophayngeal secretions [63, 67]. Since advent of the vaccination against the rubella virus in 1969, cases of acute rubella infection have fallen dramatically. Acute infection during childhood often produces a mild viral illness associated with a characteristic rash. However, primary infection acquired during pregnancy can cause devastating birth defects, called Congenital Rubella Syndrome (CRS) [63, 68, 69].

Epidemiology

In the pre-vaccine era, rubella infection occurred in epidemics and was most common in young children, ages 5 to 9 years. The last pandemic of Rubella occurred between 1963 and 1965. During this pandemic, in the United States, there was an estimated 12.5 million cases of acquired Rubella, more than 13,000 fetal or infant deaths, and a reported 20,000 infants with serious rubella related congenital defects [68].

The introduction of the rubella vaccine, now administered as part of the Measles, Mumps and Rubella vaccine, has dramatically decreased rates of Congenital Rubella Syndrome (CRS) as well as acute infections in adults. Because of vaccination programs, rates of seropositivity to Rubella in the United States are >95 % in the adult population. According to the CDC, between 2005 and 2011, only 4 cases of CRS were diagnosed in the United States. However, in developing countries, some sources estimate that up to 68 % of adults are still susceptible to acute infection. Worldwide, it is estimated that over 100,000 infants are born with CRS annually [63, 68, 70].

Congenital Rubella Syndrome (CRS) occurs because the rubella virus is able to cross the placenta during gestation. The risk of developing CRS declines with advancing gestational age. For instance, infection during the first 12 weeks of gestation is associated with a 90 % chance of developing CRS and almost a 100 % chance of congenital defects, while primary infection from 18 to 24 weeks has a 25 % risk of CRS [71].

Systemic Manifestations

The most important historical finding is a history of maternal infection with rubella during pregnancy or a lack of immunity against rubella during pregnancy.

Acquired rubella infection has a usual incubation time of 15–21 days followed by the appearance of a maculopapular rash which begins on the face and head and spreads downward to the trunk and then extremities. Some patients may experience a prodromal illness several days before the appearance of the rash which may include malaise, fever, lymphadenopathy, anorexia, headache and conjunctivitis. Forchheimer's spots are small petechial lesions of the soft palate which can sometimes be seen in the prodromal phase. Prodromal symptoms are more common in adults than children. Young adults often experience arthralgia and joint swelling. Other less common findings include thrombocytopenic purpura, encephalitis, and testicular pain [63, 71].

Congenital rubella infection can affect essentially any organ system. The traditional CRS triad consists of cardiac, ocular, and hearing disorders. Some of the most common clinical sequelae that have been reported include; deafness, mental retardation, microcephaly, ocular sequelae (detailed below) and cardiovascular defects such as patent ductus arteriosus, interventricular septal defects, and pulmonic stenosis. Other reported systemic findings include intrauterine growth restriction, thrombocytopenia, hepatosplenomegaly, hypospadias, hepatitis, interstitial pneumonitis, cerebral calcifications, meningio-encephalitis, nephrosclerosis, nephrocalcinosis, bone lesions, skin lesions and dental defects. In more severe cases, CRS can cause intrauterine death [63, 68, 70]. Late sequelae of CRS include thyroid disease and significantly higher rate of diabetes mellitus than the general population [68].

Ophthalmic Manifestations

Ocular signs of acquired rubella tend to be mild. Conjunctivitis is the most common manifestation seen in approximately 70 % of cases. A central epithelial keratitis is seen in <10 % of patients and typically completely resolves within a few days. Only a few cases of acquired rubella retinitis have been reported. These cases were described as disseminated chorioretinitis with multiple bullous retinal detachments, RPE depigmentation and mild vitritis and uveitis all of which resolved with some remaining atrophic areas [63].

Ocular sequelae are considered part of the CRS triad. Nuclear cataracts, microphthalmia, glaucoma, and a pigmentary retinopathy are the most commonly described manifestations. Rubella cataracts are essentially always nuclear, either unilateral or bilateral and opaque in appearance. The fetal lens nucleus acts as a viral reservoir post-natally which may explain why the cataract progresses [63, 72]. CRS retinopathy is a non-progressive pigmented retinopathy which can involve any quadrant but characteristically involves the posterior pole and macula. The pigmentary changes described range from fine powdery deposits to discrete black patches throughout the fundus and represent areas of retinal pigment epithelium atrophy. It has previously been described as a "salt-and-pepper" retinopathy [63, 68, 72]. Visual prognosis is relatively good in these patients unless complicated by a neovascular membrane or scarring [68]. Congenital and secondary glaucoma are less frequent findings but have been reported in up to 10 % of CRS patients [63, 72].

Diagnosis

Acquired and congenital cases of rubella are often suspected clinically but require laboratory confirmation for formal diagnosis. Identification of the virus in serologic samples or increasing titers of rubella specific antibodies over time (IgM or IgG) can be used for diagnosis [63, 68]. Serologic tests include, Enzyme-linked immunosorbent assay (ELISA), Complement fixation testing (CF), Hemagglutination inhibition test (HI), fluorescence immunoassay (FIA), radioimmunoassay (RIA), latex agglutination (LA) and passive hemagglutination (PHA) [63]. PCR is the preferred test for rubella diagnosis [73]. In infants with CRS, IgM can be identified in their cord blood for up to 6–12 months after birth [70]. Amniocentesis, chorionic villus sampling (CVS) and fetal blood testing can be performed to diagnose a rubella infection during pregnancy [68].

Management

Acquired cases of rubella are treated supportively and sequelae are treated as appropriate. Systemic complications from CRS should be treated as they are identified. Since CRS cataracts are centrally located they are considered visually significant and therefore early extraction is recommended to prevent sensory deprivation, amblyopia and strabismus. If glaucoma is present it too should be appropriately addressed early. CRS retinopathy rarely requires any treatment unless complicated by a neovascular membrane [63, 68].

The immune status of all pregnant women and patients of unknown immunity should be investigated. Patients without evidence of prior immunization should be immunized immediately. The vaccine, however, is contraindicated in immunocompromised patients, pregnant women, and those who intend to become pregnant within 3 months of the immunization date. Gamma globulin administration can prevent clinical disease in unimmunized pregnant women exposed during pregnancy, however transmission to the fetus can still occur [63].

Cytomegalovirus Infection (CMV)

Definition

Cytomegalovirus (CMV) is a member of the herpes virus family *(Herpesviridae)*. It is a ubiquitous virus and its pathogenicity relies on both the mode of transmission and the immune status of the host.

Patient History Related to Eye

Patients infected congenitally with CMV are often asymptomatic. Symptomatic patients most commonly present with hearing loss and are subsequently referred for eye exam. In severe cases, patients infected with CMV in utero will have visual impairment [74] but will not have eye pain or redness or other findings that would be noted by parents.

Patients who acquire CMV and have eye symptoms may complain of decreased vision, scotoma, photopsias, floaters, and rarely eye pain [75].

Epidemiology

The two pediatric populations most commonly affected by CMV are those with congenital infection and patients who are immunocompromised. CMV is the most common congenital infection in humans and is acquired congenitally in up to 1–2 % of live births however up to 90 % of these congenital CMV cases are thought to be asymptomatic [74].

The rate of CMV viremia in patients after hematopoeietic stem cell transplants (HSCT) ranges in the literature from 18[57] to 51 %[77]. Of those who develop viremia, the rate of CMV retinitis is also variable (5–23 %) [76, 77]. In the authors' experience there has been an increase in the rate of CMV retinitis in pediatric patients who have received HSCT [78].

Pediatric patients with acquired immunodeficiency syndrome (AIDS) have a lower rate of CMV retinitis than their adult couterparts and tend to have lower CD4 counts before developing disease [79].

Ophthalmic Manifestations

During an acute infection with rubella, patients may complain of visual changes, ocular irritation, redness or hyperemia [63].

Optic atrophy, macular scarring, and cortical visual impairment are the most common eye abnormalities in patients with congenital CMV infection [74]. Patients who have asymptomatic congenital CMV infection are much less likely to have or visual problems than those who have symptomatic infections[74] Approximately 22 % of symptomatic patients with congenital CMV infection will have some degree of vision loss [74].

The retinitis in acquired CMV causes a granular appearance of the retina in mild cases and more severe forms present with retinal necrosis, hemorrhage and exudates. Rhegamatogenous retinal detachment can occur, usually when a large amount of the retina is involved. Vitreous cell may or may not be present and is usually mild.

Systemic Manifestations

Most children are asymptomatic from congenital CMV infection. The most common symptom in congenital CMV infection is hearing loss [74, 80]. Intrauterine growth retardation (IUGR), hepatomegaly, and microcephaly are seen in more severe congenital CMV infections [5].

Immunocompetent patients who acquire CMV generally have a mild illness with fever and mild hepatitis. Patients who are immunocompromised, however, can have primary or reactivation disease that is systemic or organ-specific including pneumonia, colitis, hepatitis, and encephalitis [5].

Diagnosis

Cytomegalovirus can be detected in the cell culture in a variety of body fluids. Additionally PCR of viral DNA of white blood cells can be used to diagnose CMV. CMV retinitis is often a presumed, or clinical diagnosis in the right clinical setting. A positive PCR of aqueous or vitreous fluid can help aid in the diagnosis but is not necessary [5].

Management

Congenital CMV is typically not treated unless the baby is symptomatic or there is concern for central nervous system involvement. In these cases, treatment with 6 months of oral valganciclovir is thought to help aid in the protection of the nervous system and prevention of continued hearing loss [81].

The systemic antivirals ganciclovir, foscarnet and cidofovir can all be used alone or together to treat systemic CMV infection. CMV can become resistant to antivirals, particularly in immunocompromised patients, and combination or changing therapies may be required to effectively treat the retititis.

In cases of CMV retinitis that threatens the fovea, optic nerve, or is progressive despite systemic treatment, intravitreal injections of ganciclovir and/or foscarnet are recommended.

Relapse of CMV is common and the ultimate treatment is to reestablish natural immunity.

Epstein-Barr Virus Infections (Infectious Mononucleosis)

Definition

Epstein-Barr virus (EBV), also known as *human herpes virus 4* (HHV-4), is a DNA virus of the herpes virus family. It is a ubiquitous virus with >90 % of the adult population having serologic evidence of previous infection [82, 83]. It is transmitted via direct contact with bodily fluids, most often saliva [84].

Epidemiology

The EB virus can be serologically identified in >90 % of the adult population. Infection is generally subclinical in children and infants. However, when exposure is delayed and primary infection occurs in adulthood, it manifests as Infectious Mononucleosis (IM) [82, 83].

EBV has been linked to Burkitt Lymphoma, nasopharyngeal carcinoma, and thyroid carcinoma as well as other lymphoproliferative disorders [85]. Burkitt Lymphoma is endemic to certain equatorial regions of Africa with a reported incidence of 100 cases per million children in these regions [86]. A possible association with Sjogren's syndrome has also been proposed [85, 87].

Systemic Manifestations

Primary infection during infancy or childhood is traditionally subclinical. Primary infection during adolescence or adulthood manifests as infectious mononucleosis (IM). IM is

characterized by a triad of pharyngitis, lymphadenopathy, and fever. Associated symptoms may include fatigue, malaise, anorexia, nausea or vomiting, myalgia, arthralgia, headache, chills. Splenomegaly is found in up to 50 % of patients. After initial infection, the virus remains latent in the body [82–85].

Ophthalmic Manifestations

Reported cases of systemic EBV related ocular findings include all segments of the eye and therefore initial presenting complaints vary greatly. Ophthalmic symptoms may include but are not limited to visual impairment, ocular irritation, orbital and adnexal masses, photophobia and pain [85].

Ocular manifestations of EBV divided based on the segment affected, include:

- External and adnexal disease: periocular edema, dacryoadenitis, eyelid masses, and Parinaud's oculoglandular syndrome. Presence of a granulomatous conjunctival mass in addition to an enlarged pre-auricular lymph node is diagnostic of Parinaud's Oculoglandular syndrome [85, 87].
- Anterior segment: follicular conjunctivitis, stromal or epithelial keratitis, episcleritis, scleritis, conjunctival lesions, dry eye syndrome and bilateral anterior uveitis [85, 87].
- Posterior segment: macular edema, papillitis, retinal hemorrhages, vitritis, retinitis, choroiditis, progressive subretinal fibrosis and secondary choroidal neovascularization. Choroidal lesions appear as gray to yellow infiltrates that later become punched out areas of pigment epithelial scarring. Vitreous inflammation is commonly present with retinal or choroidal involvement [85].
- Neurologic: optic nerve edema, optic neuritis, bilateral ptosis, ophthalmoplegia, and cranial nerve palsies [85, 87]. Cranial nerve III, IV, VI, and VII palsies have also been reported.

Of those reported, the most common manifestation is a mild, follicular conjunctivitis which occurs early in the course of the primary infection [85, 87]. Though rare, congenital EBV has been associated with congenital cataracts [66].

Diagnosis

Epstein-Barr virus and Infectious Mononucleosis are both typically diagnosed clinically. A variety of serologic tests exist which detect antibodies against EBV specific antigens; Viral Capsid Antigen (VCA), Early Antigen (EA) and EBV Nuclear Antigen (EBNA). Both anti-VCA IgM and IgG can be identified and are used to delineate active versus past infection. Anti-Early Antigen IgG, if present, is traditionally a sign of active infection. The EBNA antibody is not present until 2–4 months after symptom onset and is therefore a marker of past infection [82, 84]. The Monospot test or Heterophile Antibody Test has both high false positive and false negative rates. While previously traditionally used, according to the CDC, this test should no longer be routinely used for diagnosis [84].

Management

Acute EBV infection and infectious mononucleosis (IM) are usually self-limited infections. Therefore, treatment consists of supportive therapy and symptomatic relief. Those with spleen or liver involvement of IM are advised to avoid contact sports and strenuous activity [85]. The utility of antivirals have not been established [87]. Treatment of the various ocular manifestations varies based on presentation [82–85].

Molluscum Contagiosum

Definition

Molluscum contagiosum is considered a benign, self-limited skin eruption caused by a large double-stranded DNA virus of the *Poxvirus* family and *Molluscipox* genus. It most commonly affects children and is transmitted via direct physical contact with a lesion or via fomites. There are also reports of sexual transmission, which more commonly affects young adults [88, 89].

Epidemiology

Molluscum contagiousum most commonly affects children and is spread via direct contact with lesions. More recently, there have been increasing reports of sexually transmitted cases in young adults affecting the genital region [88, 90]. Anecdotal reports have suggested transmission via public swimming pools or saunas, but these reports have been unable to be substantiated [91]. Typical or atypical lesions are also seen in immunocompromised individuals and when present tend to be more severe, more widespread and less responsive to traditional treatment [88, 90, 92].

Systemic Manifestations

Molluscum lesions are found on the skin or mucous membranes. They are traditionally small, 2–5 mm in diameter, firm, pearly-white or skin colored papules with central umbilication [88]. They are found in clusters primarily on the face, trunk, limbs and genitalia and are usually asymptomatic. Occasionally, a patient will complain of itching around the site of a lesion [88–90].

In immunocompromised patients, the presentation may be more severe and widespread. In such cases atypical appearing lesions are common. Rather than clusters of individual lesions, immunocompromised patients often present with larger, confluent, coalescing plaques. Further, lesions in HIV patients are more likely to recur after treatment than in immunocompetnant individuals. Prior to the advent of

HAART therapy, 5–18 % of HIV positive patients suffered from severe molluscum infections. Widespread molluscum infection is now often considered a marker for immunodeficiency [88, 92].

Ophthalmic Manifestations

Ocular molluscum lesions most often occur on the eyelids, though conjunctival lesions have been reported [90]. Other ocular manifestations include a chronic follicular conjunctivitis and keratitis. The conjunctivitis can be accompanied by a punctuate keratopathy and epithelial or subepithelial corneal infiltrates as well. It is hypothesized that the follicular reaction is secondary to either a hypersensitivity or toxic reaction to virus particles shedding into the tear film from the associated lesion. This conjunctival reaction can appear prior to identification of a lid lesion and subsequently is often initially misdiagnosed and inadequately treated [89–91].

Diagnosis

Diagnosis is primarily clinical, based on history and characteristic appearance of lesions. In some cases, histopathological diagnosis is warranted and can be obtained via biopsy or excision [90]. In such cases histopathologic examination reveals large, eosinophilic, cytoplasmic inclusion bodies, called Molluscum Bodies or Henderson-Patterson bodies [93]. These inclusion bodies may also be observed within the material at the lesion's core if aspirated [90, 91, 93].

Management

Skin and eyelid lesions are generally self-limited. However, various modalities do exist to treat these lesions. Podophyllotoxin 0.5 %, Imiquimod 5 % cream, and cryotherapy have all been used with relative success. Curettage and pulsed dye and light emitting lasers have been used on non-genital lesion with varying degrees of success and there is no strong data to support their use. Other topical modalities, such as silver nitrate, salicylic acid and benzoyl peroxide have been described, but again there is little published data to support their use and such treatments are often irritating to surrounding skin [88].

Conjunctivitis is treated by excision of the causative lesion which results in complete resolution of symptoms as well as the follicular reaction within weeks of excision [89, 90]. Patients should be warned of the risk of direct spread to others as well as auto-inoculation to prevent spread of the lesions to different areas of the body [88].

Human Papilloma Virus (HPV)

Definition

Human Papilloma virus (HPV) is a DNA virus of the papillomavirus family. The virus infects epithelial cells in either the skin or mucous membranes. It is transmitted by contact, sexual contact, autoinoculation, or vertically during birth. There are over 150 known genotypes of the virus and each have different clinical associations ranging from benign lesions such as papillomas or warts to cancerous lesions [94, 95].

Epidemiology

The Centers for Disease Control and Prevention (CDC) estimate that 14 million people become infected with HPV annually and that HPV currently infects approximately 79 million Americans. According to the CDC approximately 360,000 people will obtain genital warts and 11,000 women will get cervical cancer in the United States annually. Nearly all cases of cervical cancer are associated with HPV infection [98]. Two FDA-approved HPV vaccinations now exist; the quadrivalent vaccination which targets strains 6, 11, 16, and 18, and the bivalent vaccination which targets subtypes 16 and 18. While early studies show excellent efficacy in preventing precancerous lesions in certain groups of women, controversy still exists over the high cost, the unknown duration of protection, as well as certain social implications surrounding vaccinating women at a young age [99–101].

Systemic Manifestations

HPV infects the skin, genital and oral mucosa. Specific subtypes vary in their carcinogenic potential. Low-risk subtypes are often associated with benign warts and papillomas while high-risk subtypes have been linked to cervical intraepithelial neoplasia which can lead to cervical cancer [94, 96, 99]. Twelve "high-risk" subtypes have been associated with cervical cancer thus far with just eight of them accounting for 95 % of all cervical cancers [95, 99]. The two most commonly associated subtypes are subtypes 16 and 18 [94, 95]. Both squamous cell carcinoma and adenocarcinoma of the cervix can arise from an HPV infection [99]. These "high risk" subtypes have also been linked to anal, vaginal, vulvar and penile neoplasia and neoplasias of the head and neck. Cutaneous HPV subtypes have been associated with actinic keratosis and squamous cell carcinoma of the skin, but may be less associated with basal cell carcinoma than previously thought [95].

The "low-risk" subtypes, namely 6 and 11, are associated with anogenital warts, also known as condyloma acuminata and ocular surface squamous neoplasia [96, 99]. Fortunately, infections with these subtypes are often self-limited and resolve without serious complications [99].

Ophthalmic Manifestations

Patients may report a history of a progressively enlarging eyelid or conjunctival lesion. It is important in such cases to ask about previous efforts to remove such lesions as well as episodes of recurrence. Conversely, patients may offer no history as ocular lesions secondary to HPV are often asymptomatic and found incidentally on exam [94, 96]. Rarely, in the case of a papilloma affecting the lacrimal gland, a history of unilateral epiphora, may be elicited [97].

With an incidence of 0.02–3.5 per 100,000, ocular surface squamous neoplasia (OSSN) is a spectrum of ocular surface lesions which range from mild dysplasia to squamous cell carcinoma of the conjunctiva [94]. It may appear as a focal nodule or atypical area of conjunctiva and can be associated with adjacent dilated blood vessels. These lesions have been linked to UV radiation exposure as well as HPV infection, though the reported degree of association varies. Therefore, the prevalent theory at this time is that HPV infection is one of several factors which may contribute to the development of OSSN but is unlikely the sole cause [94]. Squamous cell carcinoma of the conjunctiva can invade locally either intra-ocularly or intra-orbitally. It rarely metastasizes, but when it does, spreads first to the pre-auricular and submandibular lymph nodes [97].

HPV subtypes 6 and 11 are most commonly associated with conjunctival papillomas, though as a study published in 2010 reported, subtypes 16, 33 and 45 have also been identified [96, 102]. Papillomas may present as either exophytic, mixed, or inverted lesions, of which the exophytic subtype is the most common. They are most commonly seen in men and among people aged 20–39 and are traditionally found on the bulbar conjunctiva, by the caruncle, or, less often, at the limbus [102, 103]. Rarely they can affect the lacrimal drainage system and cause nasolacrimal duct obstruction [97].

Pterygia have also been postulated to be associated with HPV infections, though published viral detection rates in pterygia range from 0 to 100 % [94].

In one study in 83 cases of unilateral retinoblastomas (Rb) in an Asian Indian population, HPV was detected in 24 % of cases, 70 % of which contained "high-risk" subtype 16. However, the association between Rb and HPV needs to be further elucidated as multiple other small studies on this subject had contradictory reports and HPV identification rates varied greatly based on geographic population of the study [104].

Diagnosis

Polymerase Chain Reaction (PCR) and DNA sequencing are reliable for detection of HPV in tissues samples [96, 99]. Use of impression cytology pre-operatively for diagnosis of conjunctival intra-epithelial neoplasia (CIN) has been reported but it's use is limited [94]. Diagnosis of conjunctival papilloma, pterygia, and OSSN is made primarily by clinical exam and excisional biopsy when indicated.

Management

Management of a conjunctival papilloma includes observation, as some reports describe spontaneous regression of lesions, or surgical resection, usually with cryotherapy if indicated. Unfortunately, there is a high rate of recurrence of these lesions. Systemic and topical interferon therapy have been used as adjunctive therapy in cases of recurrent or multiple lesions though these each have their own associated side effects [96]. Mitomycin C, Oral Cimetidine, and Carbon Dioxide Laser have also been used with varying success in cases of recurrent or recalcitrant papillomas [105–107].

In cases of conjunctival intraepithelial neoplasia and squamous cell carcinoma of the conjunctiva, surgical excision with clear margins in addition to local cryotherapy is traditionally employed. Other therapies such as topical chemotherapy (i.e. Mitomycin-C or local interferon therapy) and irradiation have been investigated. Recurrence rates vary based on tumor size and invasiveness as well as treatment modalities and range from 17 to 41 % [108, 109].

West Nile Virus

Definition

West Nile virus (WNV) is a single-stranded, enveloped RNA arbovirus in the genus *Flavivirus* It is a member of the Japanese encephalitis virus serocomplex. The virus is transmitted to humans through the bite of the *Culex* mosquito, which acquires the virus by feeding on infected birds. Human-to-human transmission through mosquito bites does not occur. However, there have been reported cases of transmission through blood transfusion, organ transplantation, and transplacental transmission [110].

Epidemiology

There are 2 distinct lineages of the virus with differing distribution. Lineage 1 has a global distribution and is found in North America, Eastern Europe, the Middle East, West Africa, and Australia. Lineage 2 is endemic in Africa [110]. In 2014, WNV infection was reported in a total of 47 states and the District of Columbia with 2122 total cases. The largest number of cases and deaths in 2014 were in the state of California [111]. West Nile virus infection is seasonal and corresponds to mosquito season, with more than 85 % of cases being reported in August and September. Illness has been reported in the U.S. between May and December [110].

Systemic Manifestations

WNV has three clinical categorizations: asymptomatic, West Nile fever, and West Nile meningoencephalitis. Most infected individuals are asymptomatic. The symptoms of West Nile fever include sudden onset high-grade fever, headache, myalgias, and gastrointestinal symptoms. The acute illness is self-limiting and lasts less than 1 week. Neurologic disease may present as an aseptic meningitis, encephalitis, meningoencephalitis, myelitis, polyradiculitis, or optic neuritis. WNV may also affect other organs in the body as well, which can manifests as hepatitis, pancreatitis, or myocarditis [110].

Ophthalmic Manifestations

Patients may present with subjective complaints of decreased vision, floaters, photophobia, or eye pain. Reported visual acuities range from 20/25 to hand motion. Symptoms may be bilateral or unilateral [110].

The most common ophthalmic manifestation of WNV is chorioretinitis, with chorioretinal lesions in either a scattered or linear organization. The lesions appear deep, flat, yellow-white in color, may vary in size, and can become pigmented. The chorioretinits may have an associated iritis, vitritis, and intraretinal hemorrhage. Patients may also have iritis or vitritis in the absence of chorioretinitis. Another, more rare, ocular manifestation is an occlusive, hemorrhagic retinal vasculitis. There has also been one reported case of congenital chorioretinal scarring in an infant born to a mother diagnosed with WNV meningoencephalitis during her pregnancy.

As noted above, optic neuritis may be seen in association with WNV meningoencephalitis [110].

Diagnosis

ELISA to detect IgM in serum of CSF is the most commonly used diagnostic method for acute WNV infection [110].

Management

There is no proven treatment for WNV infection. Treatment is supportive. Intraocular inflammation may be treated with topical corticosteroids [110]. Ocular findings tend to be self-limited, and most patients have improvement in vision and reduced inflammation over a course of a few months [112].

Zika Virus

Definition

The Zika virus is a flavivirus related to Dengue and yellow fevers. It is transmitted mainly by infected *Aedes* mosquitoes [113]. Inter-human transmission has been described through sexual intercourse, perinatal, and through breast milk [114].

History Related to Eye Findings

Patients with primary infection may complain of symptoms commonly associated with conjunctivitis, including redness, tearing, discharge, itching/burning, blurred vision, or sensitivity to light. Mothers of infants with congenital infection may be asymptomatic or describe a self-limited illness in the first or second trimester, as described below [114].

Epidemiology

Zika virus was first isolated in humans in Uganda and Tanzania in 1952, after which few sporadic cases were reported in several countries in Africa and Asia. Reported outbreaks have occurred in Yap, Micronesia in 2007 and in French Polynesia in 2013, which spread to other Pacific islands. Circulation of Zika in the Americas was first confirmed on Easter Island, Chile in 2014. Since April 2015, an epidemic outbreak has been occurring in Brazil and has been transmitted to 27 other countries in the Americas. It is estimated that between 440,000 and 1,300,000 cases of Zika occurred in Brazil in 2015 [115]. As of April 2017, 5264 cases have been reported in the continental United States: 4963 cases in travelers from affected area, 224 cases through presumed local mosquito-borne transmission in Florida and Texas, and 77 through other routes (sexual transmission, congenital infection, laboratory transmission, and unknown) [116].

Systemic Manifestations

An estimated 80 % of people with a primary Zika infection are asymptomatic [114]. Symptomatic patients manifest with a self-limited, Dengue-like, illness characterized by low-grade fever, xanthema, conjunctivitis, and arthralgia. The rate of Guillain-Barre syndrome has been reported to increase during outbreaks [113].

Congenital infection in the first or second trimester is associated with microcephaly and central nervous system abnormalities in infants [113].

Ophthalmic Manifestations

As described above, individuals with primary infection may present with a self-limited conjunctivitis. Reported ophthalmic findings in infants with presumed congenital infection include pigmentary maculopathy, torpedo and torpedo-like maculopathy, chorioretinal atrophy, abnormal retinal vasculature, optic nerve abnormalities, iris coloboma, and lens subluxation [113].

Diagnosis

The only method of confirming infection with Zika virus is through polymerase-chain reaction (PCR) in the first days of infection. PCR does not confirm congenital infection in infants. Zika-related microcephaly is diagnosed clinically [114].

Management

There is no specific medicine or vaccine for Zika virus. Treatment is symptomatic [116].

Fungal

Coccidioidomycosis

Definition

Coccidioidomycosis, also known as Valley Fever, is a systemic fungal disease caused by two species of fungi, *Coccidioides immitis* (California species) and *Coccidioides*

posadasii (non-California species). Infection is acquired through inhalation of fungus arthroconidia in endemic areas [117].

Epidemiology

Coccidiodes is endemic in Nevada, Utah, Arizona, New Mexico, Texas, and California with the highest prevalence in Arizona. The fungus is also found in northern Mexico. Dust storms in dry, endemic regions can facilitate fungal infection in humans. Approximately 150,000 cases are reported yearly in the United States. Filipinos, African Americans, and Hispanics are more susceptible to acquiring severe or disseminated infections [117].

Systemic Manifestations

Coccidioidomycosis infection is classified in three ways: primary pulmonary, chronic pulmonary, and disseminated infection. The fungus most commonly affects the respiratory system and lungs. Sixty percent of infected individuals are asymptomatic, while the remaining 40 % will have a flu-like illness. Most people recover within 2–3 weeks, but in severe infections, patients may manifest with military lung lesions, pneumonia, hilar adenopathy, and pleural effusion, with some of these changes becoming progressive or chronic [117]. Erythema nodosum is seen in 5–10 % of females and 25 % of males with primary lung disease [118].

Disseminated disease is most often seen in immunocompromised individuals and can involve many organs including the skin, lymph nodes, spleen, liver, kidneys, bones, joints, meninges, and central nervous system. Meningeal and brain involvement is the most life-threatening [117].

Ophthalmic Manifestations

Ocular symptoms are nonspecific, ranging from no visual complaints to sudden visual loss, blurry vision, eye pain, photophobia, redness, and foreign body sensation [118].

Ocular involvement is rare, and is mainly occurs in disseminated coccidioidomycosis but can also be seen in the other forms of the disease [118].

Anterior segment findings include conjunctivitis with phlyctenules, keratoconjunctivitis, episcleritis, or scleritis, and may occur with primary pulmonary infections. These manifestations are thought to be due to a hypersensitivity response to coccidioidal antigens and resolve with time [118].

Intraocular disease may manifest as a granulomatous iridocyclitis or anterior uveitis, choroiditis, chorioretinitis, and rarely endophthalmitis. Posterior segment involvement is characterized by multiple, discrete, yellow-white fundus lesions <1 disk diameter in size. Intraocular disease is most commonly associated with disseminated coccidioidomycosis [118].

Diagnosis

Serologic testing for IgG or IgM antibodies is used to confirm the diagnosis. Sputum or tissue culture or tissue biopsy are other diagnostic options [119].

Tissue biopsy may reveal coccidioidal granulomas, which often contained double-walled spherules with endospores that can be seen on tissue pathology with H&E or periodic acid Schiff (PAS) stains [117].

Management

As noted above, most cases of primary disease will resolve spontaneously over time. The Infectious Disease Society of America recommends that antifungal treatment is warranted for patients who are immunosuppressed, have diabetes, cardiopulmonary disease, are pregnant, are Filipino or African American, or have severe illness. Extrapulmonary disease also warrants treatment. The initial treatment of choice for non-meningeal disease is an oral azole, such as ketoconazole, fluconazole, or itracanazole. Amphotericin B is an alternative therapy used in cases with rapidly progressive disease or infections in critical areas such as the spine [120].

Cryptococcosis

Definition

Cryptococcosis is a systemic fungal infection caused by the encaspsulated yeast *Cryptococcus neoformans.* The fungus lives in pigeon and bird droppings, as well as the fruit and bark of various trees. Infections in humans occur mainly through inhalation, and rarely through skin contact or ingestions [121].

Epidemiology

Cryptocooccus neoformans has a universal geographic distribution with most clinical cases occurring in the Americas or Africa. Clinically-significant infection was very rare until the onset of the AIDS pandemic. Since then 90 % of cases have been associated with AIDS, but disease is also seen in individuals with other immunocompromised states [121].

Systemic Manifestations

The initial and primary site of infection is the lung, which usually is asymptomatic or a mild illness that is self-limited. Chronic lung disease can manifest similar to tuberculosis and lung cancer with weight loss, fever, anorexia, fatigue, cough, mucous or mucopurulent sputum, hemoptysis, dyspnea, and pleural pain [121].

Primary skin infection appears as a tubercle, nodule, or abscess at the primary site of inoculation and rarely with satellite lymphangitis and lymphadenopathy. In disseminated disease, skin lesions appear as painless, ulcerative papules [121].

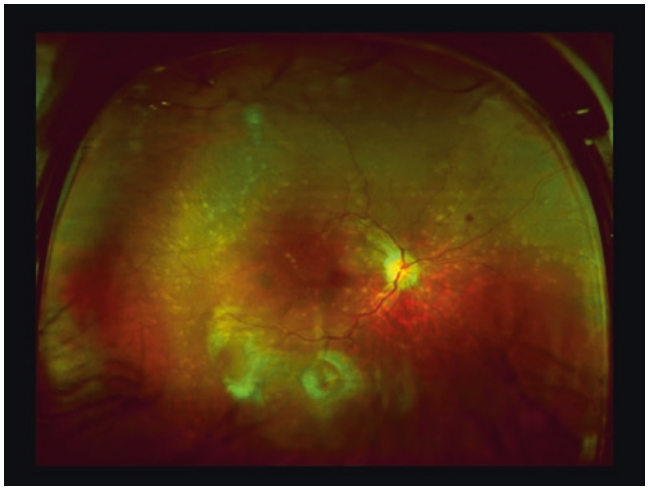

Fig. 12.8 Multifocal choroiditis in a patient with Cryptococcus (photo courtesy of Scott Oliver, MD)

Disseminated cryptococcosis presents as a severe, multi-organ disease in severely immunocompromised patients with HIV and a CD4 count of <100. Systemic signs and symptoms include fever, fatigue, weight loss, anemia, lymphadenopathy, and hepatosplenomegaly [121].

CNS cryptococcocis can occur in HIV positive or negative individuals. Those that are HIV negative may manifest with a subacute or chronic meningoencephalitis that particularly affects the basal ganglia, a mass occupying lesion, or a meningomyeloradiculitis. Immunocompromised individuals, particularly those with AIDS, will have a more acute meningoencephalitis. CNS cryptococcosis has a guarded prognosis, and without treatment is fatal [121].

Ophthalmic Manifestations

Ocular symptoms are nonspecific and may include partial or complete loss of vision, eye pain, eye redness, or photophobia.

Approximately one-third of individuals with CNS cryptococcosis will have ocular abnormalities, most commonly papilledema from elevated intracranial pressure, visual loss caused by optic atrophy, and oculomotor nerve palsy. Optic atrophy caused by intracranial hypertension, and less commonly by optic neuritis from fungal invasion of the nerve, can also occur [121].

Ocular involvement may also manifest as conjunctivitis, iritis, multi-focal choroiditis (Fig. 12.8) or chorioretinitis, or endophthalmitis [122]. The most frequent intraocular findings is multifocal chorioretinitis with solitary or multiple discrete yellow-white lesions in various sizes on fundus exam. Associated findings may include vitritis, vascular sheathing, and exudative retinal detachments [18].

Diagnosis

Diagnosis is made by observation of the encapsulated yeast via microscopy, isolation of the fungus by culture, or by demonstration of the capsular antigen in serum or CSF by latex-particle agglutination. Observation via microscopy is performed using diluted India-ink staining or phase-contrast microscopy [121].

Management

Ocular disease is treated in the same manner as CNS disease. The treatment of choice is intravenous amphotericin B and 5-fluorocytosine orally. In AIDS patients, this should be followed by 6–8 weeks of oral fluconazole. Secondary prophylaxis for AIDS patients includes oral fluconazole, oral itracanazole, or amphotericin. Secondary prophylaxis can be discontinued in AIDS patients with HAART therapy with two CD4+ cell counts of >150 in a 3-month period [121].

Histoplasmosis or POHS (Presumed Ocular Histoplasmosis Syndrome)

Definition

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum,* a dimorphic, encapsulated fungus [123]. The fungus thrives in areas contaminated with bird or bat droppings, and infection is acquired by humans through inhalation of microconidia [124].

Epidemiology

Histoplasmosis is endemenic in North, Central, and South America, as well as Europe and Africa [124]. In the United States, it is endemic in the Ohio and Mississippi river valleys, also known as the "Histo Belt."[123]. It is the most prevalent endemic fungal infection in North America [124]. Approximately 200,000–500,000 new cases occur annually in endemic areas. Exposure is common, however only ~4 % of those exposed develop ocular disease [123]. Activities that put people at risk for high inoculum exposure include cleaning chicken coupes, cleaning attics and barns, caving, construction, and other soil-disrupting activities [124].

Systemic Manifestations

The vast majority of individuals exposed to histoplasmosis are asymptomatic or minimally symptomatic and do not seek medical attention [124]. Clinically symptomatic disease is usually a self-limited flu-like illness with respiratory symptoms. However, the course and severity of the disease depends on the number of inhaled spores and the individual's immune status [123]. Clinical disease that may require anti-fungal treatment is classified into acute pulmonary histoplasmosis,

chronic-cavitary pulmonary histoplasmosis, progressive disseminated histoplasmosis and mediastinal lymphadentitis. Other disease entities include pulmonary nodules, mediastinal granuloma, mediastinal fibrosis, bronchiolithiasis, and inflammatory pericarditis, arthritis, and erythema nodosum [124].

Ophthalmic Manifestations

Patients with presumed ocular histoplasmosis may be asymptomatic or can present with acute or chronic painless, progressive blurring of central vision with metamorphopsia [123].

Ocular histoplasmosis is also referred to as Presumed Ocular Histoplasmosis Syndrome. The classic manifestation of POHS includes discrete, atrophic choroidal scars or "punched-out" lesions, peripapillary atrophy, and the absence of vitritis or anterior chamber inflammation. About 5 % will also have linear atrophic scars in the mid-periphery. The lesions are thought to be caused by disseminated *Histoplasma* that had reached the choroidal circulation leading to a subclinical choroiditis. Less than 5 % of patients with POHS will develop choroidal neovascular membranes (CNVM) from the scarring that can cause foveal compromise and severe visual decline. Smokers are at about a three times increased risk of developing CNVM from POHS [123].

Diagnosis

Diagnosis of POHS is mainly based on clinical exam findings. Antigen or antibody detection in serum or urine can aid in diagnosis [125].

Management

Treatment of ocular disease is directed toward management of CNVM. No therapy is known to reduce the risk of development of CNVM and anti-fungal do not play a role in treatment. The current standard of treatment involves intravitreal injection with anti-vascular endothelial growth factor therapy or photodynamic therapy [123].

Endogenous Fungal Endophthalmitis (Aspergillosis and Candidiasis)

Definition

Fungal endophthalmitis is infection of the ocular cavity and adjacent structures caused by fungi. We have already discussed a few causes of fungal endophthalmitis, including crytococcus and coccidiodes. Endogenous fungal endophthalmitis occurs in patients with hematologic dissemination of a fungal infection, i.e. fungemia. This section will focus on opportunistic endogenous fungal endophthalmitis caused by *Candida* species and *Aspergillus* species, although other fungi can cause same disease entity [126].

Epidemiology

Endogenous fungal endophthalmitis is very rare. Its risk factors are the same as those for fungemia and include the use of broad-spectrum antibiotics, steroids, parenteral nutrition, central venous catheters, diabetes, cytotoxic therapies, suppressive infections, and intravenous drug users. The most common causes of endogenous fungal endophthalmitis include *Candida albicans* and other *Candida* species, followed by *Aspergillus* [126].

Systemic Manifestations

As noted above, patients with endogenous fungal endophthalmitis will likely also have fungemia. Candidal fungemia is the most common cause of nosocomial fungal infections worldwide. Endophthalmitis caused by *Aspergillus* is seen in patients with pulmonary aspergillosis as well as in immunocompromised patients. Immunosupressed individuals can develop endophthalmitis from *Aspergillus* even with negative blood cultures [126].

Ophthalmic Manifestations

Patients with endogenous fungal endophthalmitis may be asymptomatic or may present with visual loss and eye pain [126, 127].

Ophthalmic manifestations involves the development of yellow-white circumscribed lesions that can be focal, diffuse, or disseminated (panophthalmitis). Patients may also develop necrosis with retinal detachments, particularly in *Aspergillus* endophthalmitis [126].

Diagnosis

Collection of vitreous humor via a vitreous tap is the most reliable method of diagnosis fungal endophthalmitis and is considered more valuable than collected aqueous humor by anterior chamber paracentesis. Vitreous and aqueous humor can be prepared on a wet mount with 10 % potassium hydroxide to visualize fungal pathogens. In candida albicans endophthalmitis, budding yeasts will be seen. Dichotomous branched hyaline septated hyphae are found in aspirates of those with *Aspergillus* endophthalmitis. Gram stain of aspirated fluid can also allow visualization of fungal elements. Definitive diagnosis is made by culture of vitreous or aqueous fluid, which should be plated on blood, chocolate, and Sabaroud agar plates and inoculated in thioglycolate broth [126]. PCR testing can also be performed on vitreous or aqueous fluid and is a more rapid method of confirmed the diagnosis compared to culture [127].

Management

The treatment of choice for fungal endophthalmitis is intravitreal injection of 5–10 micrograms of amphotericin B, without or without vitrectomy. However, amphotericin B is known to have significant potential retinal toxicity and

should be injected with caution [126]. Intraocular steroids may also be considered to help reduce inflammation [126, 127]. Systemic therapy should be administered to treat fungemia and systemic infection. Polyene and azole antifungal agents are commonly used [127].

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Ocular Manifestations of Inborn Errors of Metabolism

13

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Introduction

Inborn errors of metabolism (IEM) became recognized as a clinical field after Sir Archibald Garrod described the pathogenesis of alkaptonuria in 1902, and discovered a new class of human disease based on hereditary factors [1]. IEM are a heterogeneous group of disorders due to inherited defects that affect metabolic processes fundamental to produce essential compounds, to remove toxic compounds from body organs or to produce energy inside the cells. The manifestations of IEM are consequent to detrimental effects of accumulation of substrate or abnormal metabolic products which are toxic or interfere with normal function, or deficiency of products of the affected pathway (Fig. 13.1).

Most inborn errors of metabolism are inherited as autosomal recessive conditions. Some follow an X-linked recessive inheritance pattern, while disorders caused by mitochondrial mutations are inherited along the maternal lineage. More than 1000 IEM are now recognized, and with improving genomic, metabolomic and proteomic technologies, the number has been steadily increasing. At present, IEM collectively constitute a significant cause of morbidity and mortality worldwide, with a cumulative incidence of up to 1/800 births [2–4]. Given that most IEM are recessively inherited, it is not surprising to see them more prevalent in populations with high consanguinity rates or in inbred populations.

The diagnosis of IEM may be challenging. Clinical manifestations such as sepsis, vomiting, failure to thrive, developmental delay, regression of milestones, dysmorphism, seizures and hypotonia are non-specific. Without high index of suspicion, IEM frequently remain undetected until late, often with tragic consequences and irreversible damage, and, at times, even death. History often provides valuable clues such as positive family history, consanguinity, loss of developmental milestones, and siblings with unexplained infant or neonatal death.

The eye has often been described as providing a diagnostic window on the body. Ocular features can be very useful for the diagnosis of disorders with wider implications than the eye alone. Anomalies of the eye are easily recognized due to accessibility of the phenotype. Many IEMs have ocular manifestations. Some of them strongly point towards a specific IEM disorder and help in confirming diagnosis. The age of onset of the eye abnormalities in IEM is very variable, but in the majority of patients, eye involvement is often seen from childhood. Prompt and accurate recognition of eye manifestations aids targeted diagnostic work-up, thus facilitating early diagnosis and institution of appropriate therapy. Improvements in understanding the biochemical and molecular basis of IEM have led to significant advances in our ability to treat many of these disorders, substantially improving the prognosis for many patients.

In this chapter, IEMs with major ocular manifestations are reviewed. The disorders have been grouped according to the biochemical defects into disorders of amino acid, carbohydrate, fatty acid, mitochondrial function, sterol, and lipid metabolism, glycosylation disorders, lysosomal storage

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diseases, peroxisomal disorders, and disorders of vitamins and metal metabolism, and membrane transport.

Section One: Disorders of Amino Acid Metabolism

Organic Acidurias

"Organic aciduria" is a group of metabolic disorders that result from abnormalities in the metabolism of lysine, hydroxylysine, tryptophan and the branched-chain amino acids (leucine, isoleucine, and valine) The main organic acidurias are: glutaric aciduria type I and branched chain aminoacidurias (maple syrup urine disease, isovaleric aciduria, methylmalonic aciduria, propionic aciduria, and methylglutaconic aciduria). They are usually diagnosed in infancy and are characterized by urinary excretion of organic acids. Neurological manifestations are common and a major component of morbidity in organic acidurias. Acute, non-specific illnesses seem to precipitate an encephalopathic crisis with a rapid onset of neurological deficits. Focal brain lesions in the absence of large vessel rupture or occlusion due to metabolic dysfunction has been termed metabolic stroke. Metabolic stroke occurs consequent to mitochondrial energy failure due to metabolic abnormalities, which results in neuronal edema and ischemia due to impingement of brain capillaries [5].

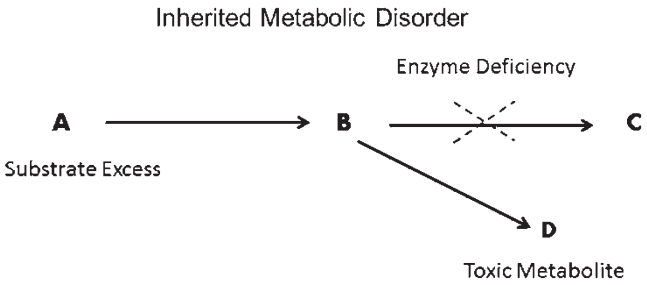

Fig. 13.1 Sir Archibald Garrod's one gene-one enzyme hypothesis. A genetic defect leads to an enzyme deficiency which affects a step in the metabolic pathway. This leads to accumulation of the substrate (A), or a toxic metabolite (D) produced as a result of alternate pathway taken by the substrate, or a deficiency of the product (C)

Glutaric Aciduria Type I (GA1)

Definition

Glutaric aciduria type 1 (GA1) is an autosomal recessive disorder of organic acid metabolism due to a deficiency of glutaryl-CoA dehydrogenase (GCDH), which is involved in the metabolism of lysine, hydroxylysine, and tryptophan (Fig. 13.2).

This leads to an accumulation of glutaric acid and 3-hydroxyglutaric acid. Part of the accumulating glutarlyl-CoA is esterified with carnitine leading to an increased ratio of acylcarnitine to free carnitine, and contributing to secondary carnitine deficiency. It has been suggested that

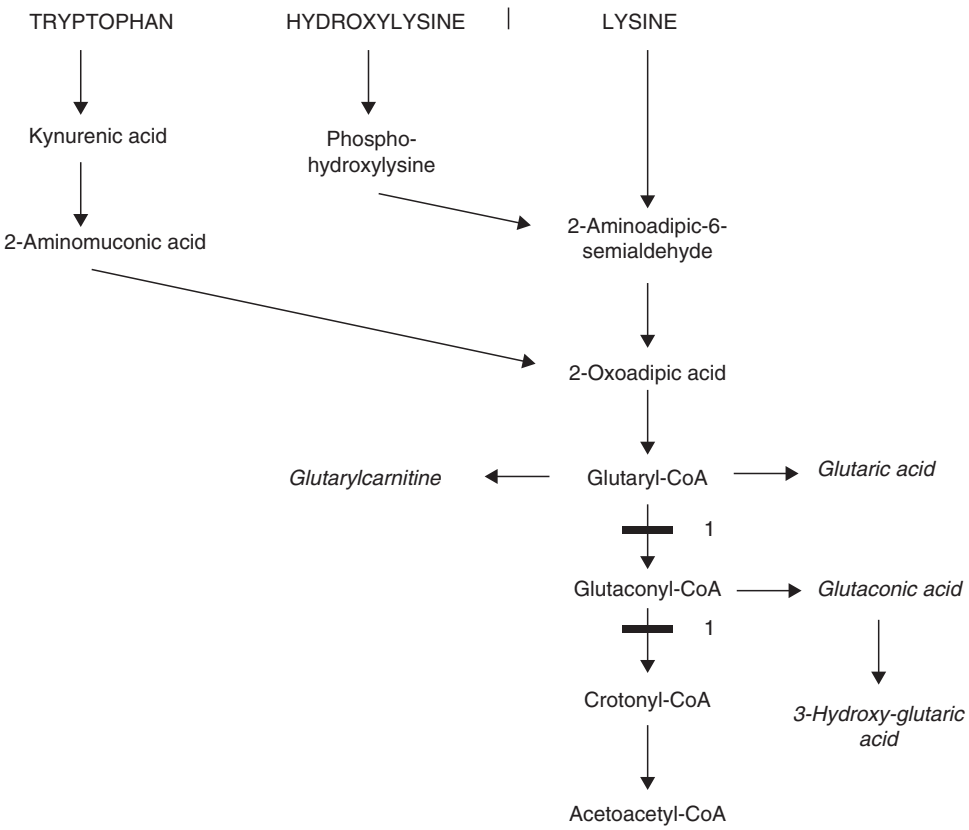

Fig. 13.2 Organic Aciduria—Tryptophan, hydroxylysine and lysine catabolic pathways: Deficiency of Glutaryl-coA dehydrogenase leads to an accumulation of glutaric acid and 3-hydroxyglutaric acid, and secondary carnitine deficiency. Accumulation of 3-hydroxyglutaric acid and carnitine depletion, affect neuronal cell function, lead to acute striatal damage, and metabolic crises. 1-glutaryl-coA dehydrogenase

3-hydroxyglutaric acid, generated in the liver, and carnitine depletion, affect neuronal cell function, lead to acute striatal damage, and are responsible for the metabolic crises [6]. GA1 is caused by mutations in the *GCDH* gene on chromosome 19p13.2.

Glutaric aciduria type 2 (GA2) is an autosomal recessively inherited disorder of fatty acid, amino acid, and choline metabolism. It is caused by deficiency of electron transfer flavoprotein (ETF) and electron transfer flavoprotein dehydrogenase (ETFDH) that are normally active in the mitochondria. This interferes with the body's ability to break down proteins and fats to produce energy. Ophthalmic involvement is not a known feature of this disorder.

History

GA1 was first described in 1975 by Goodman et al. in two siblings with a neurodegenerative disorder [7]. Massive glutaric aciduria was detected which increased by oral administration of lysine, and decreased by lowering protein intake. This led the authors to propose GA1 to be a disorder of lysine metabolism.

Epidemiology

The frequency of GA1 is estimated to be 1:30,000. The prevalence is increased among the Old Order Amish of Lancaster County in Pennsylvania, and in the North American Indians in Ontario, due to founder mutation effects [8].

Systemic Manifestations

Affected children are generally well in the first months of life, or show only mild neurological symptoms until the first encephalopathic event, which has an average age of onset of 12 months old, and develops almost always during an infectious illness [8]. The crisis may also develop in association with fasts required for surgery, after routine immunizations, or following minor head trauma. Macrocephaly is either present at birth or develops in the first year of life, preceding the severe neurological disease. Increasing macrocephaly is often the earliest sign of GA1 [6]. The distinctive picture of a dystonic-dyskinetic and alert looking child with relatively well-preserved intellectual functions and a prominent forehead is characteristic of GA1. The predominant late clinical findings in GA1are dystonia and/or choreoathetosis (extrapyramidal signs) and spasticity. Episodes of decompensation and encephalopathy are mild or absent in approximately 25 % of affected children. These patients have mild illness with no symptoms, or may have motor delay and intellectual disability [8, 9]. Many infants have feeding difficulties because of orofacial dyskinesia. There does not seem to be any relationship between the severity of the neurological disorder and the extent of the enzyme deficiency [10]. Radiologically, the acute neurological decompensation seen in GA1 is usually accompanied by acute symmetric striatal necrosis, similar to a stroke (metabolic stroke) [6]. The mechanism by which metabolic dysfunction leads to focal brain injury in metabolic stroke is not well understood. Other radiographic findings include brain atrophy, fronto-temporal hypoplasia, white-matter disease particularly involving the basal ganglia, and internal/external hydrocephalus. It has been suggested that neuro-radiological changes may be used to identify patients with GA1 pre-symptomatically. Approximately 20–30 % have subdural effusions with or without hemorrhage [8]. Subdural hemorrhage can be the presenting feature of GA1, and may be mistakenly attributed to abusive head trauma/shaken baby syndrome [11]. A possible mechanism of acute intracranial hemorrhage in GA1 is increased fragility of bridging veins that are stretched because of cerebral atrophy (microcephalic macrocephaly). This may make the bridging veins more susceptible to rupture as a result of a short fall or other minor single acceleration-deceleration events. Widening of the Sylvian fissures with a 'bat-wing' appearance is a characteristic finding. Early death may occur in the course of intercurrent pneumonia and respiratory failure, during hyperpyrexic crises or suddenly without warning.

Ophthalmic Manifestations

Retinal hemorrhages are a rare manifestation which may lead to further confusion with child abuse. However, only a few intraretinal hemorrhages in the posterior pole are observed in patients with GA1 unlike the multiple, too numerous to count and multilayered retinal hemorrhages seen in child abuse [6, 12–15].

Diagnosis

The diagnostic work-up should include urine for organic acids, plasma carnitine and acylcarnitine, fibroblast enzyme activity and/or mutation analysis. Large amounts of glutaric acid (average of 2000 μmol/kg-day) and 3-hydroxyglutaric acid (average of 2000 μmol/kg-day) are found in the urine. Repeated organic acid analyses may be necessary. While total plasma carnitine levels are consistently low, the acyl carnitine to free carnitine ration is elevated in serum and urine [6]. The enzyme deficiency can be detected in leukocytes or fibroblasts. Prenatal diagnosis is possible by analysis of amniotic fluid. GA1 has been included in the disease panels of expanded newborn screening in some areas. The presence of subdural effusion and retinal hemorrhage should also invoke a work-up to rule out possible shaken baby syndrome in the absence of clear evidence for GA1, or while studies are pending.

Management

Early diagnosis and treatment of the asymptomatic child is essential as treatment has very little effect after the encephalopathic crisis. Treatment is by special low lysine-restricted diet containing the minimum natural protein required for growth, and carnitine and riboflavin (co-factor of GCDH)

supplementation. Treatment with baclofen may be helpful for dystonia. Anti-seizure medication may be required. Surgery may be needed to remove intracranial collections of fluid and blood. A high-calorie, low- or no-protein emergency treatment protocol during acute illnesses such as infectious disease during the first 2 years of life is recommended to prevent striatal injury [16].

Branched Chain Aminoacidemias

The three branched chain amino-acids, leucine, isoleucine, and valine, are initially catabolized by a common pathway involving branched chain keto-acid dehydrogenase to form respective coenzyme (CoA) derivatives (Fig. 13.3).

Subsequently the metabolic pathways diverge with end-products entering the Krebs cycle. Patients with branched chain acidemias develop severe acidotic episodes during catabolic stress, and have three main clinical presentations depending on the amount of residual enzyme activity, namely (1) a severe neonatal-onset presentation with metabolic distress when the enzymatic deficiency is complete, and (2) an acute, intermittent, late-onset form and (3) a chronic, progressive form presenting as hypotonia, failure to thrive, and developmental delay, when the enzyme deficiency is partial.

Maple Syrup Urine Disease (MSUD)

Definition

Maple syrup urine disease (MSUD) is an autosomal recessive disease caused by a deficiency in branched-chain α-ketoacid dehydrogenase (BCKDH). This results in elevated branched chain keto acids, and corresponding branched chain amino acids in plasma (Fig. 13.3).

Among these, leucine and its keto acid are most neurotoxic. Leucine has a high affinity for the L1-neutral amino acid transporter through which other amino acids are transported into the central nervous system; high leucine plasma concentrations causes cerebral deprivation of other amino acids such as phenylalanine, tyrosine, and tryptophan. The consequent depletion of neurotransmitters such as dopamine and serotonin disrupts cerebral function and has an important role in the neurological manifestations. Energy deprivation through Krebs cycle disruption associated with branched-chain ketoacid accumulation, also contributes to brain injury. MSUD is caused by homozygous or compound heterozygous mutation in one of three BCKDH enzyme complex genes, the *BCKDHA* (chromosome 19q13; MSUD type IA), *BCKDHB* (chromosome 6q14; MSUD type IB), or *DBT* (chromosome 1p21; MSUD type II). Mutations in both alleles encoding any subunit can result in decreased activity of the enzyme complex. Traditionally, the metabolic phenotype of MSUD is termed classic or intermediate on the basis of residual BCKDH enzyme activity.

History

This disorder was first described by Menkes et al. in 1954 as a familial syndrome in which 4 siblings had progressive infantile cerebral dysfunction associated with an unusual urine odor resembling maple syrup [17]. All four patients died in the neonatal period. Elevated blood levels of leucine, isoleucine, and valine and massive excretion of the corresponding ketoacids of these amino acids in the urine was found [18].

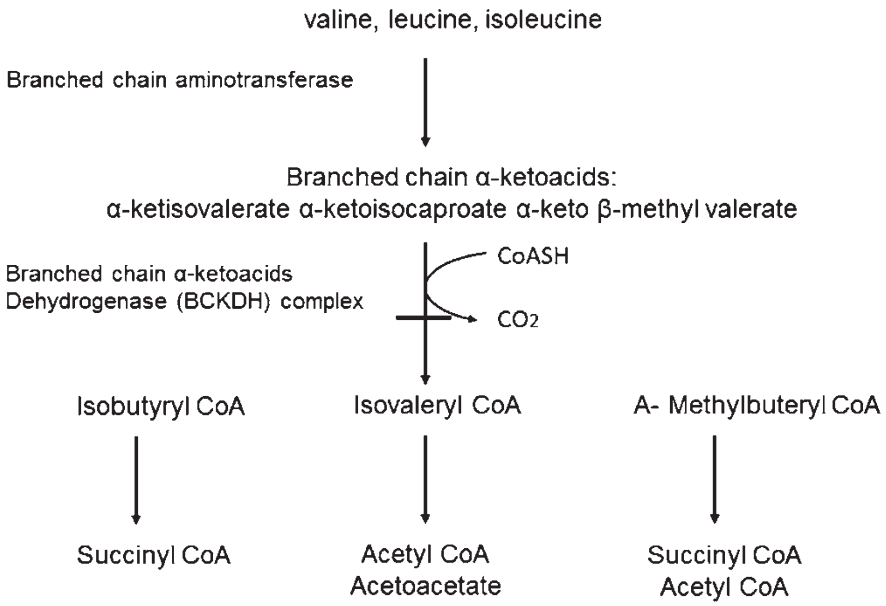

Fig. 13.3 Branched chain aminoacid (BCAA) catabolic pathways. After transamination of the BCAAs [valine, leucine, isoleucine] into their branched chain ketoacids (BCKA) byproducts, oxidative decarboxylation catalyzed by the branched chain keto-dehydrogenase (BCKDH) enzyme complex leads to formation of propionyl-CoA. Deficiency in any subunit of BCKDH complex results in Maple syrup urine disease with progressive accumulation of BCAA and BCKA

Epidemiology

General population has an approximate incidence of 1 in 250,000–1 in 500,000 live births. In the Old Order Mennonites of Pennsylvania, United States, the incidence is reported to be very high, at 1 in 380 live births [19]. About 75 % of the affected suffer from the severe classic form.

Systemic Manifestations

In the classical severe form of the disease, 50 % or more of the keto-acids are derived from leucine, and the activity of the BCKD complex is less than 2 % of normal. It becomes clinically manifest a few days after birth with feeding intolerance, vomiting, and periods of alternating irritability and lethargy, usually provoked by inter-current illness, fasting, injury, or surgery. Maple syrup (intense sweet and caramel-like) odor in cerumen is detectable within 12 h after birth. The condition progresses relentlessly despite supportive therapy, and with no apparent cause, to coma and respiratory distress, due to life-threatening cerebral edema (metabolic stroke). Irreversible brain damage is common in babies who survive, particularly those whose treatment is delayed. Patients with partial enzymatic deficiencies may present later in life with intermittent ketoacidosis, prostration and recurrent ataxia. Plasma concentrations of branched chain amino acids are elevated during these episodes, but they may be normal or near normal during the periods when patients are metabolically compensated. Children with chronic, progressive forms of MSUD present with delayed development and failure to thrive. Persistent anorexia and chronic vomiting are common. More than two thirds of patients exhibit a movement disorder on clinical examination, mainly tremor and dystonia or a combination of both, which may persist even when on a strict dietary regimen in the absence of intercurrent metabolic decompensation [20]. The clinical course may be complicated by acute or chronic pancreatitis and acute cardiac failure due to cardiomyopathy. Ketoacids give the urine a distinct odor of maple syrup or burnt sugar.

Ophthalmic Manifestations

Cases of MSUD with ophthalmoplegia have been reported [21]. Large, superficial corneal epithelial defects may develop in the course of decompensations in MSUD. They often occur in conjunction with diarrhea and can be ascribed to protein malnutrition, especially to isoleucine deficiency. Other ocular complications in untreated cases include strabismus, nystagmus, optic atrophy, and cortical blindness [22]. Purtscher retinopathy has been reported in a patient with MSUD who developed pancreatitis [23]. Since the levels of branched chain amino acids were normal through-out the episode, the exact role of MSUD in the causation of pancreatitis and associated retinopathy is debatable.

Diagnosis

In general, neonatal MSUD does not display pronounced abnormalities on routine laboratory tests. Patients are not severely dehydrated, and have no metabolic acidosis, no hyperammonemia, or only a slight elevation, and no blood lactate accumulation. Quantitative plasma amino acid profile shows elevated (frequently greater than 10-fold increase) plasma levels of branched chain amino acids. This is associated with increased urinary excretion of the branched chain amino acids. Leucine levels are usually higher than those of the other amino acids. Clinically significant fasting hypoglycemia has been observed in patients with classical MSUD. Newborn screening test (presence of 2-keto acids in urine) is available. Enzymatic studies are useful for confirmation. Diffusion-weighted MRI of the brain is useful in the assessment of intracranial change [24]. Reliable and rapid prenatal diagnosis can be performed by testing amniotic fluid around the 14th week of gestation. Direct enzyme assay or genetic testing can be performed using cultured amniocytes or by chorionic villi sampling.

Management

Treatment of MSUD is divided into acute (symptomatic) stage treatment and chronic (asymptomatic) stage treatment. Episodes of metabolic decompensation must be recognized early and require appropriate supportive therapy. Quick removal of the branched-chain amino acids and their metabolites from the tissues and body fluids is desirable. Peritoneal dialysis is the most effective mode of therapy and should be instituted promptly. Treatment in the intercurrent stages requires continuous dietary restriction of the branched chain amino acids. This is accomplished by administration of special dietary formulae [25]. Vigilant clinical monitoring, frequent measurement of the complete amino acid profile, and ongoing dietary adjustments that match nutritional intake to the metabolic demands of growth and illness allow a benign course, normal growth and development [26].

Isovaleric Aciduria (IVA), Propionic Aciduria (PA), and Methylmalonic Aciduria (MMA)

Definition

Isovaleric aciduria (IVA) is an autosomal recessive disorder caused by the deficiency of enzyme isovaleryl-coA dehydrogenase (IVD) catalyzing the third step in the leucine degradation pathway. Mutations in the *IVD* gene cause isovaleric acidemia. Propionic aciduria (PA) is caused by a deficiency in propionyl-CoA carboxylase (PCC) that converts propionyl-CoA to methylmalonyl-CoA in the presence of co-factor biotin. This leads to accumulation of propionyl-CoA inside mitochondria (Fig. 13.4).

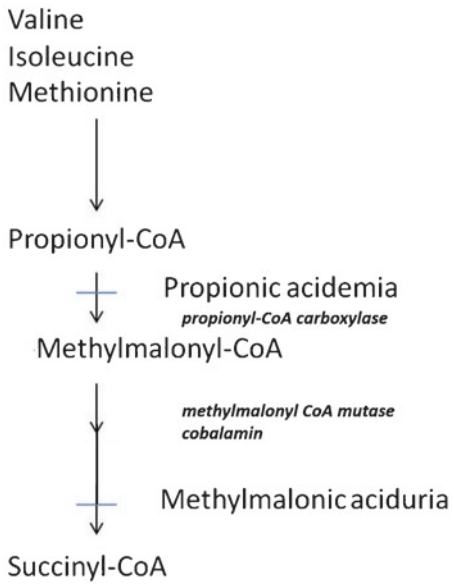

Fig. 13.4 Branched chain aminoacid (BCAA) catabolic pathways. Propionic acidemia is caused by a deficiency in propionyl-CoA carboxylase that converts propionyl-CoA to methylmalonyl-CoA in the presence of co-factor biotin. This leads to accumulation of propionyl-CoA inside mitochondria. Methylmalonic academia is caused by a deficiency of mitochondrial enzyme methylmalonyl CoA mutase which in the presence of its cofactor, cobalamin in the reaction that mediates the isomerization of methylmalonyl CoA to succinyl CoA

PCC deficiency is caused by mutations on either of the two genes, *PCCA* or *PCCB* that encode subunits of the enzyme. Methylmalonic aciduria (MMA)is caused by a deficiency of mitochondrial enzyme methylmalonyl CoA mutase which in the presence of its cofactor, cobalamin (vitamin B12), mediates the isomerization of methylmalonyl CoA to succinyl CoA. MMA can also be caused by deficiency of cobalamin (Fig. 13.4). Three genes *MMAA*, *MMAB*, and *MUT* are known to be associated with isolated MMA.

History

IVA was the first of the branched-chain aminoacidemias to be described. The two original patients were 4 and 2½ years old, respectively, and had similar histories of recurrent episodes of vomiting and lethargy that resolved with supportive therapy including glucose infusions [27].

Epidemiology

The prevalence of IVA is estimated to be 1 in 250,000. PA has an incidence of less than 1 in 100,000. The prevalence of MMA falls somewhere between 1:48,000 and almost 1:100,000 cases.

Systemic Manifestations

Classically IVA, PA and MMA present in the neonatal period with vomiting, poor feeding, seizures and increasing lethargy which progresses to coma and death if untreated. Infants who survive this acute manifestation, are at risk of developing a chronic form which presents later and is characterized by recurrent acidotic episodes during catabolic stress such as during intercurrent illness, but sometimes without any overt cause. Coma, lethargy, irritability with ataxia are the main presentations of these episodes. Some patients also manifest focal neurological signs such as hemiplegia. In between these episodes there may be no clinical findings, except for mild motor dysfunction and cognitive deficits. Most patients show a normal physical development [28].

Long-term prognosis for MMA or PA is less favorable, as patients may develop multisystem long-term complications involving the heart, renal, or neurological systems. In both MMA and PA, Renal tubular acidosis may be an early and presenting sign in some patients with MMA. Chronic renal failure is increasingly recognized in patients older than 10 years. The organic acids indiscriminately inhibit the bone marrow, causing pancytopenia. Patients with IVA can be differentiated from PA or MMA by an unpleasant sweaty odor of their feet. Overall neurocognitive outcome of patients with IVA is less devastating compared to MMA and PA [29]. Large superficial desquamation of the skin may occur during periods of metabolic decompensation in patients with PA, MMA or MSUD. Basal ganglia stroke leading to extrapyramidal movement disorders is increasingly observed. Chronic renal failure invariably affects all patients.

Ophthalmic Manifestations

Moderate to severe bilateral optic atrophy was reported in 3 patients aged 2 years, 9 years, and 10 years with PA [30]. Williams et al. reported a later onset in 2 male patients with MMA and 1 female patient with PA who, despite lifelong dietary restrictions developed optic atrophy and visual dysfunction at ages 16 years, 21 years, and 20 years, respectively [31]. The development of optic atrophy, as with other neurological complications, has been attributed to accumulation of toxic metabolites upstream of the enzymatic block, defective mitochondrial oxidative phosphorylation and energy deficit due to insufficient substrates for the Krebs cycle. There appears to be no correlation between metabolic [32] control and the development of optic atrophy [31]. Other ocular manifestations include rapidly progressive pigmentary retinopathy and corneal ulceration (Fig. 13.5) [32–34].

There is one report of an infant with MMA due to cobalamin C deficiency presenting with retinal hemorrhages and subdural hematoma, thus sharing some features with non-accidental injury. The retinal hemorrhages were all posterior to the equator, and one eye had vitreous hemorrhage. Authors hypothesized that the hemorrhage may have resulted from direct vascular endothelial damage

from raised levels of homocysteine associated with the condition [35].

Diagnosis

IVA, PA, and MMA are diagnosed by their specific urinary organic acid profiles using gas chromatography with mass spectrometry (GC/MS). In contrast to MSUD, dehydration is a frequent finding in patients with IVA, PA, and MMA. They have metabolic acidosis, ketosis, and hyperammonemia. Blood glucose may be normal, reduced or elevated. Pancytopenia is frequently confused with sepsis. Enzyme studies and molecular genetic testing are useful for diagnostic confirmation. Neonatal screening test is available.

Management

Therapy is based on rigorous emergency treatment of metabolic crises and maintenance of a low protein, high-energy diet. The above measures along with carnitine and glycine supplementation lead to better survival rates and neurocognitive outcomes. Subgroups of patients with MMA and cobalamin defects respond well to pharmacologic doses of vitamin B12.

Fig. 13.5 Bilateral, large corneal abrasions in a 10-year-old boy with propionic academia admitted during a period of metabolic decompensation. This patient had a history of developing recurrent corneal abrasions during episodes of metabolic crises. The abrasions resolve without sequelae with normalization of metabolic status

3-Methylglutaconic Aciduria (3-MGA)

Definition

There are five clinical forms of 3-Methylglutaconic Aciduria (3-MGA). Type I 3-MGA is the classic form and occurs due to an abnormality of leucine metabolism. The other types (II-V) are known as secondary 3-MGAs with the origin of 3-MGA still unclear but believed to be independent from leucine metabolism (Table 13.1) [36].

Classic, Type I 3-MGA occurs due to a deficiency of the enzyme 3-methylglutaconyl-CoA hydratase and is characterized by significantly increased urinary excretion of 3-methylglutaconic acid and 3-methylglutaric acid. This branched-chain organic acid 3-methylglutaconic acid is excreted only in trace amounts in the urine of healthy individuals. Urinary excretion of 3-methylglutaconic acid in secondary (Types II-V) 3-MGA urinary excretion of 3-methylglutaconic acid is a minor finding and not the hallmark of the phenotype.

History

Greter et al. described a brother and sister with choreoathetosis, spastic paraparesis, dementia, optic atrophy in 1978. Urinary level of 3-methylglutaconic acid was found to be high and the excretion was increased by leucine loading [37].

Epidemiology

Type I MGA is very rare, with only 13 patients reported in the literature as of 2003. Type III MGA has only been reported in Iraqi-Jews. The inheritance is autosomal recessive and most affected children have been the product of consanguineous marriages [38].

Systemic Manifestations

Type I 3-MGA is characterized by mild neurological disease (failure to thrive, psychomotor retardation, spasticity, athetosis, and delayed speech). Type II 3-MGA (Barth syndrome) is an X-linked recessive cardiomyopathy. In addition patients have neutropenia, developmental delay, short stature and

Table 13.1 Classification of 3-methyl glutaconic aciduria

I Classic	Organic aminoaciduria	Rare, autosomal recessive disorder of leucine metabolism due to deficiency of 3-methylglutaconyl-CoA hydratase	*AUH*	9q22.31
II Secondary	Defective phospholipid remodeling	Barth syndrome; X-linked recessive	*TAZ*	Xq28
		MEGDEL syndrome; autosomal recessive	*SERAC1*	6q25.3
		3-MGA with deafness, encephalopathy, and Leigh-like syndrome		
III Secondary	Mitochondrial Membrane associated Disorder	Neuro-ophthalmic disorder	*OPA3*	19q13.2–13.3
		Costeff optic atrophy syndrome or optic atrophy plus syndrome		
IV Secondary	Unknown	Extremely heterogeneous with moderate-severe neurological disease, sometimes associated with cardiac, ophthalmic, hepatic and renal symptoms	*TMEM70*	8q21.11
V Secondary	Mitochondrial Membrane associated Disorder	DCMA syndrome; dilated cardiomyopathy, non-progressive cerebellar ataxia, testicular dysgenesis and growth failure	*DNAJC19*	3q26.33

typical facial features. Onset ranges from birth to adulthood. Patients with MEGDEL (3-MGA with deafness, encephalopathy, and Leigh-like syndrome) syndrome present in childhood with deafness, progressive spasticity and dystonia, psychomotor retardation and Leigh like syndrome on MRI. Type III MGA (Costeff syndrome) is characterized by a triad of 3-MGA, ataxia or extrapyramidal manifestations (spasticity, hypertonia) and optic atrophy [38, 39]. Severe neurologic symptoms develop in infancy with failure to thrive, developmental delay, and loss of milestones [38]. Adolescent onset spasticity, hypertonia, ataxia, seizures, and dyskenesis have been noted. Life span of affected patients appears to be normal. Type IV MGA has a very heterogeneous phenotype including neurologic disease, and possible cardiac, hepatic and renal involvement. Perhaps the most characteristic systemic feature of Type V MGA is the delayed onset and milder severity of neurologic manifestations which include cerebellar signs, increased deep tendon reflexes (which may be the earliest neurologic sign), and spasticity. Cranial nerves and sensation are not affected. The degree of neurologic involvement may vary between families; patients may be mildly affected or may be wheelchair bound in childhood. Intelligence is usually not affected although mild retardation may occur.

Ophthalmic Manifestations

The most prominent ophthalmic finding in 3-MGA is bilateral early onset symmetric optic atrophy, particularly in type III disease [38, 39]. Optic atrophy manifests as decreased visual acuity within the first years of life, sometimes associated with infantile-onset horizontal nystagmus. Milder mutations may cause isolated onset of optic atrophy in adulthood. In type IV MGA, optic atrophy has been noted as early as 2–3 years old and may precede the onset of other neurologic signs. Optic atrophy has also been described in type I MGA [37]. Patients may also have nystagmus and in one reported case, head nodding. Decreased visual acuity may precede the diagnosis of optic atrophy. The visual acuity deteriorates early and then stabilizes at a level of 6/21–6/30. Visual evoked potential abnormalities are variable and include delayed latency or undetectable first component. The electroretinogram is normal.

Diagnosis

The diagnostic test is detection of 3-methylglutaconic and 3-methylglutaric acid in the urine. In 3-MGA, other organic acids may also be excreted in the urine in excessive amounts. Detection of mutations in the respective genes by molecular genetic testing is confirmatory.

Management

Treatment is supportive with involvement of a neurologist, ophthalmologist, biochemical geneticist, and physiotherapist. A possible role for coenzyme Q10 (CoQ_{10}), the active form of ubiquinone, has been hypothesized. Use of tobacco, alcohol, and medications known to impair mitochondrial function is best avoided.

Canavan Disease

Definition

Canavan disease is a rare autosomal recessive leukodystrophy resulting in spongy deterioration of the brain. It is caused by mutations in the aspartoacylase (*ASPA*) gene located on chromosome 17p13.2, which leads to accumulation of N-acetylaspartate (NAA) in the brain. The pathological buildup of NAA in white matter extracellular fluid results in increased extracellular osmotic-hydrostatic pressure and initiation of the demyelination process.

History

Canavan disease was first described in 1931 by Myrtelle Canavan. In 1967, Hagenfeldt et al. reported cases of N-acetylaspartic aciduria in patients with leukodystrophy and progressive cerebral atrophy [40]. However, they did not link the findings to Canavan disease. In 1989, Matalon et al. found increased NAA in urine and plasma of 3 patients (2 families) of Ashkenazi descent with a diagnosis of Canavan disease [41]. Aspartoacylase was assayed in cultured skin fibroblasts from 1 patient of each family, and a profound deficiency of the enzyme was found.

Epidemiology

Canavan disease has been reported world-wide, but is prevalent among Ashkenazi Jews, and a majority of cases with this ethnic background have two common mutations (founder effect).

Systemic Manifestations

Although infants with Canavan disease appear normal at birth, they develop a triad of hypotonia, macrocephaly and head lag by the age of 3–5 months. The neurologic findings are due to demyelination and leukodystrophy. Developmental delays become progressively more apparent. Most patients develop seizures, feeding difficulties, irritability, and spasticity. Life expectancy is reduced and average survival is until 10 years old. Neuroimaging shows diffuse white matter disease. There is a mild/juvenile form of Canavan disease with less severe neurological findings. These children have mild motor developmental delay and problems with speech or achievement at school. Affected individuals are usually compound heterozygotes with one mild mutation allowing for residual ASPA enzyme activity and one severe mutation. Neuroimaging does not show the generalized white matter disease seen in the severe infantile form.

Ophthalmic Manifestations

Affected children are often visually impaired due to cortical visual loss. Optic atrophyand nystagmus are also common [42, 43].

Diagnosis

Increased N-acetylasparticacid (NAA) in urine, cerebrospinal fluid (CSF), and blood is the biological hallmark of Canavan disease. Abnormally elevated NAA may be measured quantitatively in the brain using noninvasive proton magnetic resonance spectroscopy [44]. Enzyme assays reveal reduced aspartoacylase activity in cultured skin fibroblasts. Diagnostic confirmation is obtained by molecular genetic testing of *ASPA*, the gene encoding the enzyme aspartoacylase. Prenatal diagnosis of Canavan disease is possible by the measurement of N-acetylaspartate in the amniotic fluid and by DNA analysis.

Management

Treatment is supportive and directed to providing adequate nutrition and hydration, managing infectious diseases, and protecting the airway, and physiotherapy to minimize contractures and maximize motor abilities. Seizures are treated with antiepileptic drugs. Gastrostomy may be needed to maintain adequate food intake and hydration when swallowing difficulties exist. Gene therapy for Canavan disease using recombinant AAV2 is promising and clinical trials have shown a decrease of brain NAA concentrations, with consequent behavioral and histopathological improvements, including a decline in seizure frequency [45, 46].

Disorders of Phenylalanine and Tyrosine Metabolism

Phenylalanine Hydroxylase Deficiency (Phenylketonuria; PKU)

Definition

PKU is an autosomal recessive disorder which results from a deficiency of hepatic phyenylalanine hydroxylase (PAH) activity. This enzyme catalyzes the irreversible hydroxylation of phenylalanine to tyrosine. A defect in PAH results in hyperphenylalaninemia, as well as a deficiency of tyrosine and its metabolites—L-Dopa, dopamine, melanin, and catecholamines. Phenylalanine is converted to phenylpyruvic acid (a ketone) which is excreted in large quantities in the urine (Fig. 13.6).

The *PAH* gene encoding the enzyme PAH is located on the long arm of chromosome 12. Over 500 mutations in the gene are recognized which may result in abnormal enzyme variants having activity levels ranging from 0 to 70% [47, 48]. Variable levels of severity have been classified as classic, moderate, or mild PKU, and mild hyperphenylalanemia [48]. Classic PKU is caused by a complete or near-complete deficiency of enzyme activity. Families have been reported in which both mild hyperphenylalanemia and classic PKU have affected different family members [49].

History

Classic PKU was first recognized by Asjbørn Følling in 1934 [50]. He recognized that a certain type of intellectual disability was caused by elevated levels of phenylalanine in body fluids. He called the condition "phenylpyruvic oligophrenia." In the mid-1950s, it was demonstrated that patients with PKU had a deficiency of PAH activity. Guthrie introduced the concept of newborn screening for PKU in 1963 [51]. Prompted by mental retardation in his second son and a niece, he developed the Guthrie test, which facilitated population screening for PKU.

Epidemiology

The prevalence of PKU varies in different populations, with Turks having the highest prevalence (1: 2600), followed by Irish (1:4500). The estimated prevalence in Northern Europeans and East Asians is 1:10,000. PKU is rare in Africans and Japanese with estimated prevalence of 1:100,000 and 1: 143,000 respectively. The establishment of newborn screening programs has significantly altered the natural history of the disease, and symptomatic classic PKU is now rare (1:10,00,000 live births).

Systemic Manifestations

The most striking effect of untreated classic PKU is profound and irreversible intellectual disability (IQ < 50). Other associated features include microcephaly, behavioral abnormalities (aggressive, hyperactive, and highly disruptive patterns), seizures, spasticity, EEG abnormalities, and MRI changes in the brain. Low levels of tyrosine, an important substrate for melanogenesis, may result in hypopigmentation of skin and hair. Patients often emanate a mousy odor due to excretion of phenylacetic acid in body fluids. Despite strict adherence to diet many patients still have some underlying sequelae and suboptimal cognitive outcome. In treated individuals, psychological problems are increased as compared to normal sibs or children [52].

Ophthalmic Manifestations

A predominance of pale blue irides and blonde fundi is seen in patients with PKU [53]. Iris transillumination, foveal hypoplasia, increased incidence of strabismus, or chiasmal misrouting, all characteristics of albinism have not been reported in PKU; this is consistent with the reports of others that these patients do not have a form of albinism [53]. Visual evoked potentials are often abnormal with a significant reduction of amplitude and prolongation of latency in both

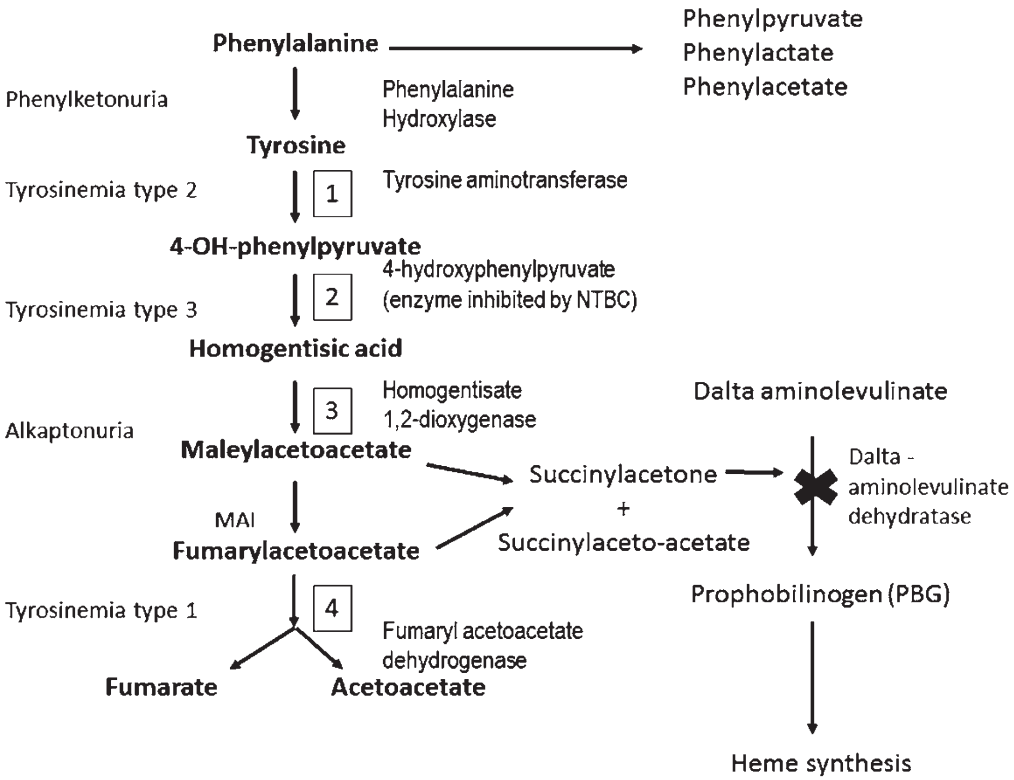

Fig. 13.6 Phenylalanine hydroxylation system. Phenylalanine is irreversibly catabolized to Tyrosine by Phenylalanine hydroxylase (PAH). In PAH deficiency, excess phenylalanine gets transaminated into Phenylpyruvate due to defects in PAH or BH_4. Tyrosine is one of the least soluble amino acids. Its catabolism occurs predominantly in the liver cytosol. Tyrosinemia II occurs due to a deficiency of hepatic tyrosine amino transferase (TAT). Alkaptonuria is an autosomal recessive disorder resulting from deficient activity of homogentisic acid dioxygenase, the third enzyme in tyrosine degradation. Tyrosinemia type 1 (hepatoprenal Tyrosinemia) results from fumarylacetoacetate deficiency and the disease symptoms are related to the accumulation of succinylacetone and fumarylacetocetate

untreated and treated patients with PKU [54, 55]. These changes may be seen despite the absence of visual symptoms and abnormalities on routine neuro-ophthalmological examination, indicating a high incidence of subclinical visual pathway involvement in older children and adults with PKU [54, 55]. VEP may be more sensitive than the EEG in detecting the neurological dysfunction in patients with PKU [56]. In one study, the amplitude of VEPs significantly correlated with IQ, but no correlation between VEP and dietary state and phenylalanine concentration was found [54]. Sudden onset of cortical blindness has been reported in adults with poorly controlled disease [57].

Diagnosis

Blood phenylalanine is normal at birth in infants with PKU, but rises rapidly within the first days of life. In most Western nations, PKU is detected by newborn population screening utilizing the Guthrie card bloodspot obtained from a heel prick. Although some controversy exists about the proper timing for neonatal screening, there appears to be no significant difference between results obtained during or after the first 14 days of life [47]. Early diagnosis is most preferable. In the neonatal period, plasma levels of phenylalanine in excess of 120 μmol/L (2 mg/dL) along with phenylketones in the urine is indicative of PKU. Use of phenylalanine-to-tyrosine ratios can reduce the number of false positives. After the diagnosis has been established, predictions about the eventual phenotypic severity may be possible by characterizing the specific genomic mutation [47]. These molecular techniques may also be useful for prenatal diagnosis and carrier screening, particularly in families who already have an affected child [58].

Management

The goal of treatment in PKU is to maintain blood phenylalanine levels within a safe target rage by restricting dietary phenylalanine. Recommended target phenylalanine levels differ among countries but majority accept 120–360 μmol/L as the target range for the first 6 years of like. This target is achieved with the use of phenylalanine-free medical formula or products soon after birth, and by restricting intake of natural protein. Care must be taken to ensure that the diet supplies all essential nutrients. The efficacy of dietary measures to maintain target range of phenylalanine is directly dependent

on the severity of enzyme deficiency. Although, adherence to diet and tight monitoring of metabolic control is crucial during early childhood years, a current recommendation is to maintain a phenylalanine restricted diet for life.

Late treatment may improve visual attention span along with an improvement in behavioral patterns [59]. This finding led Giffin and coworkers to suggest that assessment of visual attention span (using a slide presentation stimulus with observation of fixation behavior) may be useful in predictive screening of older PKU individuals regarding likely overall response to late institution of dietary intervention.

Tyrosinemia

Abnormalities in the tyrosine catabolic pathway 6 result in hereditary tyrosinemia types I, II and III.

Tyrosinemia Type I

Tyrosinemia type I is caused by homozygous or compound heterozygous mutation in the *FAH* gene, encoding fumarylacetoacetate hydrolase, the last enzyme on tyrosine degradation (Fig. 13.6).

It is predominantly associated with hepatorenal involvement without ocular sequelae. The disorder is fatal in childhood. Photophobia and sore eyes have occasionally been described in patients with tyrosinemia type I treated with nitisinone (previously known as NTBC). Nitisinone inhibits and enzyme in the tyrosine catabolic pathway and leads to marked elevation of serum tyrosine levels, and dendritiform corneal opacities have been reported as a potential consequence of nitisonone treatment [60, 61], particularly if dietary monitoring and a tyrosine-restricted diet is not appropriately followed. The lesions resolve with dietary restrictions. Tyrosinemia type III, given its rarity is less well characterized, but neurological manifestations are evident.

Tyrosinemia Type 2 (Oculocutaneous Tyrosinemia, Richner-Hanhart syndrome)

Definition

This autosomal recessive disorder, caused by deficiency of tyrosine aminotransferase results in elevated plasma tyrosine and its metabolites (Fig. 13.6).

Tyrosine is one of the least soluble aminoacids, and forms characteristic crystals upon precipitation. Elevated tyrosine levels results in deposition of tyrosine crystals in epithelial cells, leading to an inflammatory response and the oculocutaneous findings. Tyrosinemia type 2 is caused by mutations in the *TAT* gene (16q22.1) [62].

History

The clinical features of tyrosinemia type 2 were identified independently by Richner in 1938, and Hanhart in 1947. Goldsmith linked the clinical picture with abnormalities in tyrosine metabolism in 1973 [63].

Epidemiology

Tyrosinemia type II occurs in fewer than 1 in 250,000 individuals. However, because of the high rate of consanguinity this disorder seems to be relatively common among the Arab and Mediterranean populations [64].

Systemic Manifestations

Skin lesions occur in 80 % of cases and neurologic findings and some degree of intellectual deficit in up to 60 % of cases. Cutaneous manifestations usually begin after the first year of life but may develop at the same time as the ocular symptoms. The skin lesions (palmoplantar hyperkeratosis), consist of painful, nonpruritic, hyperkeratotic papules and plaques principally located on the palms and soles.

Patients may present with a history of walking on their knees to avoid contact with soles and palms on the floor. Central nervous system (CNS) involvement is highly variable with intellectual deficit (ranging from mild to severe) being the most common manifestation. Other signs of CNS involvement include behavioral problems, tremor, ataxia, and convulsions.

Ocular Manifestations

Ocular involvement is seen in 75 % of patients [65]. Affected patients present with redness, photophobia, excessive tearing and eye pain in the first year of life [66]. Examination reveals visual impairment, varying degree of corneal opacification with bilateral dendritiform corneal lesions (pseudodendritic keratitis), corneal or conjunctival plaques, neovascularization, and scarring [66]. Patients are often misdiagnosed as having herpes simplex keratitis. However, unlike herpes simplex keratitis, the pseudodendritic keratitis of tyrosinemia type 2 is thick and plaque-like, (Fig. 13.7), and is associated with exacerbation of symptoms with increased dietary protein. Bilateral affectation,

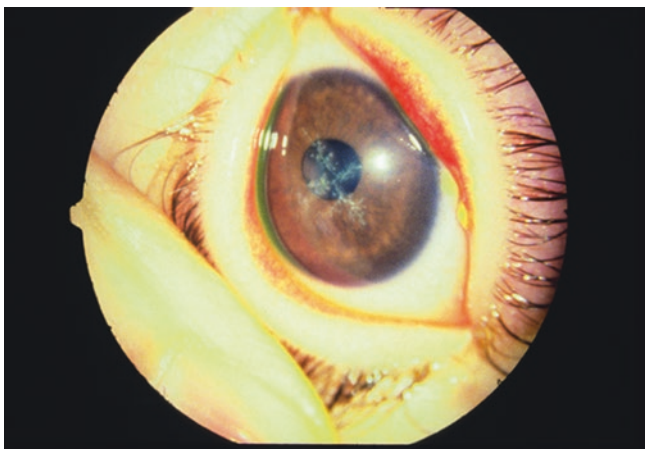

Fig. 13.7 Dendritiform corneal lesions in tyrosinemia type II. Reprinted from Levin AV, Wilson T, eds.: Hospital for Sick Children's Atlas of Pediatric Ophthalmology and Strabismus. ISBN: 9780781743099., Lippincott Williams and Wilkins, Philadelphia, 2007 [767]. © Wolters Kluwer. With permission from Wolters Kluwer

intact corneal sensations, negative viral cultures, and associated systemic manifestations, as well as failure to respond to antiviral therapy should alert the clinical to a possible diagnosis of tyrosinemia type II [65]. Pseudodendritic lesions may stain with fluorescein and Rose Bengal [65]. Uveitis is absent.

Diagnosis

Diagnosis is made by the detection of high levels of plasma and urinary tyrosine, and elevated levels of tyrosine metabolites in the urine. The plasma tyrosine concentration in this disorder typically is >1000 μmol/L, substantially higher than in other forms of tyrosinemia. Other amino acid levels, particularly those of phenylalanine and methionine are usually normal. Urine organic acids estimation will demonstrate increased excretion of p-hydroxyphenylpyruvate, p-hydroxyphenyllactate p-hydroxyphenylacetate, and small quantities of N-acetyltyrosine, and 4-tyramine. Enzyme studies are usually not necessary for diagnosis. Some patients with tyrosinemia type 2 may be identified through neonatal screening program studies. Diagnosis may be confirmed by mutation analysis of the *TAT* gene.

Management

Early institution of a phenylalanine-tyrosine restricted diet in infancy is currently the most effective therapy available to promptly reverse ocular and cutaneous abnormalities and prevent risk of cognitive impairment from tyrosinemia type II. A low-protein diet combined with a formula that is free of phenylalanine and tyrosine is instituted to lower plasma tyrosine levels below 600 μmol/L. Ocular and skin manifestations resolve on the above therapy within days to several weeks. Oral retinoids may be administered for treatment of the skin lesions.

Corneal grafting might rarely need to be performed for corneal scarring. The procedure can be complicated by recurrence of corneal lesions in the graft [67].

Alkaptonuria (Ochronosis)

Definition

Alkaptonuria is an autosomal recessive disorder resulting from deficient activity of homogentisic acid dioxygenase, the third enzyme in tyrosine degradation (Fig. 13.6).

Accumulation of homogentisic acid leads to homogentisic aciduria, accumulation of homogentisic acid in connective tissue (ochronosis), and ochronotic arthritis. The homogentisate 1,2-dioxygenase (*HGD*) gene is located at 3q13.33 [68]

History

The phenomenon of homogentesic acid deposition in tissues was first described by Rudolf Virchow in 1865, and the condition was named after the yellowish (ocher-like) discoloration of tissues on histopathological examination. Alkaptonuria was one of the first "inborn errors of metabolism" described by Sir Archibald Garrod in 1908. It also has the distinction of being among the first disorders in humans shown to conform to the principles of Mendelian autosomal recessive inheritance [69].

Epidemiology

Alkaptonuria has a frequency of 1–9/1,000,000 in the general population. The disorder is more common in Slovakia (1:19,000) [70] and the Dominican Republic [71]. In the Dominican population, the increased incidence has been shown to be consequent to a classical founder effect [71].

Systemic Manifestations

Deficiency of the enzyme homogentisic acid dioxygenase causes accumulation of homogentisic acid and its daily excretion in large quantities in the urine, which turns dark on standing (alkaptonuria). In urine, as in tissues, homogentisic acid oxidizes to benzoquinones, which in turn form melanin-like polymers. Accumulation of homogentisic acid and its metabolites in tissues causes ochronosis, with darkening of cartilaginous tissues and bone, arthritis and joint destruction, and deterioration of cardiac valves. Clinically and radiologically, ochronotic cartilage destruction closely imitates ankylosing spondylosis. The disabling arthritis is usually apparent by the fourth decade and continues to progress thereafter. Patients with alkaptonuria are prone to calcification of coronary arteries and cardiac valve dysfunction secondary to ochronosis [72], and kidney stones secondary to high levels of urinary homogentisic acid excretion [73].

Ocular Manifestations

The most common ocular finding in alkaptonuria is purple hued hyperpigmentation of the sclera which is present in over 80 % of affected patients over the age of 40 and most often located at the insertions of the extraocular muscles [74]. Dilated conjunctival vessels can be present. The ocular surface involvement is usually asymptomatic [75]. Progressive peripheral corneal thinning and astigmatism in the axis of the lesions may occur [76]. Bilateral, peripheral corneal pigmentation, in the form of discrete pinhead-sized deposits of light brown to black color [74], and increased intraocular pressure secondary to homogentisic acid deposition in the chamber angle have been reported [74, 77].

Diagnosis

One of the earliest recognized signs of this disease is the darkening of urine when oxidized spontaneously in air. The diagnosis can be confirmed via the detection of homogentisic acid in plasma or urine through gas chromatography mass spectrometry (GCMS). Although molecular confirmation is

not required for the diagnosis of alkaptonuria, diagnosis can also be established by genetic testing of the *HGD* gene.

Management

Nitisinone has been proposed as potential therapy because it inhibits the enzyme that produces homogentisic acid [73, 78]. In an international, randomized, open-label, no-treatment controlled, parallel-group study, nitisinone therapy decreased urinary homogentisic acid excretion to low levels in a dose-dependent manner and was well tolerated within the studied dose range [79]. This must be accompanied by dietary restriction of tyrosine and phenylalanine or total protein to prevent hypertyrosinemia from nitisinone therapy. High-dose vitamin C decreases urinary benzoquinone acetic acid but has no effect on homogentisic acid excretion. Surveillance for cardiac, renal, and prostate complications after the fourth decade of life and strict attention to pain control is advisable.

Disorders of the Metabolism of Sulphur-Containing Amino Acids

Classic Homocystinuria (Cystathionine β-Synthase Deficiency)

Definition

Classic homocystinuria is an autosomal recessive disorder related to the deficiency of cystathionine β-synthase enzyme and the subsequent accumulation of homocysteine, homocysteine disulfide metabolites (homocystine and homocysteine-cysteine) and methionine (Fig. 13.8a, b).

Cystathionine β-synthase enzyme is encoded by the *CBS* gene on chromosome 21q22.3, the only gene responsible for classic homocystinuria [80]. Other metabolic disorders characterized by elevated homocysteine include deficiency in methylene-tetrahydrofolate reductase (MTHFR), an enzyme that catalyzes the transformation of homocysteine to methionine via the remethylation pathway, and defects in methylcobalamin synthesis, the cofactor for methionine synthase enzyme. These disorders lead to hyperhomocystinemia, and ocular features of classic homocystinuria. They do not have the characteristic systemic features of classic homocystinuria and are characterized by low methionine levels.

History

Classic homocystinuria was first recognized in 1962, during a survey for metabolic disorders in institutionalized mentally impaired inmates in Northern Ireland. The aminoaciduria was detected using urine chromatography and ectopia lentis was noted. The discovery of cystathionine β-synthase deficiency as a causative enzymatic deficiency followed shortly thereafter [81]. In 1964, Gibson reported the association with thromboembolic complications and the confusion with Marfan syndrome owing to the presence of skeletal abnormalities and ectopia lentis [82]. Spaeth and Barber demonstrated that some patients with homocystinuria respond to pyridoxine (vitamin B_6) [83].

Epidemiology

Classic homocystinuria has a worldwide prevalence of 1:335,000 live births, while in Ireland it is higher at 1:65,000; [84] the prevalence in Qatar is believed to be the highest at 1:1800 [85]. Skovby and colleagues observed that the number of individuals identified with homocystinuria with homozygosity for the widespread c.833T>C (p.I278T) mutation in the *CBS* gene fall far short of the number of such individuals expected on the basis of the heterozygote frequency for this mutation in Denmark. They concluded that prevalence is underestimated as patients could be potentially missed by both newborn screening and clinical ascertainment [86].

Systemic Manifestations

Patients with classic homocystinuria are normal at birth but in about 60 % of patients, variable degrees of developmental delay and cognitive disability become evident with time. Other neurological findings include seizures and psychiatric disturbances. Patients develop Marfanoid habitus with tall stature and thinning and elongation of long bones (Fig. 13.9a). Osteoporosis is a major complication and predisposes patients to scoliosis, pathological fractures, genu valgum, and pectus carinatum or excavatum. They often have fair complexions and a malar reythematous skin eruption. They may have premature greying of the hair, particularly in the temples

Thromboembolism of large and medium-sized vessels is a major cause of early morbidity and mortality. Thrombophlebitis and pulmonary embolism are common, however, thrombosis of the carotid and renal arteries is a frequent cause of death. Most thrombotic events are precipitated by venous stasis, for example during general anesthesia. The thrombosis is due to a platelet aggregation defect.

Homocystinuria due to MTHFR deficiency is characterized by progressive neurological involvement. The manifestations range from mild to aggressive. Neonates may have seizures, failure to thrive and early death from neurological complications, but some affected patients may live to adulthood without symptoms. Risk for serious thromboembolic events is similar to classic homocystinuria [87, 88].

Ophthalmic Manifestations

Untreated, 90 % of individuals develop progressive ectopia lentis by 5–10 years of age, with the lens typically subluxating inferiorly, although any direction may occur [89–92]. This has been attributed to altered functional properties of zonular fibrillin-1 and tropoelastin by homocysteinylation [93]. Slit-lamp examination of patient reveals broken zonules, in contrast to Marfan syndrome where the zonules are stretched, but intact (Fig. 13.9b).

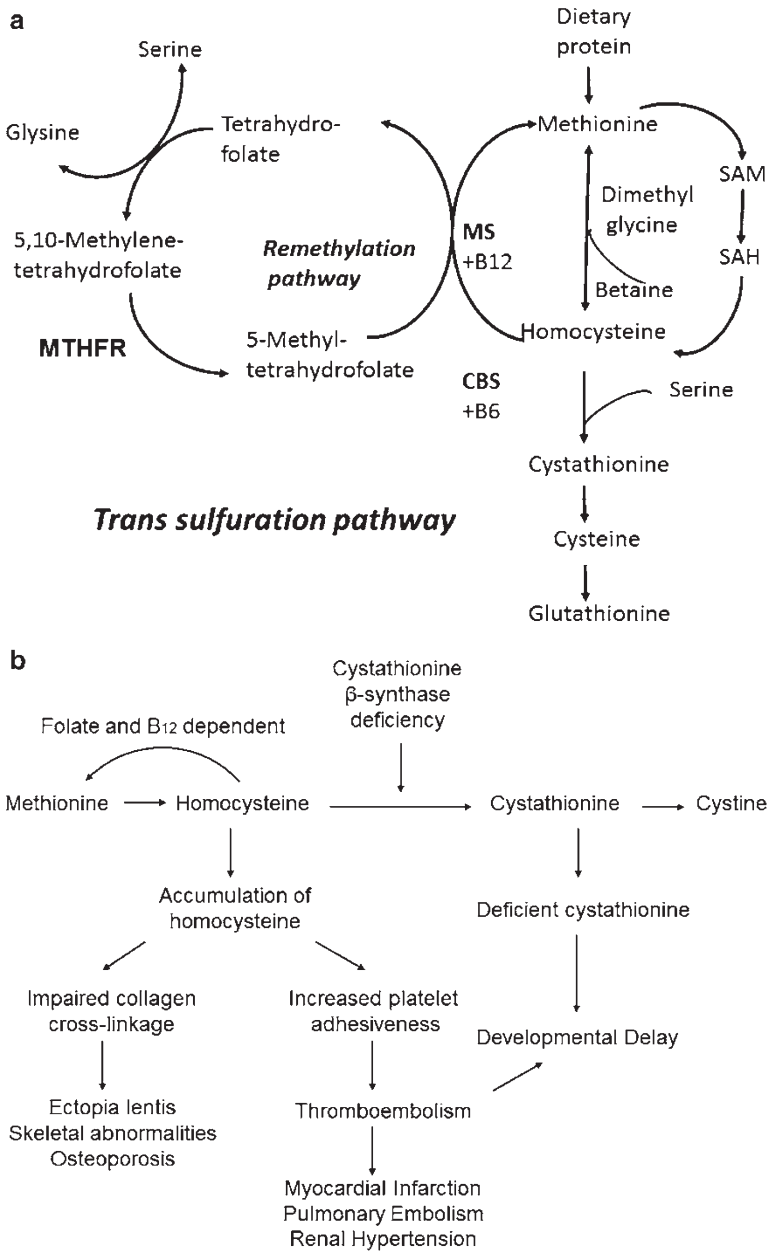

Fig. 13.8 (**a**) Metabolism of homocysteine and (**b**) clinical effects of cystathionine β-synthase (CBS) enzyme deficiency. CBS enzyme deficiency leads to accumulation of homocysteine, homocysteine disulfide metabolites (homocystine and homocysteine-cysteine) and methionine. Clinically patients develop manifestations related to nervous, vascular and musculoskeletal systems. Ophthalmic manifestations are due to underlying impairment in collagen cross-linkage. (*CBS* cystathionine β-synthase, *MTHFR* methyltetrahydrofolate reductase, *SAM* S adenosyl methionine, *SAH* S adenosyl homocysteine, *MS* methionine synthase)

As the lens becomes increasingly subluxed, the patient will experience increasing optical blur and distortion related to spherical aberrations and astigmatism from the lens edge becoming coincident with the visual axis and tilting of the lens [91]. Eventually, the aphakic visual axis may yield the best corrected vision. In addition, patients experience markedly increasing lenticular myopia due to an increase in the refractive power of the lens which becomes more globular (increased anterior-posterior diameter) from zonular breakage and dehiscence. However, increasing myopia may occur in the absence of frank ectopia lentis in untreated patients [92]. Complete recurrent anterior dislocation of the lens into the anterior chamber associated with intermittent elevation in intraocular pressure either due most often to pupillary block is commonly seen in patients with homocystinuria. This is particularly problematic in children as the vitreous is well attached to the posterior lens surface allowing it to move forward with the lens through the pupil, with subsequent "strangulation" by the encircling pupil once subluxation is completed. Other ophthalmic features of this condition include cataract, iris atrophy, retinal detachment, central retinal artery occlusion, optic atrophy, anterior staphylomas, and corneal opacities. Iris atrophy may be due to iris ischemia

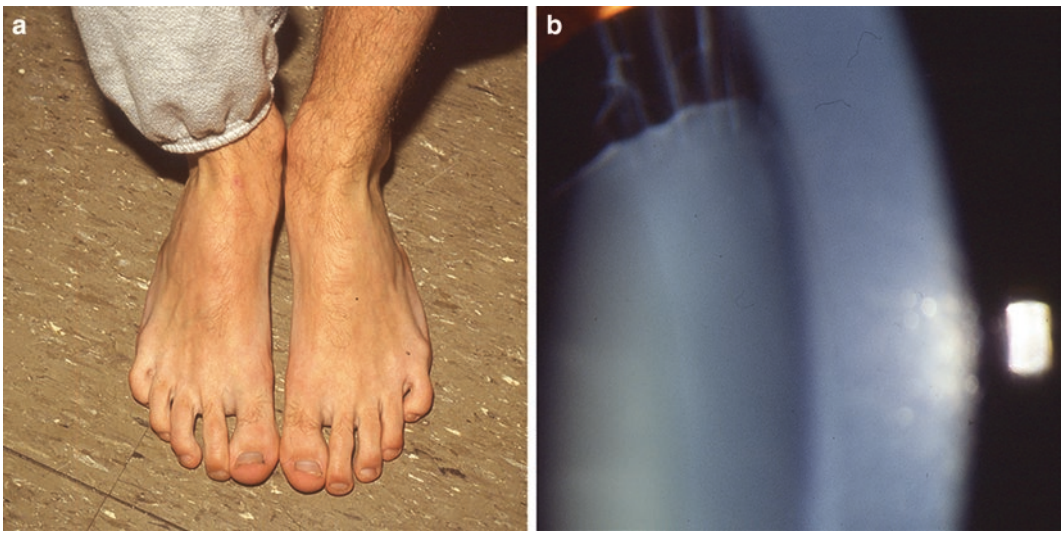

Fig. 13.9 Homocystinuria. (**a**) Arachnodactyly of the toes in homocystinuria. (**b**) Ectopia lentis in homocystinuria. Note broken zonules with resulting crenulations in lens edge. Courtesy: Prof. Alex V. Levin

from recurrent high intraocular pressure or thromboembolism of iris vessels [91]

Diagnosis

Plasma amino acid profile typically illustrates the increase in methionine, homocystine, and cysteine-homocysteine disulfide with concomitant low cystine and cystathionine. Plasma total homocysteine is an important marker of the disease with typical levels exceeding 200 μmol/L in CBS deficient patients (normal less than 15 μmol/L). Methionine levels decrease with age and may normalize in older patients, a factor that may confuse CBS deficiency with other disorders associated with elevated homocysteine. Measurement of cystathionine ß-synthase activity in cultured fibroblasts is the key for definitive diagnosis although sequence analysis of *CBS* gene has a mutation detection frequency of >95% [94]. Prenatal testing is possible through measurement of cystathionine ß-synthase activity in cultured amniocytes (but not in chorionic villi because this tissue has very low activity of the enzyme), measurement of total homocysteine in cell-free amniotic fluid, and molecular genetic testing if both disease-causing alleles of an affected family member have been identified. Blood methionine levels have been used for neonatal screening programs. False negatives may occur in pyridoxine responsive patients, breast fed babies, or individuals on low protein diets [92].

Management

Several studies have shown that early diagnosis and institution of treatment and dietary restriction slows the progression of disease in homocystinuria and reverses some of the features. Treatment lessens the risk of thrombosis and influences the progression of central nervous system damage. Patients with homocystinuria may be divided into pyridoxine-sensitive and pyridoxine-insensitive groups. Forty percent of individuals respond to high doses of vitamin B6, and for them pyridoxine, folic acid and vitamin B-12 are prescribed. Additional agents for vitamin B6 non-responders include oral Betaine which remethylates homocysteine to methionine and may be effective therapy to help lowering homocysteine level. Vitamin C supplementation is often used to ameliorate endothelial dysfunction and in turn to lower the risk of atherothrombotic events. Dietary restriction of methionine and cysteine supplementation can prevent lens luxation and learning disability in majority of patients with reported normal IQ in pyridoxine non-responsive patients treated since birth [95]. Treatment is aimed at maintaining the plasma methionine, homocystine and cystine within the normal range and the plasma homocysteine concentration as close to normal as possible.

Medical management of complete lens subluxation may include pharmacologic mydriasis in the supine position, allowing the lens to drift back behind the pupil, followed by acute and chronic pharamacologic miosis [91]. If the lens does not drift back on its own, manual compression of the cornea either with a finger or cotton swab may help the lens to reposition. Peripheral iridectomy has been tried in an effort to prevent pupillary block. Yet, recurrent subluxation usually occurs even with successful medical management [91]. In these cases, and in cases where mental retardation prevents easy medical management, surgery is recommended [91]. Surgical management of ectopia lentis in patients with homocystinuria raises two concerns: ocular risks and general anesthetic risks. Ocular risks include vitreous loss, retinal

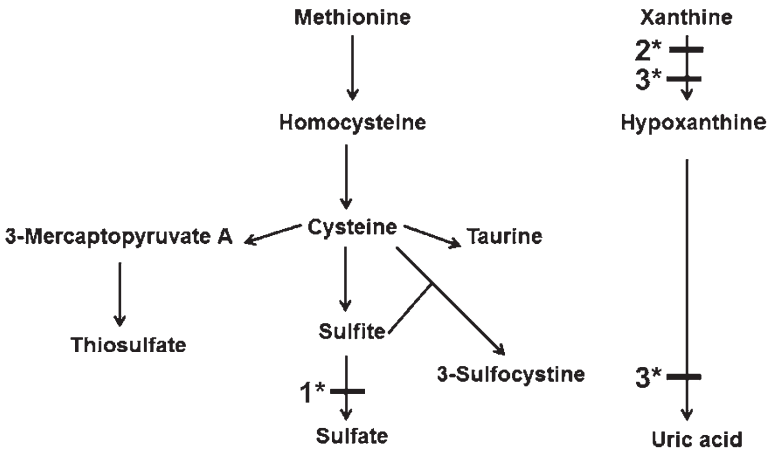

Fig. 13.10 Pathway of degradation of sulfur containing amino acids. Sulfite oxidase (*1*) catalyzes the last step of conversion of sulfite to sulfate in the degradation of sulphur containing amino acids including cysteine, an essential component of lens zonules. Sulfite can also be metabolized by other route to thiosulfate or S-sulfocysteine. Molybdenum (Mo) cofactor (*) is required for sulfite oxidase and there is thus an overlap with the phenotype of Mo cofactor (*) deficiency. But Mo cofactor (*) is also required for aldehyde oxidase (*2*) and xanthine dehydrogenase (*3*). Mo cofactor deficiency thus leads to low uric acid with accumulation of xanthine and hypoxanthine; these are normal in isolated sulfite oxidase deficiency

detachment, and the loss of lens material into the posterior segment of the eye. Anesthesia can be complicated by thromboembolic events in the intra- or perioperative period, and precautions should include maintenance of homocysteine to near normal levels, aggressive hydration (fluid at 1.5 times maintenance with close monitoring to avoid fluid overload), and prophylaxis for deep vein thrombosis during and after surgery. Rotating limb-to-limb compression bandages can assist with venous return during surgery. General anesthesia may also be complicated by hypoglycemia secondary to hyperinsulinemia, and intraoperative monitoring of glucose levels has been advocated in patients with homocystinuria undergoing general anesthesia [96]. Given the anesthetic risks, bilateral, simultaneous lens extraction under a single anesthetic should be considered. Due to the broken zonules, the lens may be very loose, requiring a posterior approach, perhaps with perfluorocarbon used to float the lens forward. With appropriate anesthetic precautions and modern microsurgical techniques, the risks associated with the surgical management of ocular complications of homocystinuria are reduced. Correction of the aphakia with glasses or contact lenses is the safest method of visual rehabilitation [97].

Isolated Sulfite Oxidase Deficiency

Definition

Sulfite oxidase catalyzes the last step of conversion of sulfite to sulfate in the degradation of sulphur containing amino acids including cysteine, an essential component of lens zonules. Sulfite can also be metabolized by other route to thiosulfate or S-sulfocysteine (Fig. 13.10).

Molybdenum cofactor is required for sulfite oxidase and there is thus an overlap with the phenotype of molybdenum cofactor deficiency. Sulfite oxidase deficiency is caused by mutations in the *SUOX* gene (12q13.2).

History

Mudd et al. found increased sulfite in the urine and decreased inorganic sulfate excretion in an infant with neurological disease and ectopia lentis. Sulfite oxidase deficiency was postulated [98].

Epidemiology

Less than 100 cases of this autosomal recessive disorder have been reported.

Systemic Manifestations

This disorder is nearly always fatal in childhood. It is characterized by early onset of intractable seizures, often in the neonatal period, severe psychomotor retardation, failure to thrive, microcephaly, hypotonia passing into hypertonia, and early death. Neuroimaging may reveal gross cerebral atrophy affecting virtually every part of the brain, cystic changes, demyelination, and calcification.

Ophthalmic Manifestations

The major manifestation is ectopia lentis although strabismus, nystagmus, non-reactive pupils, cortical visual impairment, and optic atrophy may also be observed [99, 100]. The direction of ectopia lentis is non-specific [100].

Not all patients have ectopia lentis in infancy. As in homocystinuria, zonules are broken rather than stretched.

Diagnosis

Urinary excretion with elevated blood levels of inorganic sulfite, thiosulfate, and S-sulfocysteine are diagnostic. The absence of xanthinuria distinguishes isolated sulfite oxidase deficiency from molybdenum cofactor deficiency, in which urate levels are low, with xanthinuria. Molecular genetic testing is confirmatory. Prenatal biochemical or genetic testing is available.

Management

Dietary restrictions of cysteine and methionine may be useful [101]. But most children are so severely affected at diagnosis that this is not helpful.

Molybdenum Cofactor Deficiency (MOCOD)

Definition

Molybdenum is required as a cofactor by enzymes sulfite oxidase, xanthine oxidase, and aldehyde oxidase. Sulfite oxidase is the terminal enzyme in the metabolism of sulfur containing amino acids (Fig. 13.10) and also has a role in detoxifying exogenous sulfur dioxide and sulfite. The other two enzymes are involved with purine degradation which produces uric acid production. The major clinical manifestations of molybdenum cofactor deficiency (MOCOD) are due to decreased activity of sulfite oxidase. MOCOD is usually caused by mutations in the *MOCS1* gene located in chromosome 6p21.3 [102, 103]. Other genes implicated in causing MOCOD when mutated are *MOCS2* (5q11), and *GPHN* (14q23).

History

MOCOD was first reported in 1978 in a neonate who presented with feeding difficulties, severe neurological abnormalities, ectopia lentis and dysmorphism. Combined deficiency of xanthine oxidase and sulfite oxidase was detected. Serum molybdenum concentration was normal [104]. Subsequent studies on the same patient in 1980 led to recognition of molybdenum cofactor deficiency as underlying pathology. Molybdenum was absent in the liver sample despite normal serum levels of the metal; however, the active molybdenum cofactor was not detectable in the liver [105].

Epidemiology

The condition is estimated to occur in 1 in 100,000–200,000 newborns worldwide. More than 100 cases have been reported, although it is thought that the number of affected individuals may be higher, as many patients die in early neonatal period without a diagnosis.

Systemic Manifestations

Babies are normal at birth, but within a week develop severe, intractable seizures and feeding difficulties with failure to thrive. Growth delay, axial hypotonia with peripheral hypertonia, opisthotonos, and developmental delay are seen due to toxic accumulation of sulfite in the brain. Death occurs in the first decade, usually between 2 and 6 years of age [106]. CT scan may show brain atrophy and ventriculomegaly [107]. Urinary xanthine stones are the only manifestation of the xanthine oxidase deficiency. Other minor findings include dysmorphism (redundant skin folds, coarse facies, frontal bossing, bitemporal narrowing, long philtrum, high palate, pectus carinatum, and scoliosis), kidney malformations and hip dysplasia. Some children have an exaggerated startle reaction (hyperekplexia) to unexpected stimuli such as loud noises.

Ophthalmic Manifestations

Ectopia lentis plays an important role in establishing diagnosis. Although often present in the first few years, frank ectopia may be preceded by several years of symmetric spherophakia due to abnormal zonular fibers [107]. Mild ectopia lentis may even be detected in infancy. Although direction of the lens is variable, down going is the most common. Nystagmus, visual impairment due to cortical visual loss or optic atrophy, enophthalmos and esotropia have also been reported.

Diagnosis

The biochemical profile includes hypouricemia, low urinary excretion of sulfate and urate, and increased serum xanthine, sulfite, and S-sulfocysteine. Urine sulfite screening tests are insufficient for diagnosis as false negatives may occur. Prenatal diagnosis by enzyme assay and genetic analysis chorionic villus samples has been described [108].

Management

Currently, there is no known therapy for MOCOD. Anecdotal reports of successful treatments include the administration of cyclic pyranopterin monophosphate, an intermediate in molybdenum biosynthesis [109], NMDA *N*-methyl-D-aspartate receptor inhibition with dextromethorphan, thiamine and cysteine supplementation and methionine-restricted diet [110].

Inborn Error of Serine Metabolism: 3-Phosphoglycerate Dehydrogenase (3-PGDH) Deficiency

Definition

Serine, a non-essential amino acid, is involved in biosynthetic reactions of glycine, cysteine, serine phospholipids, sphingomyelins, and cerebrosides, all important constituents of the brain, and is essential for normal brain function [111]. It is also a major source of one carbon donors that are required for the synthesis of purines and thymidine. Serine is a non-essential amino acid as it can be synthesized *de novo* from phosphoglycerate and glycine [111, 112]. Its biosynthesis is mediated by 3-phosphoglycerate dehydrogenase (3-PGDH). Deficiency of 3-PGDH is associated with autosomal recessive inborn error of L-serine biosynthesis, a very rare and severe neurometabolic disease characterized by low plasma and CSF levels of serine and glycine. The disorder is caused by mutations in the *PHGDH* gene (chromosome 1p12). Recently, Neu-Laxova syndrome, a more severe disorder characterized by severe fetal growth retardation, a

distinct facial appearance, ichthyosis, and neonatal death, has been found to be allelic to 3-PGDH deficiency [113].

History

3-PGDH deficiency was first reported in 1996 by Jaak Jaeken and colleagues in 2 Turkish brothers [111]. The authors noted that affected patients had low CSF levels of serine and glycine. Decreased activity of phosphoglycerate dehydrogenase in fibroblasts was noted in both sibs. They found that treatment with oral serine significantly increased CSF serine concentrations in a dose-dependent manner and coincided with cessation of seizures in one of the affected siblings.

Prevalence

The disorder is extremely rare with 14 reported cases in the literature to date.

Systemic Manifestations

All reported cases, with one exception, presented with congenital microcephaly of prenatal onset. Affected infants develop intractable seizures within weeks to months after birth and show little to no psychomotor development. There is progression to severe spastic quadriplegia during the first years of life. Growth retardation and hypogonadism are other associated features. Tabatabaie et al. described a mild form of genetically confirmed 3-PGDH deficiency in two siblings with juvenile onset of absence seizures and mild developmental delay who responded very well to serine therapy indicating the clinical variability of the disease and the importance of considering this treatable inborn error of metabolism in children with mild developmental delay [114].

Ophthalmic Manifestations

The younger brother of the two siblings reported by Jaeken in 1996 presented with bilateral congenital cataract [111]. Although this finding was not reported in subsequent case descriptions and the link between 3-PGDH deficiency and cataract is still to be confirmed, the presence of congenital cataract in an infant or child with seizures should alert the physician to the possibility of 3-PGDH deficiency, as early diagnosis and treatment is a key in the long term outcome.

Diagnosis

The hallmark of the disease is markedly low serine levels in CSF and plasma, and borderline low CSF glycine levels. Hypomyelination with near absence of white matter volume on brain MRI is a well-recognized feature [115]. This should be distinguished from the hypomyelination with cataract syndrome due to mutation in *DRCYNNB1A* 3-PGDH activity can be measured in skin fibroblasts and sequencing of *PHGDH* gene helps to confirm the diagnosis. Prenatal diagnosis by enzyme and genetic testing is available.

Management

Serine supplementation is the main treatment for 3-PGDH deficiency. This was reported in the first description by Jaeken and his colleagues when serine supplementation resulted in disappearance of seizures and correction of the low CSF level of serine [111]. However, psychomotor retardation and spastic quadriplegia were not affected probably due to the late treatment. Early treatment started prenatally has been reported to result in a better outcome [116]. Maternal L-serine supplementation initiated at 26 weeks gestation resulted in fetal head circumference increase. The child was continued on L-serine supplementation of 400 mg/kg/day. At 4 years old the girl had normal growth and psychomotor development, with follow-up MRI scans at 12 and 14 months showing no brain abnormalities [117]. Addition of glycine was shown to be of further benefit and resulted in complete caseation of seizures when added to serine at a dose of 200 mg/kg/day [118]. Treatment started late in the disease with established psychomotor delay does not reverse the developmental.

DISORDERS OF ORNITHINE AND PROLINE METABOLISM:

Hyperornithinemia (Gyrate Atrophy)

Definition

Gyrate atrophy is a rare, autosomal recessive disorder caused by deficiency of the pyridoxal phosphate-dependent, nuclear-encoded, mitochondrial matrix enzyme ornithine delta-aminotransferase (OAT), leading to markedly elevated ornithine levels (10–15-fold) in plasma and other body fluids (Fig. 13.11).

Gyrate atrophy is caused by mutations in the *OAT* gene on chromosome 10q26 [119, 120].

History

Although the first clinical description of the gyrate atrophy of the choroid and retina may date back to 1888, it wasn't until 1895 and 1896 that two ophthalmologists, Cutler and Fuchs recognized it as a distinct clinical entity. It took 85 years after the initial clinical description for the association with hyperornithinemia and ornithinuria to be recognized [121, 122]. In a routine examination of the urinary amino acids of an 8 year old boy who had choroidal degeneration of unknown etiology, an enlarged lysine-ornithine spot was found on the urine high-voltage electropherogram. Subsequent two-dimensional thin-layer and automatic ion-exchange column chromatography indicated that the spot was ornithine. The plasma ornithine concentration was ten times higher than normal, although the levels of other plasma amino acids were normal. The ocular changes were diagnosed as gyrate atrophy of the choroid and retina, and the diagnosis was confirmed by electroretinography [121]. Subsequently, in 9 patients with gyrate atrophy of the choroid and retina, plasma, urinary, CSF, and

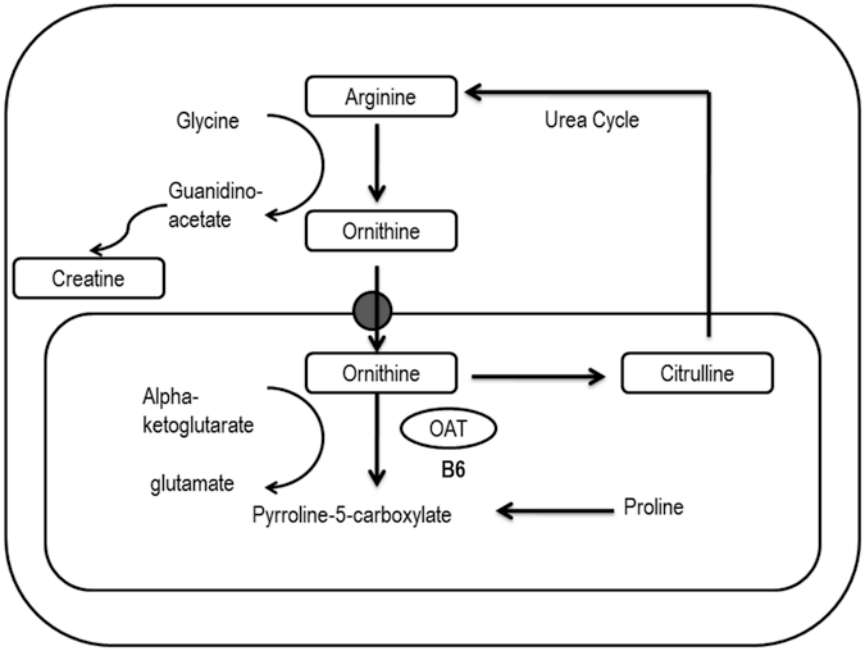

Fig. 13.11 Ornithine metabolic pathways. Ornithine produced in the cytoplasm is transferred to the mitochondrial matrix by specific transporter. Deficiency of the pyridoxal phosphate-dependent, nuclear-encoded, mitochondrial matrix enzyme ornithine delta-aminotransferase (OAT), leads to markedly elevated ornithine levels. Ornithine can be recycled via the urea cycle, by conversion to citrulline and arginine. The pathophysiology of gyrate atrophy has been attributed to direct toxic effect of high plasma ornithine concentration, reduced availability of proline, and reduced creatinine pool

aqueous humor ornithine concentrations were found to be 10–20 times higher than controls [121].

Epidemiology

The incidence of gyrate atrophy is less than one in 1,000,000, except in Finland, where the estimated frequency of gyrate atrophy is about 1 in 50,000 individuals with an estimated frequency for heterozygotes of 1 in 110 individuals [123].

Systemic Manifestations

Aside from visual impairment, patients with this condition are generally asymptomatic. Rarely, systemic signs may occasionally be seen including mild proximal weakness, mild developmental delay, cerebellar signs, and hypotonia. Brain MRI demonstrates early degenerative and atrophic changes and electroencephalogram (EEG) abnormalities may be seen [124]. Skeletal muscle biopsy shows marked abnormalities, including fatty degeneration and muscle fiber atrophy, which are out of proportion to the clinical muscle signs [125, 126]. Non-specific morphological abnormalities of the mitochondria have also been described [122]. Patchy alopecia and scaling of the scalp and skin with areas of localized hypopigmentation has been described [126].

Ophthalmic Manifestations

Patients typically report night blindness, loss of peripheral vision, or both by 10 years of age. On fundoscopy, sharply demarcated, circular areas of chorioretinal atrophy distributed around the peripheral fundus are observed that, later in the disease process, coalesce and spread posteriorly. The atrophic areas have a characteristic scalloped leading edge (Fig. 13.12a).

The macula and, central vision are often preserved into the fourth or fifth decade of life [127]. The retinal degeneration may be accompanied by vitreous syneresis, retinal vessel attenuation, loss of the retinal reflex, and mottling of the RPE. Axial moderate to high myopia with astigmatism can be seen in early childhood. Posterior subcapsular cataracts usually begin in the late teens, and fully developed posterior subcapsular cataracts with diffuse cortical opacities are almost invariably present by age 30.

Intraretinal cystoid spaces and hyper-reflective deposits in the ganglion cell layer may be demonstrable by spectral-domain optical coherence tomography (OCT), and fundus autofluorescence imaging may reveal abnormalities in areas that appear ophthalmoscopically intact (Fig. 13.12b) [128].

Elecroretinogram (ERG) shows reduction in rod and cone parameters early in the course of the disease, and may be undetectable in later stages of the disease. Electro-oculogram (EOG) reduction parallels the reduction in the rod ERG. Dark adaptation shows markedly elevated rod thresholds in areas of field corresponding to involved retina.

The pathophysiology of gyrate atrophy remains unclear, but has been attributed to direct toxic effect of high plasma ornithine concentration, reduced availability of proline [129], and deficiency of the energy-carrying phosphocreatine pool due to impaired creatine synthesis [130]. The fundus picture of gyrate atrophy can appear in the presence of normal ornithine levels; gyrate atrophy in this situation should raise the suspicion of another metabolic disorder

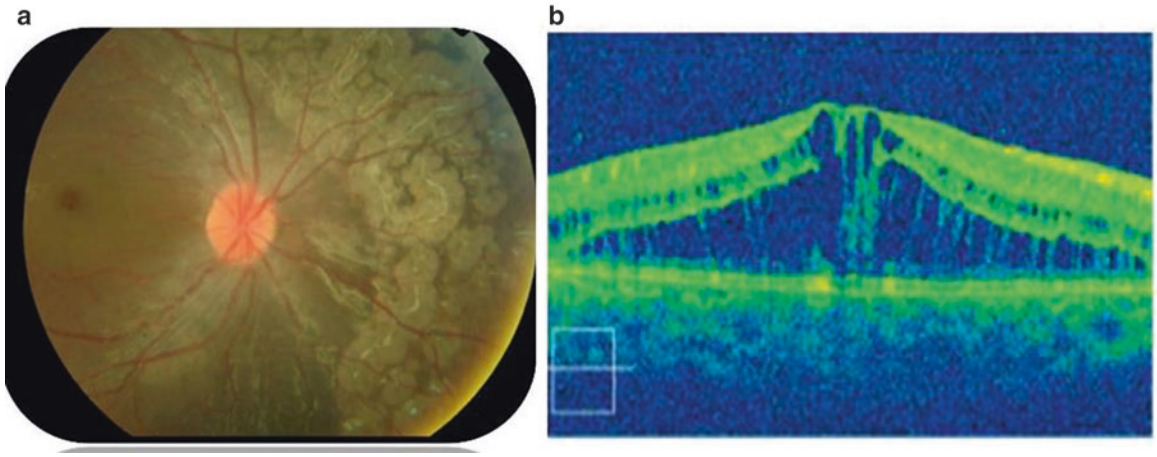

Fig. 13.12 Gyrate atrophy. (**a**) Fundus photograph showing characteristic sharply demarcated, scalloped areas of choroidal and retinal atrophy. These lesions begin in the peripheral retina and are now encroaching the posterior pole. There is waxy disc pallor and attenuation of retinal arterioles. The foveal reflex is dull due to the presence of a macular cyst. (**b**) Optical coherence tomography (OCT) reveals intraretinal cystoid spaces in the same patient

iminoglycinuria, which is characterized by proline deficiency [129, 131, 132].

Diagnosis

The biochemical hallmark of GA is hyperornithinemia with levels that are 10–15 times normal (400–1400 μM). Urine amino acids show evidence of spill-over ornithinuria. Ammonia, and plasma glutamine are normal, and urine has no detectable homocitrulline. These three features distinguish gyrate atrophy from hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome. Urine orotic acid excretion is also increased in HHH syndrome. High levels of ornithine also act as a feedback inhibitor on glycine transamidase which plays a role in the generation of creatine, with resultant low creatine levels. The diagnosis of gyrate atrophy can be confirmed by measurement of OAT enzyme activity in skin fibroblast or lymphocytes. In addition to the importance for counseling, defining the causative mutations may be helpful prognostically [120]. Degree of expression of the *OAT* gene and OAT enzyme synthesis has been linked to degree of pyridoxine responsiveness in patients with gyrate atrophy [133]. Prenatal diagnosis by estimating OAT enzyme activity in amniotic fluid is available [134].

Management

If started at an early age, long-term substantial reduction of plasma ornithine levels may appreciably slow the progression of the chorioretinal disease and, to a lesser extent, the progressive loss of retinal function [135, 136]. A number of general approaches to therapy have been explored, including stimulation of residual OAT enzyme activity with pharmacologic doses of pyridoxine, reducing intake of arginine (the precursor of ornithine), and creatine and/or proline supplementation. Restriction of arginine has been shown to slow the development of retinal lesions in animal and human studies [135–138]. Among Finnish patients, less than 5% have been reported to be responsive to pyridoxine (vitamin B6), a cofactor for OAT activity, with reduction in plasma ornithine levels [139]. The frequency of pyridoxine-responsive gyrate atrophy in other populations is unknown. A 2-week trial of pyridoxine therapy (300–600 mg/day) is recommended for all newly diagnosed patients to determine their responsiveness [140]. Creatine supplementation has been tried in some patients based on the hypothesis that creatine deficiency plays a role in the pathogenesis of the disease Management. Although it may stabilize the occasional reported skeletal muscle abnormalities, progression of the chorioretinal degeneration was not prevented [141]. Deficiency of local retinal proline synthesis has been hypothesized to play a role in the chorioretinal degeneration [142], and proline supplementation may slow the progress of retinal degeneration in some patients [135].

Disorders of Amino Acid Transport: Oculocerebrorenal Syndrome of Lowe (OCRL; Lowe Syndrome)

Definition

Oculocerebrorenal syndrome of Lowe (OCRL) is a metabolic disorder primarily affecting the eyes, brain and the kidneys, and is characterized by congenital cataracts, congenital glaucoma, neonatal or infantile hypotonia, intellectual impairment, behavioral anomalies, and renal tubular dysfunction (Fanconi syndrome). It is an X-linked disorder and is caused by mutation in the *OCRL1* gene (chromosome Xq26.1) which mediates the function of the phosphoinositide-metabolizing

enzyme phosphatidylinositol 4,5-biphosphate 5-phosphatase or OCRL-1, localized in the Golgi complex [143]. Phosphoinositide, a membrane phospholipid, plays a key role in cellular physiology and loss of OCRL-1 impacts upon a large number of cellular processes [144]. Lowe syndrome occurs almost exclusively in males.

History

The oculocerebrorenal syndrome of Lowe (OCRL), was first recognized as a distinct disease in 1952 by Lowe, Terrey and MacLachlan in three male children with organic aciduria, decreased renal ammonia production, glaucoma and mental retardation.

Epidemiology

Lowe syndrome has an estimated prevalence of 1 in 500,000 people.

Systemic Manifestations

Generalized hypotonia is noted at birth and is of CNS origin. Deep tendon reflexes are usually absent. Early onset hypotonia contributes to feeding difficulties, problems with breathing, and delayed development of motor skills such as sitting, standing, and walking. Hypotonia may slowly improve with age, but normal motor tone and strength are never achieved [145]. Almost all affected males have some degree of intellectual disability ranging from mildly to severely impaired. About one half of all patients with Lowe syndrome have seizures by the sixth year of life. A high prevalence of maladaptive behaviors, including tantrums, stubbornness, and stereotypy (complex repetitive behaviors) have been observed in patients with Lowe syndrome and is indicative of a specific effect of the mutated *OCRL* gene on the central nervous system [146]. Brian MRI may show two patterns of lesions: hyper-intensities on T2-weighted images, and periventricular cystic lesions. Initially believed to represent an accumulation of phosphatidylinositol 4,5-biphosphate, proton MR spectroscopy studies suggest the hyperintense lesions to be gliotic in nature, possibly representing a non-specific end stage of a demyelinating process [147].

Affected males have varying degrees of proximal renal tubular dysfunction of the Fanconi type. Patients are asymptomatic due to renal insufficiency in the first few months of life [145]. Symptoms appear by 6–12 months of age, with failure to thrive due to bicarbonate wasting and renal tubular acidosis, phosphaturia with hypophosphatemia and renal rickets, amino aciduria, proteinuria, sodium and potassium wasting, and polyuria. Chronic tubular injury usually results in progressive renal failure and end-stage renal disease by the second decade of life [145].

Most patients with Lowe syndrome have a typical facial appearance consisting of deep-set small eyes, frontal bossing, and an elongated face. Patients often exhibit non inflammatory arthropathy, joint swelling, and contractures. Scoliosis is frequently seen.

Ophthalmic Manifestations

Cataracts, often initially posterior polar, are a hallmark of Lowe syndrome and are seen in all affected males at birth. They are often associated with miosis, shallow anterior chamber, and microphthalmia. Glaucoma is detected in 50 % of affected infants within the first year of life, before or after cataract surgery [145]. Despite optimal management, corrected acuity is rarely better than 20/100 in boys with Lowe syndrome [145]. Characteristic, multiple (15 to >100), punctate radially oriented cortical lenticular opacities ('snowflake opacities') may be seen in 95 % of post-pubertal carrier females. Slit-lamp examination is considered a highly accurate and sensitive first-line method to ascertain the female carrier state (see renal chapter) [148, 149].

These lens changes usually have no visual impact. Approximately 10 % of carriers have a dense, central precapsular white cataract at the posterior pole of the lens that may be visually significant if it is large [145]. Carrier females develop lens changes by the latter half of the first decade. The absence of lens opacities does not exclude carrier status.

Other ocular manifestations that can cause visual impairment in affected boys include keloids that may spontaneously form over the cornea or the conjunctiva in one or both eyes without preceding trauma, and retinal dystrophy.

Diagnosis

The diagnosis of Lowe syndrome is suspected clinically in males who have a combination of bilateral cataracts, infantile hypotonia, delayed development. Urine amino acids can reveal the proximal renal tubular transport dysfunction. The diagnosis is confirmed by demonstrating reduced (<10 % of normal) activity of inositol polyphosphate 5-phosphatase (OCRL-1) in cultured skin fibroblasts or by molecular genetic testing. Mutations of the *OCRL* gene can be detected in approximately 95 % of affected males and carrier females. Mutations in this gene have been identified in a subset of patients with another X-linked disease called Dent-2 disease characterized by proximal renal tubulopathy, but Dent-2 disease patients do not manifest extra-renal manifestations such as cataract or hypotonia. Prenatal diagnosis of Lowe syndrome is possible by biochemical assay for deficiency of phosphatidylinositol 4,5-biphosphate 5-phosphatase in cultured fibroblasts, or by molecular analysis in families in which the mutation is already known. Penetrance in Lowe syndrome is usually complete, with similar phenotype in affected males within any given family.

Management

Treatment of patients with Lowe syndrome involves management of renal tubular acidosis. Careful monitoring of

acid–base status and electrolyte levels is required. Acute illness with attendant risk of dehydration and electrolyte abnormalities needs aggressive intravenous fluid and electrolyte therapy. Other measures include vitamin D supplementation for rickets, nasogastric tube feedings or feeding gastrostomy with or without fundoplication to achieve appropriate nutrition in infancy, hormonal therapy for cryptorchidism, growth hormone therapy for short stature, medication for behavioral problems, and occupational and speech therapy. Treatment of end stage renal disease with chronic dialysis and renal transplant in selected individuals may be considered.

Early surgery for visually significant cataracts is indicated in order to avoid amblyopia. Contact lenses are best avoided because of associated risk of corneal keloid formation. Intraocular lens implants carry an increased risk of glaucoma. Therefore aphakic spectacles may be the best choice for vision rehabilitation. Glaucoma in Lowe syndrome is typically difficult to treat, and may necessitate drainage devices. Routine ophthalmic evaluations with attention to measurement of intraocular pressure is recommended. To date, there is no effective treatment for conjunctival and corneal keloids in patients with Lowe syndrome.

Section Two: Disorders of Carbohydrate Metabolism

Disorders of Galactose Metabolism (Galactosemia)

Definition

Galactosemia comprises a group of inherited disorders affecting galactose metabolism (Table 13.2). Galactose is metabolized by a series of sequential reactions collectively known as the Leloir pathway (Fig. 13.13).

Table 13.2 Disorders of Galactose Metabolism

Type	Deficient enzyme	Description	Gene	Locus
I	Galactose-1-phosphate uridyltransferase (GALT)	Systemic: normal at birth. Food intolerance, failure to thrive, lethargy, hypotonia, liver and renal dysfunction within days after ingestion of galactose (breast milk or formula). Life threatening without dietary galactose restriction	*GALT*	9p13
Classic galactosemia		Ocular: congenital cataract (oil-droplet)		
II	Galactokinase (GALK)	Systemic: Nil	*GALK1*	17q25
		Ocular : Juvenile cataract		
III	UDP-galactose 4′-epimerase (GALE)	Spectrum of involvement	*GALE*	1p36
		Systemic: Asymptomatic to features similar to Classic galactosemia.		
		Ocular : Nil to congenital cataract		

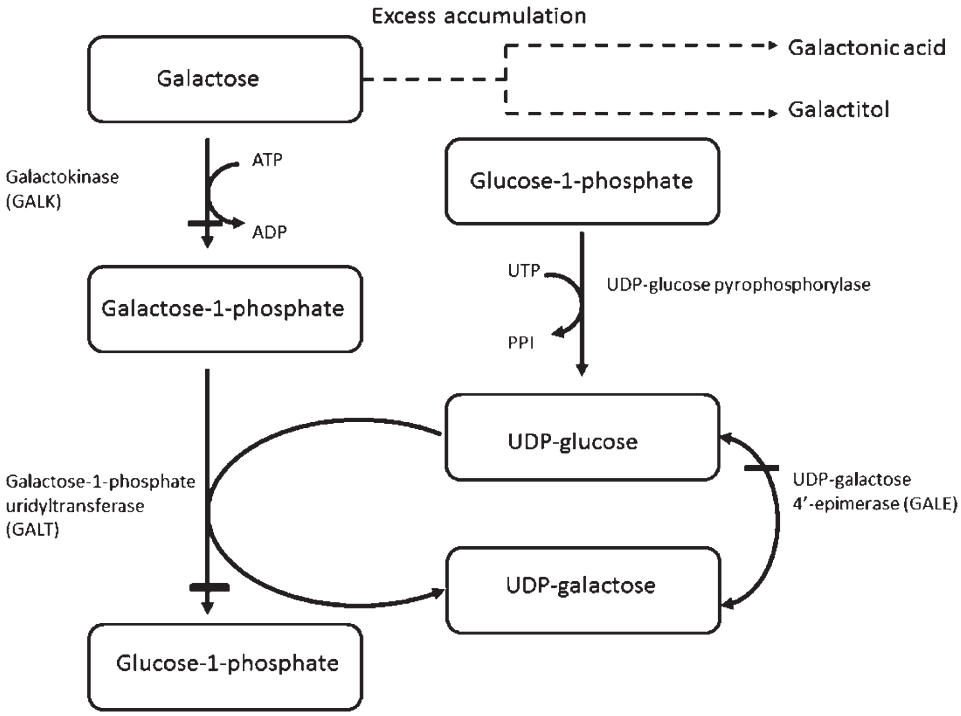

Fig. 13.13 Galactose metabolism, Leloir pathway. There are three major forms of galactosemia. Classic galactosemia occurs due to galactose-1-phosphate uridyltransferase (GALT) deficiency. Other forms of galactosemia occur due to UDP-galactose 4′-epimerase (GALE) deficiency, and galactokinase (GALK) deficiency

Depending on the specific enzyme that is deficient, three major forms of galactosemia exist. Classic galactosemia, the most common and most severe form, is caused by galactose-1-phosphate uridyltransferase (GALT) deficiency. The two other forms are caused by galactokinase (GALK) and UDP-galactose 4-epimerase (GALE) deficiency (Table 13.2).

In patients with galactosemia, galactose accumulates in tissues and gets converted to galactitol or galactonate under the action of aldose reductase (AR) and galactose dehydrogenase (GDH), respectively. Galactosemia is an autosomal recessive condition that is caused by mutations in the *GALT*, *GALK1*, and *GALE* genes that code for enzymes essential for galactose metabolism.

History

Galactosemia was first discovered by von Ruess in 1908 in a breast-fed infant with failure to thrive, enlargement of the liver and spleen, and galactosuria. This infant ceased to excrete galactose through the urine when milk products were removed from the diet. The first detailed description of galactosemia was given by Mason and Turner in 1935. Leloir described the metabolism of galactose and was awarded the Nobel prize in chemistry in 1970 for his work. Another major break-through was when it was first found to be detectable through a newborn screening method by Guthrie and Paigen in 1963. Galactosemia was the second disorder found to be detectable through newborn screening methods by Robert Guthrie.

Epidemiology

Classic galactosemia occurs in 1 in 30,000–60,000 newborns. The frequency of classic galactosemia in Ireland is 1:16,476 [150]. The other forms of galactosemia are less common. A population-based study in the United States reported a frequency of 1 in 1000, 000 live births for GALK deficiency [151], while the frequency was reported to be 1 in 10,000 in individuals of Romani origin [152]. Frequency is also increased in French Canadians. The frequency of GALE deficiency is more difficult to establish given clinical heterogeneity associated with this condition. One estimate from a newborn screening study predicts this condition to affect 1 in 70, 000 Caucasians [153].

Systemic Manifestations

(a) Classic Galactosemia:
Infants with classic galactosemia and complete or near-complete enzyme deficiency are normal at birth, but present with life-threatening illness within days after ingestion of galactose through breast milk or usual infant formula. The initial symptoms include poor feeding, vomiting, failure to thrive, lethargy, jaundice, hepatomegaly, coagulopathy, hypoglycemia, renal tubular dysfunction, hypotonia, and sepsis (particularly *E. coli* septicemia*)* [154]. Even when patients are recognized and treated early, some long-term complications continue to be encountered. About 80 to more than 90 % of affected females develop hypergonadotrophic hypogonadism [155–157]. Developmental verbal dyspraxia is also frequently encountered [158]. Classic galactosemia is associated with variability in chronic complications and long-term outcomes. Even individuals who have not been sick in the newborn period and who were begun on a lactose-free diet from birth, experience long-term complications such as verbal dyspraxia, motor abnormalities and hypergonadotrophic hypogonadism [159]. It has been suggested that long-term complications may result from endogenous galactose synthesis.

(b) Galactokinase Deficiency:
The only consistent clinical complication of GALK deficiency is cataract. Rare systemic complications likely represent coincidental findings. However, pseudotumor cerebri has been reported in more than one infant [160, 161], and it is postulated to be due to the same mechanism responsible for cataract development [162].

(c) UDP-Galactose 4′-Epimerase Deficiency:
GALE deficiency is clinically heterogeneous. Most patients with GALE deficiency are asymptomatic. Deficiency of GALE in these patients is restricted to erythrocytes and circulating leukocytes. Hence, they are said to have peripheral epimerase deficiency [163–165]. Generalized epimerase deficiency is extremely rare, and these patients may present with symptoms similar to patients with classic galactosemia [166–168].

Ophthalmic Manifestations

Cataract has been reported as the main ophthalmic finding of galactosemia [169]. It is thought that 10–30 % of newborns with classic galactosemia develop cataracts in the first few days or weeks of life. Galactitol accumulates in the lens and causes an increase in intracellular fluid and lens swelling. In the early stages refractive changes in the lens nucleus leads to an "oil-droplet" appearance on red-reflex testing (Fig. 13.14).

This however, is a nonspecific sign and may occur in many causes of cataract and even corneal disease. Nuclear abnormalities of galactosemia are seen within days or weeks of birth. Progressive accumulation of galactitol leads to disruption of the lens structure and lamellar cataract formation. Most newborns develop cataract only after exposure to galactose from the diet. Early onset juvenile cataract is the most consistent clinical complication of GALK deficiency. Vitreous hemorrhage has been reported in infants with galactosemia and has been attributed to retinal vascular fragility and coagulopathy [170–172].

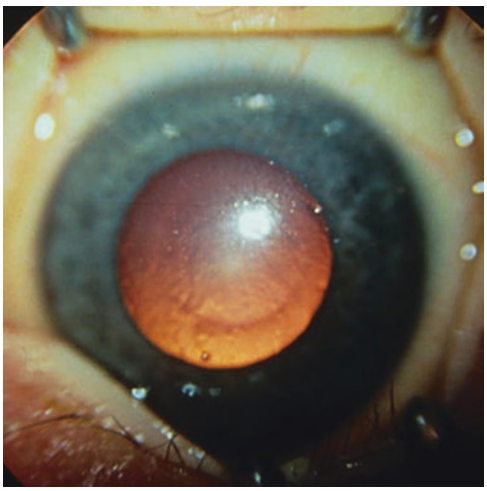

Fig. 13.14 Galactosemia cataract. Typical "oil droplet" red reflex due to cataract in Galactosemia. Courtesy: Prof. Alex V. Levin

Diagnosis

The presence of a reducing substance in a urine sample may be the first diagnostic clue of this disorder. No galactose will be present in the urine if the child is on intravenous fluids, as will be often the case during a neonatal crisis. In addition, other reducing sugars such as glucose can give a positive test. Confirmation involves quantitation of plasma and urinary galactose and galactitol. The gold standard for diagnosis of classical galactosemia is measurement of GALT activity in erythrocytes. Both GALT deficiency and GALK deficiency cause elevation of urinary galactitol. However, the former is also associated with elevated galactose-1-phosphate, which is not seen with the latter given the nature of the enzymatic block. GALK enzyme activity has been assayed in fibroblasts and cultured amniocytes [173, 174]. Elevated galactose-1-phosphate levels with normal GALT enzyme activity should prompt measurement of GALE enzyme activity in erythrocytes. Mutation analysis by sequencing all coding exons and flanking intron sequences of the *GALT/GALK/GALE* genes may be performed.

Classic galactosemia is part of the newborn screening programs of many countries. If performed on, or before, the 5th day of life, neonatal screening may prevent the acute morbidity and mortality of the disease. However, a number of long-term complications cannot be prevented [159].

Management

The mainstay of therapy in patients with classic galactosemia is galactose-free diet. Additional supportive therapies are required for complications sepsis, and coagulopathy. As soon as the diagnosis is suspected, galactose must be restricted from the diet, and resumed only when a galactose disorder has been excluded. Galactose-free diet provided during the first few days of life leads to resolution of the neonatal signs, and the complications of liver failure, sepsis, and neonatal death are prevented.

Treatment of GALK deficiency also requires life-long galactose-free diet, ideally started within the first few days to few months of life for the cataract complication to be preventable or reversible. The peripheral form of GALE deficiency requires no specific therapy, while patients with the generalized severe form are usually treated with galactose-restricted diet, although questions remain about how strict this restriction should be and for how long these patients should be treated.

With dietary treatment of the metabolic disease, most cataracts will resolve spontaneously. In rare instances cataract surgery may be needed in the first year of life. Periodic eye exams are advocated to monitor for recurrence or progression, and may serve as an indicator of dietary control. One study reported absence of correlation between occurrence of cataract and dietary control, and suggested that regular life-long ophthalmic exam of patients with classic galactosemia may be unnecessary [175].

Section Three: Disorders of Fatty Acid Metabolism

Mitochondrial Trifunctional Protein (MTP) Deficiency and Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency

Definition

Mitochondrial trifunctional protein (MTP) is a protein complex bound to the inner mitochondrial membrane that mediates β-oxidation of long chain fatty acids. Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) is one of the three enzyme activities of the MTP. Fatty acid oxidation (FAO) is a major energy-producing pathway in several human tissues, including the eye [176, 177]. MTP deficiency is caused by mutations in the *HADHA* or *HADHB* genes. LCHAD deficiency is caused by mutations in the *HADHA* gene.

History

LCHAD deficiency was first described in 1989 by Wanders and his colleagues in an infant with sudden infant death syndrome [178]. The same group identified several other cases over the following few years. In 1992, the trifunctional protein complex was identified along with identification of patients deficient in the three enzyme-subunits [179–181]. Pons et al. in 1996 provided the first description of retinopathy in patients with LCHAD deficiency [182].

Epidemiology

Data from newborn screening in the states of Oregon, Idaho, Nevada, Alaska, and Hawaii indicate a minimal disease

frequency for MTPD and LCHADD to be around 1/200,000. It had been well recognized that a single mutation in the *HADHA* gene, c.1528G>C, is prevalent in patients of European descent with significant variation of reported allele frequencies ranging from1:680 in the Netherlands [183], to 1:217 in Poland and reaching as high as 1:73 in one region of Poland [184], but almost absent in Asians populations [185].

Systemic Manifestations

LCHAD deficiency usually presents with neonatal or early infantile episodes of hypoketotic hypoglycemia that are associated with liver dysfunction, lactic acidosis and cardiomyopathy. The course is potentially fatal if aggressive management is not implemented immediately. Some patients have a more insidious presentation with failure to thrive, hypotonia, and cheolestasis with or without cardiomyopathy. A few patients develop liver cirrhosis [186]. Patients remain at risk of episodes of acute metabolic decompensations with hypoketotic hypoglycemia, liver dysfunction or acute rhabdomyolysis that are mostly related to periods of increased energy demands such as childhood illnesses or non-compliance to the dietary therapy. Some patients with MTP deficiency may have a similar or even earlier and more severe presentation than LCHADD. Other MTP deficient patients have a milder neuropathic phenotype with exercise induced rhabdomyolysis and peripheral neuropathy [187].

Ophthalmic Manifestations

A unique retinopathy develops in MTP and isolated LCHAD deficiency. Degeneration of the RPE is the primary defect in LCHAD deficiency, which secondarily disturbs either the function or the maintenance of the neural retina and the underlying choroid, especially the choriocapillaris. Alternatively, the pigment dispersion may be caused by the failing choroidal circulation. The primary role of the RPE or choroid in the pathogenesis of the ocular changes in LCHAD deficiency is supported by the initially normal responses in the ERG at a time when the pigmentary changes in the fundus are already widespread [188, 189].

In LCHAD deficiency, pigment changes in the retina are observed in more than 50 % of the patients by the age of 2 years [190], and up to 30–50 % of patients develop irreversible retinopathy. Retinopathy with vision loss occurs in 5–13 % of patients with MTP deficiency [191]. The progression of retinopathy tends to be much slower with less functional vision loss in patients with MTP deficiency as compared to patients with selective loss of the LCHAD activity [192].

Tyni et al. described retinal findings in 15 patients with LCHAD deficiency and described four stages of LCHAD retinopathy [189]. Stage 1 is characterized by normal retinal function and a hypopigmented fundus. Stage 2 is characterized by the appearance of pigment clumping in the fovea as well as progressive retinal dysfunction as measured by ERG. However, visual acuity remains intact. This stage may be seen in affected infants as early as 4 months old [176, 189]. In stage 3, central pigmentation disappears. Circumscribed chorioretinal atrophy, occlusion of choroidal vessels, and deterioration of central vision, often with relative sparing of the peripheral fundus occurs. ERG readings continue to decline, with markedly reduced amplitudes and prolonged implicit times, or become unrecordable. In stage 4, the posterior pole of the eye loses all photoreceptors, most of the choroidal vessels, and central vision is lost [189]. The observations made on long-term survivors in that series included progressive axial myopia starting at 6 and 12 years and developmental cataract [189]. Other reports on long-term survivors indicated a milder course with slower development of circumscribed atrophy of the choroid, retinal pigment epithelium, and retina [193].

Gillingham et al. showed that high level of plasma hydroxyacylcarnitines was associated with severe chorioretinopathy and was correlated negatively with maximum ERG amplitude [192].

Diagnosis

LCHAD deficiency, a potentially lethal disease, is sometimes difficult to diagnose. Unusual chorioretinal findings should alert the ophthalmologist to the possibility of LCHAD deficiency, especially if there is a history of neonatal hypoglycemia or failure to thrive.

The hallmark biochemical feature of this condition is acute hypoketotic hypoglycemia. Urine organic acid analysis and acylcarnitine profiling is diagnostic. During acute episodes, plasma carnitine levels are low and long-chain acylcarnitine levels are increased. In countries with expanded newborn screening programs, detection of LCHAD/MTP deficiency is made through acylcarnitine profiling in dried blood spots. Confirmation of the diagnosis in patients with positive screening or in symptomatic patients regardless of screening is by plasma acylcarnitine profile with characteristic elevation of C18-OH, C16-OH and C18:1-OH acylcarnitines. Confirmation and further delineation between LCHAD and MTP involves enzyme assays on cultured skin fibroblasts or gene sequencing.

Management

Patients with LCHAD/MTP deficiency require a long term dietary management plan to ensure provision of adequate calories. This includes avoidance of prolonged fasting to prevent endogenous lipolysis, along with restriction of long chain fat intake, substituting with medium chain fatty acids to bypass the metabolic block. In neonates and young infants, breast feeding is avoided and replaced by medium chain fatty acid-based infant formula. Frequent regular feeds during the day with continuous overnight tube feeding that can be replaced with a bedtime uncooked cornstarch as the child

grows older is recommended. After weaning, dietary fat should contain 20% medium chain fat and 10% long-chain fat with a minimum of 4% coming from essential fatty acids. Optimal control of the disease is associated with lower levels of hydroxyl-acylcarnitine and has been shown in several studies to be associated with slower progression of retinopathy [176, 192, 194].

Section Four: Disorders of Energy Metabolism

The mitochondria are the major source of energy production in the body. Mitochondrial dysfunction therefore, leads to energy crisis within cells and hence to multiple organ dysfunctions vastly ranging in distribution and severity. Tissues with high-energy demands are mostly affected by mitochondrial dysfunction. The brain, liver, heart, eye and the skeletal muscles are among the organs usually involved in mitochondrial diseases. The extraocular muscles and levator muscles are metabolically active tissues and their dysfunction may be the initial clinical presentation in these conditions. The retina has a very high-energy demand and is vulnerable to mitochondrial dysfunction. Photoreceptors are among the most metabolically active cells in the body. The photoreceptors contain a dense concentration of mitochondria to ensure efficient phototransduction using oxidative phosphorylation [195]. Retinal ganglion cells also have a dense mitochondrial population to efficiently transmit the action potentials required by the unmyelinated proximal parts of their axons [196]. It is therefore expected that ophthalmic manifestations will constitute an important element in the disorders of mitochondrial function, making them in many instances, the sole and initial clinical presentation.

Mitochondrial dysfunction can result from mutations in the nuclear or mitochondrial DNA. Mitochondrial DNA mutations are classified into deletions, depletions and point mutations. Mutations in nuclear DNA genes typically follow Mendelian patterns of inheritance while mtDNA mutations are characterized by maternal inheritance. Thus, mitochondrial mutations are matrilineal or *de novo*. The random distribution of mtDNA during cell division results in the presence of a mutant and normal (wild type) mtDNA within the same cell. This is called heteroplasmy. Heteroplasmy adds complexity to mitochondrial disorders with largely variable and unpredictable clinical presentations, course and outcome.

Leber Hereditary Optic Neuropathy (LHON) and Autosomal Dominant Optic Atrophy (DOA)

LHON and DOA are mitochondrial optic neuropathies. The two conditions share similarities in clinical presentation and ophthalmic findings despite their different genetic etiologies. The retinal ganglion cells (RGCs) that form the optic nerve are primarily targeted with special involvement of the papillomacular bundle. Patients with LHON and DOA manifest central visual loss, visual field defects and color vision abnormalities.

Leber Hereditary Optic Neuropathy (LHON)

Definition

LHON is characterized by acute and painless central vision loss of both eyes in a sequential fashion over a period of days to months [197]. All identified mutations, are located within mitochondrial DNA (mtDNA) genes encoding subunits of complex 1 of the respiratory electron transfer chain implying that LHON is primarily related to complex 1 dysfunction with subsequent decreased ATP production and elevated levels of oxidative stress [198]. Several point mutations in the mitochondrial genome have been identified in patients with LHON, but over 95% of individuals with LHON have one of three 'primary' LHON point mutations in mtDNA: m.3460G>A in the *ND1* gene (13%), m.11778G>A in the *ND4* gene (69%), or m.14484T>C (14%) in the *ND6* gene [199]. Secondary LHON-associated mtDNA mutations prevalent in the general population that have been identified at higher frequencies in patients with LHON include m.4216T>C, m.13708G>A, and m.15257G>A [200]. Although inheritance is always maternal, incomplete penetrance, variable expression and a predilection for males are well known. Male predominance has been attributed to existence of an X-linked susceptibility gene acting in synergy with the mtDNA mutation to precipitate visual loss. Approximately 50% of males with an LHON mutation will develop disease while only 10% of females become affected [201]. This has been attributed to the presence of modifier mutations or polymorphisms located on the nuclear and mitochondrial genomes. Various environmental modifiers have been investigated with tobacco smoking and alcohol intake being the most identified risk factors [202]. Kirkman et al. found a strong association between visual loss and smoking that was independent of gender and alcohol intake [203]. Genotype-phenotype correlation is established in LHON. LHON patients carrying m.11778G>A mutation have the least visual recovery, those who carry the m.14484T>C mutation have the greatest visual recovery and the m.3460G>A mutation carriers are in between [204–206]. Age of onset is another prognostic indicator as early age of onset of visual loss is associated with better visual outcome [207].

History

LHON was first described by Theodor Leber in 1871. Erickson in 1972 noted that LHON is maternally inherited. In 1980 Gilles et al. explained that there is cytoplasmic transmission of a genetic error in the mitochondrial genome [208]. In 1988 Wallace reported the 11778G>A mutation [209].

Epidemiology

An epidemiological study in North England indicated that LHON is the most frequent mitochondrial disorder and estimated the prevalence of LHON in that population to be 1 in 31,000 [201]. Two other studies from Holland and Finland showed prevalence of 1 in 39,000 and 1 in 50,000 respectively [210, 211]. In Australia, it was estimated that 2 % of optic atrophy is due to LHON [212].

Systemic Manifestations

Although LHON is primarily an ocular disease, LHON plus syndrome occurs when LHON is accompanied by asystemic presentation. Cardiac arrhythmias and neurological abnormalities are among the main associations. Peripheral neuropathy, myopathy, dystonia, and myoclonus have been reported in LHON patients [213, 214]. Genotypic –phenotypic association has been observed in LHON plus syndromes where systemic involvement occurs with specific mtDNA variants such as m.44160T>C, m.1169A>G, m.14596tT>A, and m.14459G>A [205, 215]. An overlap of systemic presentation between LHON and MELAS has been observed in patients carrying two point mutations affecting the respiratory chain complex I activity namely m.3376G>A and m.3697G>A [205].

Harding et al. 1992 described a combination of LHON and demyelinating disease in a female carrying the m.1178G>A mutation [216]. Similar observation was shown later on more female patients with MRI findings of periventricular white matter lesions and oligoclonal band in CSF resembling MS were found in these females after the onset of visual loss [217].

Ophthalmic Manifestations

The clinical presentation of LHON can be divided into three phases; the pre-symptomatic phase, the cute phase and the chronic phase [201]. In the acute phase, the patient usually presents with acute onset painless loss of central vision that becomes worse over a period of 4–6 weeks. Both eyes are involved at the onset in about a quarter of cases and the other eye will follow and become affected within the next 6–8 weeks in the remainder. Rare cases of unilateral LHON have been reported in literature. The majority of patients present in the second or the third decades of life and by the age of 50 years, 90 % of patients carrying the LHON mutation will experience visual dysfunction [201, 210]. The visual acuity loss may be to less than 6/60 and patient will have either dense central or cecocentral scotomas. The pupillary reaction is often normal compared to the extent of the visual loss. The fundus will show typical vascular tortuosity of the central retinal vessels, retinal nerve fiber layer swelling and circumpapillary telangiectatic microangioapathy [206]. Twenty percent of patients with LHON might have normal looking optic discs [201], and retinal nerve fiber layer (RNFL) edema without leakage on fluorescein angiography. The angiographic picture and the RNFL swelling can be present in asymptomatic female carriers [218]. Abnormal color discrimination along the blue-yellow axis, minor visual field defects, reduced contrast sensitivities and abnormal visual evoked potential have been reported in this phase as well [201]. Approximately 6 weeks from the acute phase, the optic disc becomes pale with the temporal side being usually more affected as a result of nerve fiber loss along the papillomacular bundle. In the chronic phase, optic disc cupping will be apparent reflecting severe retinal ganglion cells loss and the chronicity of the LHON [199].

Following LHON acute attacks, patients suffer severe and permanent visual impairment with minimal improvement of vision thereafter. The end point of LHON is atrophic optic nerve with persistent visual acuity and field's loss. The pupillary reaction is spared in LHON [199].

Spontaneous recovery has occasionally been reported in patients with LHON [207, 219].

Diagnosis

The clinical presentation is usually typical and may be supported by family history consistent with maternal inheritance. Up to 40 % of patients have no family history. Diagnosis is established by the identification of the disease-causing mutation through targeted mutation analysis for known LHON mutations or whole mtDNA genome sequencing. The fact that 85–90 % of patients with LHON harbor homoplasmic mutations makes analysis of DNA extracted from peripheral blood highly sensitive.

Management

LHON was until very recently considered an untreatable disease. Recent clinical data with redox-active electron carriers have demonstrated that protection and even recovery of vision may be a possibility. Use of the coenzyme Q10 derivative, idebenone, continues to show evidence as a possible treatment for LHON patients although results have not been entirely consistent. Klopstock *et al.* had shown through a placebo-controlled, randomized, double-blind study that a dose of 900 mg daily of idebenone resulted in protection against loss of vision and improvement of visual acuity. The treatment effect persisted even 30 months after termination of treatment [220]. Another compound that is being currently investigated as a promising antioxidant agent is α-tocotrienol-quinone (EPI-743) [221]. Gene therapy clinical trials either to introduce the defective gene or entire complex 1 are underway. Preclinical data of the *ex-* and *in-vivo* expression of the wild-type form of the *ND4* gene using AAV vectors are promising and hopefully may change the natural history of the disease.

Autosomal Dominant Optic Atrophy (ADOA)

Definition

Autsomal dominant optic atrophy (ADOA) is characterized by bilateral and symmetric optic nerve pallor associated with insidious decrease in visual acuity usually between ages 4 and 6 years, visual field defects, and color vision defects [222]. There are at least four known nuclear loci and three identified genes related to the disease with *OPA1* gene being the gene responsible for the 50–60 % of familial cases. *OPA1* encodes for a transmembrane protein embedded within the mitochondrial inner membrane. When mutated it results in mitochondrial fragmentation, mitochondrial dysmorphism with balloon like enlargement and disorganization of cristae, with para-crystalline inclusion bodies. *OPA1* mutations have also been detected in patients with AD-hereditary spastic paraplegia (HSP) and patients with visual loss and MS-like illness. Poor visual prognosis is observed among those with DOA plus variants. This indicates that *OPA1* mutation may not only target the RGC but also extraocular muscles, skeletal muscles and other neural tissues [201]. The gene for type 2 optic atrophy (OPA2) is located on the X chromosome and hence is not included with ADOA despite the clinical similarity. The gene which causes OPA3 encodes for a mitochondrial protein that has been associated with autosomal recessive optic atrophy, premature cataract, and 3- methylglutaconic aciduria. Other loci OPA4-6 are known but the genes have not been cloned.

History

ADOA was first described clinically by Batten in 1896 and named Kjer's optic neuropathy in 1959 after Danish ophthalmologist Poul Kjer, who studied 19 families with the disease. In 2000 a protein encoded by the nuclear gene *OPA1* was identified as the cause of ADOA [222].

Epidemiology

The prevalence of ADOA in north England is 1 in 35,000. The estimated prevalence of OPA1 is 1:50,000 in most populations, 1 in 35,000 in Northern England or as high as 1:10,000 in Denmark.

Systemic Manifestation

OPA1 disease may also involve neuromuscular manifestations in up to 20 % of patients due to secondary impairment of mitochondrial respiratory chain complex IV. In a multicenter study performed by Yu-Wai-Man et al. 2010, bilateral sensorineural deafness in late childhood to early adulthood was the most frequently observed extraocular feature of ADOA [223]. They noted also that ataxia, myopathy, peripheral neuropathy and progressive ophthalmoplegia (PEO) also developed from the third decades in those patients.

Ophthalmic Manifestation

ADOA patient usually presents with gradual loss of vision occurring in the first or second decades of life.

The visual acuity is variable, ranging from 6/6 to hand motion. Later progressive loss of vision is seen in 50–75 %. Most of the patients will have generalized dyschromatopsia. The primary defect in ADOA is in the papillomacular bundle which will result in central, centrocecal and paracentral scotoma sparing peripheral field. The optic disc pallor usually involves the whole neuro-retinal rim (NRR) but can be more obvious in the temporal side of the disc, often resulting in a typical sectorial atrophy known as "pie in the sky" atrophy. Approximately one third of affected patients may have subtle changes in optic disc that are passed as normal.

Diagnosis

The diagnosis of OPA1 is based on a combination of family history, clinical findings, and visual electrophysiologic studies. Visual evoked potentials (VEPs) are typically absent or delayed; pattern electroretinogram (PERG) shows an abnormal N95:P50 ratio. The N95 component of the PERG is specific for the retinal ganglion cell; reduction in amplitude of the N95 wave supports a ganglion cell origin for the optic atrophy. Optical coherence topography (OCT) is useful in monitoring retinal nerve fiber layer (RNFL) thickness. Molecular genetic testing is confirmatory. *OPA1* is the only gene known to be associated with ADOA.

Management

Management includes low vision aids for decreased visual acuity. Annual ophthalmic and hearing evaluation is indicated. Smoking, and excessive alcohol intake is best avoided.

IV.2. Mitochondrial Encephalopathy, Lactic Acidosis and Stroke Like Episodes (MELAS)

Definition

MELAS is a neurodegenerative disease most commonly occurring in children but can present in any age group. It involves many organs in the body but it particularly affects the brain and muscles. MELAS is caused by mutation in any of several mitochondrial genes, mainly *MT-ND1*, *MT-ND5*, *MT-TH*, *MT-TL1* and *MT-TV*. A single mtDNA point mutation in *MT-TL1* at mtDNA3243 accounts for 80–90 % of patients with MELAS. This gene encodes a transfer RNA for the amino acid leucine and thus will compromise the production of proteins within the mitochondria. Some patients with this mutation manifest MELAS in combination with PEO, as well as PEO alone. In addition, some patients with MELAS (with or without chronic PEO [CPEO]) have mtDNA deletions similar to those that occur in patients with CPEO. Patients are usually heteroplasmic for these mutations. When

MELAS is associated with a mtDNA point mutation, inheritance is maternal. Sporadic cases likely reflect variable expression within a pedigree, and heteroplasmy may play a role [224].

Epidemiology

The incidence of MELAS is not known but in the USA the frequency of the A3243G mutation in the *MT-TL1* gene is approximately 16.3 per 1,000,000. In adult Finland population the prevalence of the A3243G mutation in the *MT-TL1* gene is estimated to be 10.2 per 100,000. MELAS usually presents between 4 and 15 years of age. There is neither race nor sexual predilection.

Systemic Manifestations

The most common initial symptoms are seizures, recurrent headaches, anorexia, recurrent vomiting, exercise intolerance or proximal limb weakness. Patients typically have normal early psychomotor development. In most patients, first symptoms appear between ages of 2 and 10 years. Short stature is common. Stroke like episodes usually present as hemiparesis, altered sensorium, visual disturbances, severe headache and seizures. The cumulative residual effects of the stroke-like episodes gradually impair motor abilities, vision, and mentation [225]. Psychiatric disorders like depression, psychosis and anxiety are common as well, affecting more than 50 % of patients. Many patients develop progressive sensorineural hearing loss. Less frequent manifestations include cardiomyopathy, ataxia, diabetes mellitus and neuropathy.

Some individuals have one presentation—such as diabetes mellitus, cardiomyopathy, or deafness—almost exclusively [226]. The disease is progressive in nature with increasing morbidity and mortality over years. In a natural history study of 31 individuals with MELAS and 54 symptomatic and asymptomatic carrier relatives over a follow-up period of up to 10.6 years, neurologic examination, neuropsychological testing, and daily living scores significantly declined in all affected individuals with MELAS, whereas no significant deterioration occurred in carrier relatives. The average observed age at death in the affected MELAS group was 34.5 ± 19 years (range 10.2–81.8 years) [227]. Yatsuga et al. studied a cohort of 96 individuals with MELAS and confirmed a rapidly progressive course within a 5-year interval, with 20.8 % of affected individuals dying within a median time of 7.3 years from diagnosis [228].

Ophthalmic Manifestations

Pigmentary retinopathy, optic neuropathy, progressive external ophthalmoplegia (PEO), ptosis, cortical visual loss, and cataracts are the most common ophthalmic findings in MELAS. The retinopathy in MELAS is variable and can present with barely discernible pigmentary abnormalities in the outer retinal layers of the macula to profound chorioretinal atrophy in the macula. A classification system of the pigmentary retinopathy in MELAS was proposed by de Laat et al.; grade 1 fine pigmentary abnormalities, grade 2 yellowish or mildly pigmented deposits, grade 3 chorioretinal atrophy outside the fovea and finally grade 4 when the atrophy affect the fovea [224, 229]. Fung et al. reported a 45 year old female with MELAS and progressive deterioration of vision and night blindness. Retinal examination revealed pigmentary retinopathy, macular atrophy and subretinal deposits that showed hyperflourescence on autofluorescence testing [230]. Rummelt et al. described retinal histopathologic findings in a patient with MELAS and bilateral ptosis, PEO, diffuse choroidal atrophy, atypical pigmentary retinopathy with macular involvement and patchy atrophy of iris stroma. At the posterior pole, RPE cells were depleted of apical microvilli, photoreceptor segments were also abnormal and their outer segment atrophic. The retinal pigment epithelium and photoreceptor cells in the retinal periphery were unaffected [231].

Optic neuropathy can present in MELAS causing reduction in visual acuity and visual field defect. Pulkes et al. reported a LHON/MELAS overlap syndrome with patients presenting with symptoms characteristic of LHON before the first stroke-like episode [232]. Cortical visual loss in MELAS usually results from the disturbances in the retrochiasmal visual pathways. These disturbances usually cause homonymous hemianopic type of visual field defects. The retrochiasmal visual loss occurs in approximately 60 % of the cases. The prognosis for recovery from these deficits is better than from cerebral infarctions but recurrent attack often leads to progressive deterioration of visual fields [224]. Kunchle et al. reported a 34 year old male with MELAS syndrome who presented with reversible homonymous hemianopia, atypical retinitis pigmentosa, myopia and nuclear cataract [233]. In rare occasion, retinal vascular disease can be seen in patients with MELAS and may occur as the initial presenting symptoms of the disease. Yi-Ting Hsieh et al. reported a non-ischemic central retinal vein occlusion as a first presentation in an 11 years old initially healthy girl who subsequently was found to have G3513A mutation in the *MT-ND5* gene. The girl eventually was diagnosed with a LHON/MELAS overlap syndrome [234].

Diagnosis

Lactate is usually elevated in blood and CSF of patients with MELAS with modest elevation of CSF protein. Brain MRI is consistent with non-ischemic stroke and during stroke-like episodes typically shows areas of increased T2 signal, involving the posterior cerebrum and not conforming to the distribution of major arteries. Diffusion-weighted MRI shows increased apparent diffusion coefficient (ADC) in the stroke-like lesions, in contrast to the decreased ADC seen in ischemic strokes [235]. Some patients have basal ganglia calcifications on CT. ECG and echocardiogram may show

evidence of incomplete heart block and/or cardiomyopathy. Twenty of patients may have axonal neuropathy on nerve conduction studies but the majority show myopathic changes on electromyography [225]. On muscle biopsy, the characteristic morphologic feature of MELAS is the overabundance of mitochondria in smooth muscle and endothelial cells of intramuscular blood vessels [236]. Ragged red fibers (RRF) with positive cytochrome c oxidase (COX) staining is a typical feature that distinguishes MELAS from mitochondrial deletions syndromes in which RRF are usually associated with negative COX staining [237]. Respiratory chain enzyme analysis in muscle extracts usually shows multiple partial defects, especially involving complex I and/or complex IV. However, biochemical results can also be normal. The diagnosis is confirmed by the identification of a disease causing mutation in mitochondrial DNA. Patients with MELAS require a complete ophthalmic evaluation that includes a slit lamp examination of the anterior segment to look for cataract and dilated fundus examination to look for optic nerve atrophy and pigmentary retinopathy and to assess its grades. Visual field testing will help in detecting the extent of the retrochiasmal visual pathway damage.

Management

The management is mainly supportive and depends on careful evaluation of the extent of the disease with assessments of growth, hearing, cardiac function, presence of diabetes, seizures, migraine and level of cognitive and physical disability. There is no specific pharmacological treatment but L-arginine therapy has shown promise for the treatment of stroke-like episodes in MELAS both during the acute presentation and as a long term prophylactic measure [238]. Other cofactors that had been shown to ameliorate the symptoms of the disease are coenzyme Q10 (CoQ10) or its analogue idebenone, and L-carnitine [239, 240].

Mitochondrial DNA Deletion Syndromes

Kearns-Sayre syndrome (KSS), Pearson syndrome and PEO are three main disorders caused by the mitochondrial DNA deletions.

Kearns-Sayre Syndrome (KSS)

Introduction

KSS is a multisystem progressive disorder characterize by the triad of onset less than 20 years old, progressive external ophthalmoplegia (PEO) and pigmentary retinopathy. Affected individuals must also have a minimum of one of the following features to make the diagnosis of KSS: (1) heart block, (2) cerebellar ataxia, or (3) increased CSF protein level (>100 mg/dL) [241]. Having PEO without the other classical features of KSS is referred to as "KSS minus" or "PEO plus" [242]. (Di Mauro S et al. http://www.ncbi.nlm.nih.gov/books/NBK1203/. Accessed May 25, 2014). Except for the very rare cases of point mutation in tRNA genes or in nuclear genes involved in mtDNA maintenance (i.e. *RRM2B*), KSS typically results from single large-scale (1.3–10 kb) mtDNA deletion. Deletions of mtDNA are only exceptionally transmitted from one generation to the next and thus most cases of KSS are sporadic. The risk of a woman carrying a large size mtDNA deletion and transmitting it to her child has been estimated to be less than 4 %.

History

The syndrome was first reported in 1958 by Thomas Kearns and by George Sayre [243, 244]. They reported two patients with the retinitis pigmentosa, external ophthalmoplegia and complete heart block.

Epidemiology

KSS has an estimated prevalence of 1/30,000–1/100,000. The prevalence of KSS was found to be 1.6 in 100,000 in a study of single large-scale mtDNA deletions of adults from Northern Finland [245]. In a study that involved 136 patients, Yamashita et al. found that majority of mitochondrial DNA deletions, 94/136, were associated with PEO in comparison to 33 patients who met the criteria for KSS [246].

Systemic Manifestations

KSS is a progressive heterogeneous syndrome with involvement primarily of the musculoskeletal, central nervous, cardiovascular, and endocrine systems depending on the tissue distribution of the mtDNA deletion. Neurological manifestations are second in prevalence to the eye features of the disease and include weakness, ataxia, cognitive decline, dysphagia, dysarthria, and seizures in addition to a high prevalence of sensorineural hearing loss [246, 247]. In the review by Khambatta et al., weakness was found in 27/35 patients (77 %), which varied from mild weakness to extreme disability, with the motor disability strongly correlated to cognitive decline [247].

Cardiac involvement includes variable degrees of heart block, cardiomyopathy, and cardiac arrest with sudden cardiac death. Sudden cardiac death and progressive cardiomyopathy are the major cause of mortality in patients with KSS [247]. Endocrine abnormalities include insulin dependent diabetes mellitus, hypothyroidism, growth hormone deficiency and adrenal insufficiency [246, 247]. Other known associations are Fanconi syndrome (reported in up to 12 %) and renal failure [246]. Typically, onset of disease usually occurs in childhood, with death commonly reported in early adulthood. (Di Mauro S et al. http://www.ncbi.nlm.nih.gov/books/NBK1203/. Accessed May 25, 2014). Patients

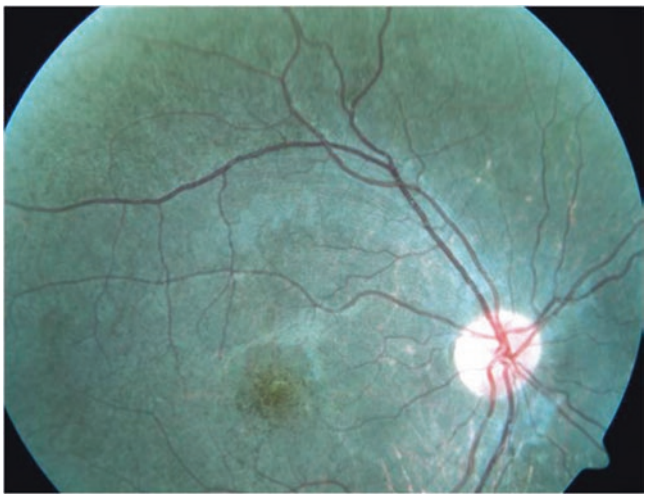

Fig. 13.15 Salt and pepper retinopathy in a child with mitochondrial deletion. This child had progressive visual impairment due to a cone-rod dystrophy. Fundus photograph shows disc pallor, mild arteriolar attenuation, dull foveal and macular reflex with pigment disturbance in the macula, and salt and pepper retinopathy

confirmed to have KSS by muscle biopsy at more than 40 years old have been reported [248].

Ophthalmic Manifestations

The eye may be the first organ to be affected in KSS. Ophthalmologic abnormalities were the most frequent presenting features (63 %) in a cohort of 35 patients with KSS which then developed in all patients during follow up years [247]. Ophthalmoplegia is the most common ocular abnormality and was seen in 86 % patients, followed by ptosis which was among the initial presenting signs (83 %) and was seen in 86 % in the follow up period. Pigmentary retinopathy was present in 17 % [247].

All extraocular muscles are commonly symmetrically involved in the two eyes. Diplopia therefore is not the usual complaint of these patients although it may present in some. The medial rectus muscles are the first to be involved and the patients may present with convergence insufficiency.

A characteristic salt and pepper retinopathy is seen in most patients. "Bone spicule" pigment clumps seen in patients with retinitis pigmentosa are not seen in KSS patients (Fig. 13.15).

Both peripheral and macula regions can be affected. Ota et al. described four stages of the ocular manifestation of KSS: Stage I: pigmentary retinopathy with normal visual function and ERG. Stage II: abnormal visual function and ERG with retinopathy, stage III: chorioretinal atrophy progresses around the optic disc and nasal retina and the ERG response is absent. Stage IV; retinopathy demonstrates the appearance of choroidal sclerosis [249]. Histopathological studies describe a local absence of rods and cones with an almost complete absence of RPE in peripheral retina. The outer retinal layer was absent in areas and most retina was gliotic [244]. Others described the presence of enlarged mitochondria in the RPE, photoreceptor inner segments and ciliary body [250]. Eagle et al. proposed that the primary defect in this type of pigmentary retinopathy resides in the RPE with secondary photoreceptor loss [251]. The ERG may show rod-cone dysfunction. Kriss and Thompson observed an increased latency of the VEP and reduced amplitude of pattern VEP in patients with KSS. In most cases, visual acuity is not affected unless the patient develops corneal exposure or maculopathy. The visual field is normal, although superior peripheral constriction may be present due to the presence of eye lid ptosis.

Diagnosis

The diagnosis is based on the identification of the causative mtDNA deletion. The vast majority (>90 %) of these deletions are often undetectable in blood. In a series of 136 patients, eight (6 %) had mtDNA deletion that was detected in blood [246]. Hence, muscle biopsy is the gold standard for diagnosing KSS. Histology typically shows abnormal mitochondrial proliferation and RRFs on modified Gomori trichrome stain, as well as cytochrome *c* oxidase-deficient fibers. Southern blot analysis of muscle DNA detects the mtDNA deletion. Succinate dehydrogenase histochemical staining is even more sensitive than Gomori trichrome. [241] Grady et al. found that skeletal muscle mitochondrial DNA heteroplasmy, mitochondrial DNA deletion size and deletion location are predictive of severity and progression of a single large scale mtDNA deletion [252].

Patients with KSS require a complete ophthalmic evaluation that includes orthoptic evaluation to measure the severity of the PEO/ptosis, a slit examination of the anterior segment to look for corneal exposure and a dilated fundus examination to look for optic nerve atrophy and pigmentary retinopathy and to assess its grades. ERG, VEP and visual field testing are useful to evaluate retinal and optic nerve functions in these patients.

Management

Treatment of KSS is supportive. Regular cardiac surveillance is recommended. Although the presence of high-grade heart block is an indication for permanent pacemaker, recent data support prophylactic pacemaker/defibrillator device even in the absence of significant ECG changes [247]. Timing of such intervention remains unclear. Hearing aids may be given to those with sensorineural deafness. Supplementation with coenzyme Q10 alone or in combination with other cofactors is a common practice. However, there is currently no clear evidence supporting the use of any intervention

Patients with ptosis may use spectacle mounted lid crutches. Ptosis surgery may be performed with extreme caution as these patients usually have poor Bell's phenomena and overcorrection of their ptosis might result in exposure keratopathy [253]. Patients with exposure keratopathy may benefit from adhesive tapes and moisture chambers. Strabismus surgery may be offered to selected patients [254]. Indications for strabismus surgery in such patients may include severe abnormal head posture, large strabismus angle and diplopia. Surgeons should ensure the stabilization of the strabismus measurements for at least 6 months before the surgery.

Pearson Syndrome

Introduction

Pearson syndrome is a rare multisystem disorder characterized by the presence of sideroblastic anemia and pancreatic insufficiency [255]. The syndrome is caused by oxidative phosphorylation dysfunction due to mtDNA deletion. There is high variability in the disease phenotypic expressions either between different patients or between the organs involved in same individual. This phenotypic heterogeneity is primarily related to heteroplasmy caused by random distribution of mtDNA during cell division.

History

Pearson in 1979 initially described the syndrome in four unrelated patients [255].

Epidemiology

The syndrome mainly occurs in infancy. All races can be affected and there is no sex predilection. Approximately 60 cases have been described in literature, with prevalence less than 1/1,000,000.

Systemic Manifestations

Pearson syndrome is characterized by refractory sideroblastic anemia in childhood with vacuolization of marrow precursors and exocrine pancreatic dysfunction. Severe, transfusion-dependent, macrocytic anemia begins in early infancy and is associated with a variable degree of neutropenia and thrombocytopenia. Patients with Pearson syndrome usually die in infancy because of metabolic crisis. Death usually occurs due to severe lactic acidosis [256]. Disease survivors will have evolution of their symptoms and signs with recovery of their hematological manifestations and appearance or worsening of their neurological and myopathic abnormalities. Some develop typical KSS features with ophthalmoplegia, ptosis and pigmentary retinopathy. Pearson syndrome may be confused with Shwachman-Diamond syndrome in the presence of bone marrow dysfunction and exocrine pancreatic insufficiency. Favareto et al. summarized three main differences including the bone marrow in Pearson is normocellular compared to the leukopenic marrow seen Shwachman-Diamond syndrome, the pancreas in Pearson syndrome is fibrotic instead of the fatty infiltrated pancreas seen in Shwachman-Diamond syndrome and bony lesions are only found in Pearson syndrome [257].

Ophthalmic Manifestations

Pearson syndrome survivors develop typical ophthalmic features of KSS. Kasbekar et al. reported a boy with Pearson syndrome who developed corneal endothelial dysfunction at the age of 12 years [258]. Cursiefen et al. in reported a 6 year old boy with Pearson syndrome and zonular cataract [259].

Diagnosis

Metabolic acidosis and lactic academia is seen due to the mitochondrial respiratory enzyme defect. The diagnosis is clinched based on the presence of macrocytic anemia and ringed sideroblasts in bone marrow. Pancreatic insufficiency is diagnosed by detecting excessive fat in the stool by qualitative (Sudan stain) and quantitative (fecal fat) tests. Some patients have evidence of having deficiencies of thyroid, parathyroid, or growth hormones. The causative deletions of mtDNA can be demonstrated with molecular genetic analysis. Because of heteroplasmy, not all tissues contain abundant amounts of mutant mitochondrial DNA. Peripheral blood cells are usually the first analytic sample. If Pearson syndrome is strongly suspected with normal findings in the blood, analysis of bone marrow is performed.

Management

No specific therapy is available for individuals with Pearson syndrome or other mitochondrial cytopathies. Awareness of possible complications and early intervention may prevent death and minimize morbidity. Red blood cell transfusions are often needed to manage the macrocytic anemia, and patients may be dependent on transfusions. Erythropoietin has been tried to decrease the frequency of transfusions. Pancreatic enzyme replacement is needed for patients with malabsorption due to exocrine pancreatic insufficiency. Supplementation with fat-soluble vitamins (ADEK) may also be needed. Although without controlled evidence of benefit, many clinicians offer supplementation with coenzyme Q and additional supplementation with carnitine and riboflavin.

Mitochondrial DNA Depletion Syndromes

Definition

Mitochondrial DNA depletion syndrome (MDS) comprises a genetically and phenotypically heterogeneous group of severe and usually lethal diseases in infancy and childhood

characterized by a profound reduction of mtDNA copy number to less than 30% of normal content. It results from defects in mtDNA replication or deoxyribonucleoside triphosphate (dNTP) supply mechanism. Regulation of mtDNA replication and transcription is tissue specific as observed by different subtypes of MDS, which include a myopathic form associated with mutations in *TK2*; an encephalomyopathic form associated with mutations in *SUCLA2*, *SUCLG1*, or *RRM2B*; a hepatocerebral form associated with mutations in *DGUOK*, *MPV17*, *POLG*, or *C10orf2*; and a neurogastrointestinal form associated with mutations in *TYMP*. Mitochondrial DNA depletion of liver is the most common form of MDS, patients falling into two major phenotypes, the hepatocerebral form and the Alpers-Huttenlocher syndrome (AHS). Inheritance of all the mtDNA depletion syndromes identified so far is autosomal recessive.

History

MDS was first described during the last decade of the twentieth century with *POLG*-related MDS being the earliest form described. The first clinical description of severe encephalopathy with intractable epilepsy and hepatic failure was made by Bernard Alpers, in 1931, and Peter Huttenlocher, with his colleagues described the associated liver disease and autosomal recessive inheritance, hence the name of Alpers-Huttenlocher syndrome (AHS) [260]. In 1987, Lestienne provided evidence for a role of DNA polymerase gamma (POLG) in the replication of human mitochondrial DNA and mitochondrial depletion as the underlying defect in the above AHS [261].

Epidemiology

POLG1-related disorders are by far the most common among all MDS. Prevalence of *POLG1*-related Alpers-Huttenlocher syndrome (AHS) was estimated to be 1:51,000 with some alleles having a founder effect and thus prevalence is much higher in some populations [262]. There are no population-based studies to determine the prevalence of the other forms of MDS but *DGUOK*-related MDS appears to be more common with over 100 cases reported compared to *TK2*, *MPV17*, *RRM2B, SUCLA2 eash* with case reports of less than 50. A founder mutation for *SUCLA2* in families of Faroese origin has been identified with an estimated carrier frequency in that population of 1:33 [263].

Systemic Manifestations

Hepatocerebral MDS result from mutations in *POLG*, *PEO1*, *DGUOK* or *MPV17*. It usually presents in infancy with a spectrum of combined hepatic, neurologic, and metabolic manifestations. The age of onset, primary organ involvement and progress may vary among different genes and mutations. *POLG*-related Alpers-Huttenlocher syndrome (AHS), one of the most severe phenotypes, is characterized by childhood-onset progressive and ultimately severe encephalopathy with intractable epilepsy and hepatic failure. Childhood myocerebrohepatopathy spectrum (MCHS) presents between the first few months of life up to age 3 years with developmental delay or dementia, lactic acidosis, and a myopathy with failure to thrive. Other findings can include liver failure, renal tubular acidosis, pancreatitis, cyclic vomiting, and hearing loss. Hearing loss, sensory axonal neuropathy, ataxia, hypogonadism and Parkinsonism can occur. Similar spectrum of presentations is noted in *MPV17* mutations with 90% progressing to liver failure in infancy or early childhood, and a quarter developing liver cirrhosis. Hepatocellular cancer has been reported [264], in two children who survived up to 7 and 11 years of age [265]. The majority of *DGUOK*-related patients have a similar hepatocerebral disease with cholestatic hepatic disease and neurologic dysfunction evident within weeks of birth. A small subset of patients has isolated hepatic disease that develops later in infancy or childhood.

Encephalomyopathic forms, such as *SUCLA2*-related MDS, are characterized by early infantile onset of severe hypotonia, dystonia, seizures, growth retardation and severe sensorineural hearing impairment [266]. Myopathic MDS, such as *TK2*-related disease, present with progressive proximal muscular weakness that in its severe form can lead to progressive respiratory failure and death within a few years after diagnosis. Severity is a continuum from very severe to mild and some cases may be associated with evidence of liver disease.

Ophthalmic Manifestations

POLG-related hepatocerebral form: Patients with this form of MDS manifest with progressive external ophthalmoplegia (PEO) resulting in ptosis and ophthalmoparesis (Fig. 13.16).

Patients may be free of systemic manifestations at presentation; many patients with isolated PEO at the onset develop other manifestations of *POLG*-related disorders with time. Patients with the AD form of *POLG*-related PEO may develop cataracts [267]. Recessive mutation of *POLG* gene can cause adult onset sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO syndrome) [268].

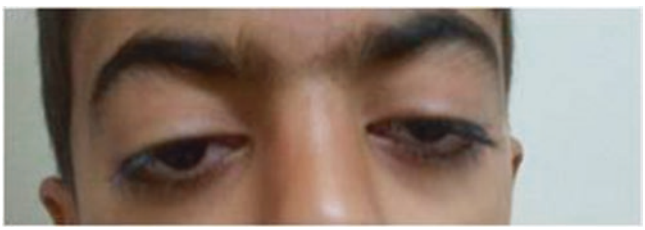

Fig. 13.16 Bilateral ptosis and progressive external ophthalmoplegia in a child with hepatocerebral mitochondrial depletion syndrome due to mutation in *POLG* (Alper syndrome)

MPV17-related hepatocerebral form: Corneal anesthesia, ulceration and scarring are present in this form of MDS. These ocular manifestations can also present in the Navajo neurohepatopathy. Affected individuals are often found to have homozygous p.Arg50Gln mutation in *MPV17* [269, 270].

RRM2B-related Encephalomyopathic form: Affected patients with this form present with ophthalmoplegia and ptosis [271].

TK2 -related myopathic form: Chronic progressive external ophthalmoplegia may be seen infrequently in this form of MDS [272].

SUCLA2, SUCLG1-related Encephalomyopathic form: Patients may present with ptosis and strabismus in this form of MDS.

DGUOK-related hepatocerebral form: Most patients have prominent ocular movement disturbances, including oscillating and disconjugated eye movements and rotatory, pendular, or multidirectional nystagmus [264].

Diagnosis

The suspicion of MDS is usually based on the clinical presentation, which may range from well-defined syndromes to non-specific multisystem phenotypes, and usually includes neurological involvement.

Biochemical findings that support the clinical presentation include elevated lactate, derangement of liver function, and elevated serum creatine phosphokinase (CK) concentration. *SULCA2*-related MDS is typically associated with increased urinary excretion of methylmalonic acid (MMA), elevated plasma methylmalonic acid and increased C3-carnitine and C4-dicarboxylic-carnitine on acylcarnitine profile. Characteristic histopathologic findings in skeletal muscle (dystrophic features, endomysial fibrosis, abnormally shaped mitochondria) as well as increased succinate dehydrogenase (SDH) activity and low-to-absent cytochrome *c* oxidase (COX) activity is characteristic of *TK2*-related MDS. Defects in respiratory chain function is a usual finding especially when the assay is performed on affected tissue. Reduced mtDNA copy number in liver or muscle can be used to confirm mtDNA depletion. However, normal respiratory chain function or absence of mtDNA depletion can be seen in some cases and should not be used to exclude the consideration of MDS [273]. A reduction in mtDNA copy number to 60–65 % of the average recorded in age-matched controls is the empirical cut-off level for a diagnosis of primary MDS. Gene sequencing is the gold standard diagnostic test. Identification of specific gene mutation establishes the exact diagnosis and provides the base for further management and genetic counseling. Next generation sequencing enables sequencing of several genes that have an overlapping phenotype at once and results in significant reduction of invasive testing, cutting down the time and cost to establish the diagnosis.

Treatment

There is no cure or targeted treatment modality that alleviates the progressive nature of MDS.

Ideally management is by a multidisciplinary team. Even when liver failure ensues, liver transplantation is not usually offered for patients with this progressive neuromuscular disease.

Leigh Syndrome (Subacute Necrotizing Encephalomyelopathy)

Definition

Leigh syndrome (LS) is a neurodegenerative disease with variable symptoms resulting from mitochondrial dysfunction [274]. Hallmarks of the disease are symmetrical lesions in the basal ganglia or brain stem on MRI, and a clinical course with rapid deterioration of cognitive and motor functions. The diagnostic criteria for Leigh syndrome include progressive neurologic disease with motor and intellectual developmental delay, signs and symptoms of brain stem and/or basal ganglia disease, and raised lactate concentration in blood and/or cerebrospinal fluid (CSF). These criteria were recently revised by Baertling et al. in 2014 and excluded elevated lactate as a constant feature [274]. Mitochondrial dysfunction in Leigh disease can result either from disruptions of the function of the oxidative phosphorylation (OXPHOS) pathway, abnormal pyruvate metabolism or coenzyme Q10 deficiency. Since OXPHOS enzyme complexes are encoded by mitochondrial or nuclear genes, LS can be caused by mutations in mitochondrial or nuclear DNA making the syndrome widely genetically heterogeneous with different possible modes of inheritance including mitochondrial (maternal), X-linked or autosomal recessive. The phenotypic heterogeneity of the syndrome is further contributed by different in mutations in same nuclear gene, variable pattern of X-chromosome inactivation in females and the heteroplasmic load of mtDNA mutation [275].

History

In 1951, a British neuropsychiatrist Archibald Dennis Leigh, described an infant with focal bilateral subacute necrotizing lesions extending from thalamus to brainstem and posterior column of spinal cord. The first links to mitochondrial energy metabolism were established in 1968 by Hommes *et al.* who reported a patient with pyruvate carboxylase deficiency [276]. In 1977 the first link between Leigh's encephalomyelopathy with defects in the respiratory chain dysfunction was reported Willems et al. who identified cytochrome c

oxidase deficiency in muscle tissue from an affected patient [277]. In 1979, DeVivo et al. reported the association between pyruvate dehydrogenase deficiency and Leigh syndrome [278].

Epidemiology

Leigh syndrome is considered to be the most common inherited mitochondrial disorder in infancy. The prevalence of LS has been estimated to be at 1 in 36,000 newborns and the syndrome is common in certain population, for example 1 in 2000 in Lac -Saint jean, Quebec Canada. In a multicenter study of 130 patients with Leigh syndrome Sofou et al. reported that the median age of the disease was 7 months with 80.8 % presenting by the age of 2 years [278]. The male /female ratio was found to be 3:2 in a review of 173 patients with Leigh syndrome. Rahman et al. postulated that this gender difference is not related to the type of molecular defect causing the disease as the difference is present in one or more defects in the X chromosome as well.

Systemic Manifestations

Most children start to develop symptoms after a period of normalcy that classically lasts for 3–18 months. The onset of symptoms usually corresponds to infection or any other metabolic stress. The initial symptoms include neuroregression with loss of previously acquired milestones. This is often accompanied by other neurological manifestations such as hypotonia or spasticity, dystonia, seizures, ataxia, dysphagia, breathing irregularities such as apnea, feeding difficulties, failure to thrive and psychomotor retardation. Age of onset can be variable and some patient may have prenatal presentation as well. Acute exacerbations and relapses are observed in patients who have the disease at birth and the presence of seizure. In many cases, the onset of symptoms is followed by a rapid clinical deterioration, possibly leading to death in infancy. Survival rate is about 20 % at 20 years and death usually occurs between the ages of 2–3 years [274]. Han et al. found that brain atrophy, early age of onset and high serum lactate level at presentation were among the factors seen in Leigh syndrome with poor prognosis.

Ophthalmic Manifestations

Sofou et al. found that the ocular manifestations are the second most common clinical feature after neurological abnormalities [279]. Abnormal ocular findings were present in 79 patients (60.8%), the most prevalent being nystagmus (23.8%), followed by strabismus (19.2%), visual impairment (16.2%), optic atrophy (14.6%), ptosis (13.1%) and ophthalmoplegia (12.3%). Han et al. found that strabismus (40.9%), pigmentary retinopathy (22.5%), and optic atrophy (22.5%) were the most frequent ocular findings, followed by ptosis (15.9%) and nystagmus (13.6%). None of the cases in the literature had both optic atrophy and pigmentary retinopathy [280]. The visual evoked potentials in PDC deficiency Leigh syndrome may be normal initially and become abnormal as the disease progress [281]. The VEP changes however were not specific for the disease. No correlation between ophthalmic manifestations and disease prognosis has been observed [280].

Diagnosis

Neuroimaging shows typical findings that include the classical bilateral, symmetrical hyperintensities in T2-weighted images that involve the basal ganglia and brainstem. Many, but not all, patients will have elevated lactate and lactate/pyruvate ratio in blood/urine and CSF. Plasma amino acids may reveal elevation of alanine and proline and urine organic acids may show intermediates of the citric acid cycle [274]. Other metabolites on urine organic acids may include elevated metabolites include ethylmalonic acid, methylmalonic acid and 3-methylglutaconic acid [282]. Measurements of OXPHOS activity in muscle tissue and/or cultured fibroblasts may show defects that involve one or more of the respiratory chain complexes. Genetic testing to identify the underlying genetic defect is the ultimate tool to confirm the diagnosis. However, the tremendous genetic heterogeneity makes genetic testing a challenging task. Assessment of the family pedigree along with other clinical and biochemical parameters indicated above can guide to suggest the testing strategy. Where family history is not suggestive for autosomal recessive or X-linked inheritance, mitochondrial genome sequencing may be the first choice. The current availability of gene panels for genes involved in Leigh disease had made this challenge easier, more time and cost effective.

Management

Treatment is supportive and includes use of sodium bicarbonate or sodium citrate for acidosis and antiepileptic drugs for seizures. Dystonia is treated with drugs such as baclofen, and gabapentin alone or in combination, or by injections of botulinum toxin. Anticongestive therapy may be required for cardiomyopathy. Regular nutritional assessment of daily caloric intake and adequacy of diet for the affected individual is essential. The aim is to improve the ATP production and to lower the lactate levels. Thiamine, a cofactor of pyruvate dehydrogenase complex has been reported to improve the neurological status in some patients [283]. Neurologic, ophthalmologic, and cardiologic evaluations at regular intervals to monitor progression and appearance of new symptoms.

Myoclonic Epilepsy Associated with Ragged Red Fibers (MERRF)

Definition

MERRF is a syndrome with a recognized pattern of clinical manifestations that arise from a single mutation in the mitochondrial DNA and is transmitted by maternal inheritance.

The most common MERRF associated mutation that is present in more than 80 % of affected individuals is the m.8344A>G in the MT-TK gene encoding for $tRNA^{Lys}$. This mutation, along with three other MT-TK gene pathogenic variants (m.8356T>C, m.8363G>A, and m.8361G>A) account for approximately 90 % of pathogenic variants in individuals with MERRF [284]. Mutations in tRNA genes impair mitochondrial protein synthesis and cause respiratory chain dysfunction. Other genes associated with MERRF are MT-TF, MT-TL1, MT-TI, and MT-TP.

Like other maternally inherited mitochondrial disorders, the expression of clinical symptoms in MERRF is influenced by heteroplasmy (varying tissue distribution of mutated mtDNA) and thus variable range of clinical presentations, age of onset and severity is expected. In a study that included 42 MERRF patients, 80 % of cases had positive family history consistent with maternal inheritance [284], compared to 20 % sporadic cases.

Epidemiology

Three epidemiologic studies of mtDNA-related diseases in northern Europe that included the m.8344A>G pathogenic variant gave the following estimates: 0–1.5:100,000 in the adult population of northern Finland [245], 0.39:100,000 in the adult population of northern England [285], and 0–0.25:100,000 in a pediatric population of western Sweden [262, 284].

Systemic Manifestations

The typical clinical manifestations of MERRF include myoclonus, generalized epilepsy, cerebellar ataxia and ragged red fibers (RRF) on muscle biopsy. Patients typically have normal early childhood development with typical onset of myoclonus as the first symptom followed by generalized epilepsy, ataxia, weakness, and dementia. The age of onset may be different among affected members of the same family [286]. All patients develop myoclonus and epilepsy. Cerebellar ataxia is one of the most common clinical manifestations of MERRF and is occurring in up to 83 % of cases. Most patients may develop additional manifestations including sensorineural hearing loss, myopathy, peripheral neuropathy, progressive dementia and exercise intolerance [284]. Short stature is a common feature as well. Other documented associations that are found in less than 50 % of patients include cardiomyopathy, pyramidal signs and multiple lipomas.

Ophthalmic Manifestations

There are very few specific descriptions of the ocular manifestations of MERRF. The most frequent known ocular complication in MERRF is optic nerve atrophy. Other established features include pigmentary retinopathy and ophthalmoparesis [287]. In the case series of 62 patients with MERRF by Hirano and DiMauro, optic atrophy was identified in 14 out of 36 evaluated patients (39 %), pigmentary retinopathy was seen in 4/26 and ophthalmoparesis in 3/28 evaluated patients [284]. Isashiki et al. reported the ocular manifestations in three patients with established diagnosis of MERRF. Two out of the three patients had optic neuropathies with chronic bilateral visual loss and central scotomas. One of these two patients had additional features of mottled macula and subtle pigmentary changes in the retina. The third patient had isolated external ophthalmoplegia [288].

Diagnosis

The cardinal clinical features of myoclonus, epilepsy and ataxia in combination with the finding of ragged red fibers on muscle biopsy are the diagnostic criteria for MERRF. Ragged red fibers (RRF) are muscle fibers that appear red in the modified Gomori trichrome stain due to subsarcolemmal and interfibrillar increase in mitochondrial number and volume [289]. RRF are seen in most but not all of patients with MERRF [290]. On the other hand RRF are not specific to MERRF and may be seen in several mitochondrial myopathies including MELAS and Kearns-Sayre syndrome. MERRF muscle fibers (both RRF and non RRF) are characterized by negative staining for cytochrome C oxidase (COX) with a strong reaction to succinate dehydrogenase (SDH). Electron microscopy usually reveals abnormal shape and distribution of mitochondria. Respiratory chain enzyme assay usually shows non-specific decreased activity of respiratory chain complexes containing mtDNA-encoded subunits that typically spares complex II. The marked deficiency in cox activity corresponds to the marked deficiency of cox staining.

Other non-specific diagnostic clues in MERRF include elevation of lactic acid in blood and cerebrospinal fluid (CSF) and mild elevation in serum creatine kinase. Electrophysiological studies are often abnormal but are non-specific. Electroencephalogram (EEG) usually shows generalized spike and wave discharges with background slowing, but focal epileptiform discharges may also be seen. Electrocardiogram often shows pre-excitation; heart block has not been described. Electromyogram (EMG) and nerve conduction velocity (NCV) studies are consistent with a myopathy, but neuropathy may coexist [284]. Genetic testing by targeted mutation analysis for variants described above or mitochondrial genome sequencing are diagnostic and can aid in appropriate genetic counseling as well.

Treatment

Similar to the majority of mitochondrial disorders, there is no specific and effective therapy for MERRF and supportive measures for multiple organ dysfunctions are continued to be the gold standard. The two main pharmacologic agents used are coenzyme Q 10 and carnitine and that work through improving respiratory chain function or reducing the levels

of reactive oxygen species arising from disrupted mitochondrial metabolism respectively.

Patients continue to require multidisciplinary care with regular evaluations by cardiology, neurology, endocrine and ophthalmology specialties.

Section Five: Disorders of Sterol Metabolism

Cholesterol is a key component of cell membranes and the immediate precursor for the synthesis of all known steroid hormones and bile acids. Lipid rafts, that play important roles in cell membrane function, are enriched in cholesterol. The 27 carbon cholesterol molecule is synthesized in a series of approximately 30 enzymatic reactions with all of the carbon atoms originally derived from acetate. Cholesterol metabolism involves esterification and storage of free cholesterol droplets. Approximately 50 % of *de novo* synthesized cholesterol is converted to bile acids daily in the adult liver.

Cerebrotendinous Xanthomatosis (CTX)

Definition

CTX is an autosomal recessive disease that occurs from accumulation of cholesterol and cholestanol as a result of a block in hepatic synthesis of bile acids from cholesterol (Fig. 13.17).

Patients have a deficiency of mitochondrial 27-hydroxylase, due to mutations in the *CYP27A1* gene on chromosome 2q25. As a result of this metabolic defect, cholesterol is metabolized by an alternate pathway, into cholestanol.

History

The disease was first described in 1937 in a patient with dementia, ataxia, cataracts and xanthomas of the tendons and brain. In 1974, Setoguchi et al. stated that CTX is linked to a defect in bile acid synthesis [291]. The gene *CYP27A1,* coding for the enzyme 27-hydroxylase was cloned and characterized in 1991.

Epidemiology

Although CTX is rare, the incidence is substantially greater than previously recognized [292]. The estimated prevalence is of 1 case per 50,000 individuals in the Caucasian population. Increased prevalence of 1:440 is seen in the Druze population in Israel.

Systemic Manifestations

Cholestatic jaundice in infancy, and persistent diarrhea in early childhood is often the first manifestation [293]. Developmental delay is apparent in childhood. However, CTX often leads to severe neurologic deterioration before the diagnosis and start of treatment are established. Brain or spinal xanthomas result in adult-onset progressive neurological impairment, with mainly pyramidal tract signs, cerebellar ataxia and psychiatric symptoms (delusions, hallucinations). Bilateral xanthomas of the Achilles tendons are detectable by the second to fourth decade of life [294]. In contrast to the xanthomas in patients with familiar

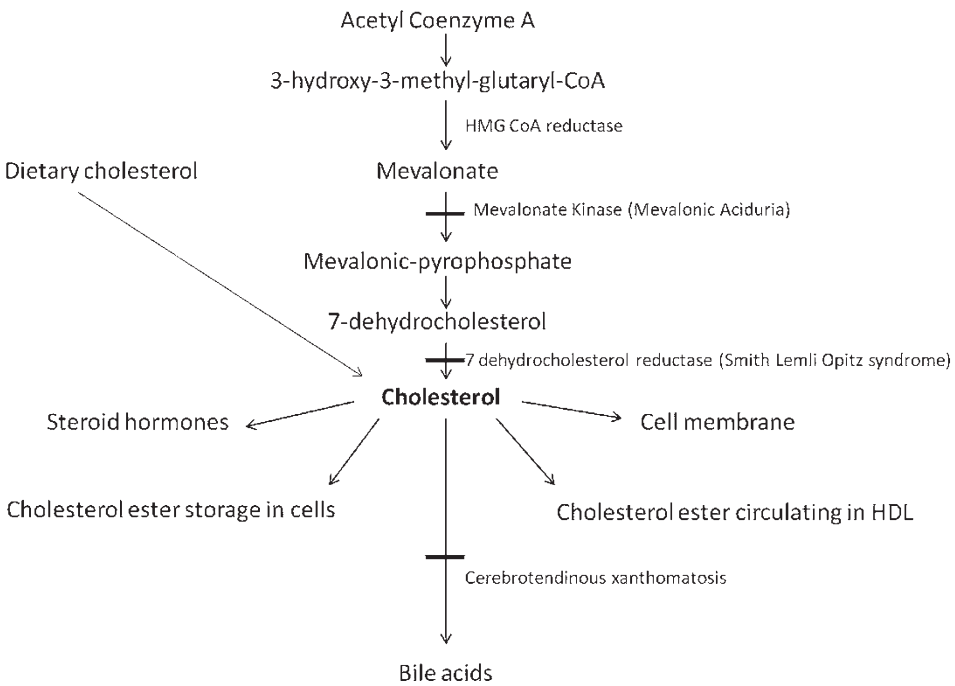

Fig. 13.17 Cholesterol metabolism. Cellular cholesterol has two sources—dietary and synthesis from acetyl coA. Deficiency in the enzyme mevalonate kinase which catalyzes the conversion of mevalonic acid to mevalonic-pyrophosphate, an early step in cholesterol synthesis, results in mevalonic aciduria. Smith-Lemli-Opitz syndrome is caused by accumulation of 7-dehydrocholesterol, the ultimate precursor of synthesized cholesterol. Cholesterol is the precursor of all other steroids in the body, i.e. corticosteroids, sex hormones, vitamin D, bile acids. Cerebrotendinous xanthomatosis results from accumulation of cholesterol as a result of a block in hepatic synthesis of bile acids from cholesterol

hypercholesterolemia, xanthomas from CTX patients contain high levels of cholestenol. Premature atherosclerosis leading to death from myocardial infarction occurs in some patients. Extensive osteoporosis and predisposition to fractures has been reported [295].

Ophthalmic Manifestations

Bilateral cataracts may be present as early as 5 years old. Unlike other disorders of cholesterol metabolism, CTX has a high incidence of childhood cataracts [294]. Cholestanol has been detected in the lens at markedly elevated levels [294]. It is not known how this substance, which is produced in the liver, gets to the lens postnatally. Optic neuropathy has been reported to occur along with cataracts [296]. Xanthelasma of both eyelids and corneal lipoid arcus are also seen in CTX [297].

Diagnosis

The diagnosis can be made by demonstrating elevated cholestanol in serum and tendons. Plasma cholesterol concentrations are normal to slightly elevated in CTX patients. Bile acids are reduced, with an almost complete lack of chenodeoxycholic acid. Later in the curse of the disease, MRI of the brain reveals diffuse or focal cerebral and cerebellar white matter disease. Sterol 27-hydroxylase enzyme assays in cultured skin fibroblasts, liver or WBC and genetic testing are confirmatory.

Management

Supplementation with bile acids may be useful. Treatment with chenodeoxycholic acid has been reported to result in a favorable biochemical response, arrest of progression, and partial reversal of manifestations in some patients [298].

Optic nerve function must be evaluated carefully prior to cataract surgery. Cataract surgery is generally associated with a good visual prognosis [297].

Smith-Lemli-Opitz Syndrome (SLOS)

Definition

SLOS is an autosomal recessive hereditary disease caused by a defect in the last step in cholesterol biosynthesis—the reduction of the Δ7 double bond of 7-dehydrocholesterol (7DHC), resulting in the abnormal accumulation of 7DHC and diminished levels of cholesterol in all tissues, including the lens. The defective enzyme is 7DHC reductase. The decreased cholesterol level may further complicate the metabolic error by causing an up-regulation of HMG CoA reductase gene transcription [294, 299]. Other abnormalities in cholesterol metabolism or trafficking may be able to produce phenocopies. The SLO phenotype has been classified as mild (type I) or severe (type II) [300]. These two forms are allelic. The gene for SLO (*DHCR7*) has been cloned at11q12-13 [301].

History

Over 30 years ago, Smith, Lemli and Opitz recognized a new syndrome of multiple congenital abnormalities. It was named RSH syndrome based on the last name of the three families first described with the disorder [302]. The primary defect remained unknown until Natowicz and Evans found undetectable levels of normal urinary bile acids, and a more than 1000-fold increase in the level of 7-DHC in an affected patient (Fig. 13.17) [303]. It is one of the first malformation syndromes attributable to a defect in metabolism.

Epidemiology

The incidence is has been reported to be between 1:20,000 and 1:50,000 [304].

Systemic Manifestations

SLOS is characterized by a combination of mental retardation, malformations, and dysmorphism. There is a wide range of SLO phenotypes ranging from severe multiple malformations to essentially normal children with syndactyly of the 2nd and 3rd toes; perhaps one of the most frequent abnormalities observed (>97 % of cases). Even in the absence of significant malformations, the developmental delay and behavioral problems may still be severe [305]. Neonates may experience feeding difficulties and irritability. Other features include growth retardation, genitourinary anomalies (in particular hypospadias and cryptorchidism), cardiac anomalies, hypotonia, and possible sex reversal. Characteristic facial dysmorphism includes microcephaly, broad nasal root, anteverted nares, an elongated philtrum, thin upper lip, low set posteriorly rotated ears, and micrognathia [305, 306]. Structural anomalies may also involve the lungs, brain, kidneys, and gastrointestinal tract. Limb abnormalities include post-axial polydactyly, clinodactyly, club feet, and hypoplastic thenar eminence [305, 307].

Ophthalmic Manifestations

Cataracts are the primary ocular manifestation. Congenital cataracts are present in 20 % of affected patients. Cataracts may also develop acutely. Abnormal concentrations of cholesterol and cholesterol precursors in the ocular tissues has been noted [294, 308]. Other oculofacial features may include unilateral or bilateral ptosis and epicanthus. The ptosis is usually mild with good levator function.

Diagnosis

The diagnosis of SLOS relies on clinical suspicion and sterol analysis of plasma or tissues. Detection of elevated 7DHC concentration is diagnostic. Serum concentration of cholesterol is

usually low. 7DHC reductase enzyme activity can be assessed in fibroblasts in culture to confirm diagnosis. Molecular analysis of the *DHCR7* gene may be performed. Prenatal diagnosis is possible by enzyme assay or genetic testing.

Treatment

Protocols are currently underway to investigate the use of cholesterol, both pre- or postnatally, in treating SLOS. Dietary cholesterol supplementation appears to have a beneficial effect [309]. The treatment may have limited effect on the neurological manifestations due to inability of exogenous cholesterol to cross the blood–brain-barrier. Whether this could have an effect on the cataract is unknown, although it seems unlikely given the lack of vascularity of the lens. More recently, promising results have been reported for an alternative strategy of reducing levels of 7-DHC and 8-DHC through administration of simvastatin (an oral HMG-CoA reductase inhibitor). Statin therapy may provide more benefit for the CNS manifestations of SLOS when compared with cholesterol supplementation alone [310].

Cardiovascular, ophthalmic and other anomalies observed in SLOS frequently require surgical correction. Many affected children require nasogastric tube feedings early in life and eventually gastrostomy tube placement for optimum nutritional support.

Mevalonic Aciduria

Definition

Mevalonic aciduria is an autosomal recessive disorder caused by a deficiency in the enzyme mevalonate kinase which catalyzes the conversion of mevalonic acid to mevalonic-pyrophosphate, an early step in cholesterol synthesis (Fig. 13.17). Mevalonic aciduria is caused when the enzyme activity is markedly reduced. Patients who have approximately 1–20 % of normal mevalonate kinase activity typically develop a milder form of mevalonate kinase deficiency called hyperimmunoglobulinemia D syndrome. Most of the characteristic clinical manifestations of mevalonate kinase deficiency are thought to be due to accumulation of mevalonic acid or a shortage of sterols. Mevalonate kinase deficiency is caused by mutations in the *MVK* gene located on chromosome 12q24 [311].

Epidemiology

Mevalonic aciduria is a rare disease. As of 2006, approximately 30 patients had been reported [312].

Systemic Manifestations

This disorder presents in infancy with high mortality and morbidity. About half of patients succumb in infancy or early childhood to the disease. Mevalonic aciduria is characterized by developmental delay, failure to thrive, hypotonia, ataxia, myopathy, fat malabsorption, anemia, hepatosplenomegaly, lymphadenopathy, progressive brain atrophy, and facial dysmorphism (microcephaly, dolichocephaly and wide irregular fontanels, as well as low set and posteriorly rotated ears) [313]. Patients may also suffer from recurrent febrile crises with vomiting and diarrhea associated with elevated sedimentation rate, leukocytosis, rash, arthralgia, edema and elevated creatinine kinase which may lead to misdiagnosis of sepsis [314]. Sometimes hematological abnormalities predominate with anemia, leukocytosis, thrombocytopenia and extramedullary hematopoeisis. Mevalonate kinase deficiency can thus mimic hematologic conditions such as myelodysplastic syndromes or chronic leukemia [315]. Malformations may include hydrocephalus, congenital heart disease, and hypospadias [313, 315]. Neuroimaging reveals selective and progressive atrophy of the cerebellum. The milder hyperimmunoglobulinemia D syndrome is characterized by milder form of mevalonate kinase deficiency

Ophthalmic Manifestations

One third of patients with mevalonic aciduria have cataracts which have been described as nuclear sclerosis, and cortical punctate changes [312, 316]. Characteristic oculofacial features include down-slanting palpebral fissures, long eyelashes, blue sclera and optic atrophy [312, 315]. Uveitis and pigmentary retinopathy may occur [313]. ERG and dark adaptomtery confirm the presence of severely reduced rod and cone mediated retinal responses [316]. Visual prognosis is guarded; patients surviving to adulthood have progressed to apparent legal blindness caused by cataracts and/or retinopathy [317]. Pigmentary retinopathy in mevalonic aciduria has recently been attributed to depletion of prenyl moieties and defective prenylation of many proteins synthesized in the retina [318].

Diagnosis

Marked (in excess of 10,000-fold) elevation of serum and urinary mevalonic acid is characteristic [313]. Prenatal testing by enzyme assay and genetic testing is available.

Management

Currently, there is no effective treatment for mevalonic aciduria.

Section Six: Disorders of Lipid and Lipoprotein Metabolism

Familial Hypercholesterolemia (FH): Type IIA Hyperlipoproteinemia

Definition

FH is a disorder of lipoprotein metabolism resulting in elevation of plasma levels of total and low-density lipoprotein (LDL) cholesterol [319]. The serum triglyceride and very

low-density lipoprotein (VLDL) levels are normal. LDL is the major cholesterol-carrying lipoprotein. FH is caused by mutations in the LDL receptor (*LDLR*) gene which makes the body unable to absorb LDL from serum [320]. Mutations in apolipoprotein B (*ApoB-100*), *PCSK9* and *LDLRAP1* genes also result in FH. The disorder occurs in two clinical forms: homozygous and heterozygous, with homozygous patients having a more severe phenotype characterized by an earlier onset of manifestations [321]. Heterozygous and homozygous FH are inherited in an autosomal co-dominant manner. The penetrance of FH is almost 100 %.

History

FH was first described by Müller in 1938. Initially FH was thought to occur due to increased production of cholesterol. In 1964 Khachadurian, at the American University in Beirut, showed that FH exists in two forms: the less severe heterozygous form and the more severe homozygous form [321]. In 1974, Brown and Goldstein described LDL binding to cultured fibroblasts in a manner consistent with a receptor and in 1979 they further described the mechanism of LDL receptor-mediated endocytosis and its role in cholesterol metabolism [320].

Epidemiology

FH is one of the most common inherited metabolic disorders, and affects 1/500 worldwide. The disorder is reported to be 10 times higher in certain populations including French Canadians, Christian Lebanese, and South Afrikaners due to founder effects. There are between 14 and 34 million individuals with FH worldwide [322]. Homozygous FH is rare with a frequency of 1:1,000,000.

Systemic Manifestations

Cholesterol is deposited in various body tissues including the tendons (xanthomas), skin (xanthelasma) and coronary arteries (atherosclerosis). Approximately, 85 % of affected males and 50 % of affected females with heterozygous FH will suffer a coronary event before the age of 65 years if they are not treated [322, 323]. Homozygotes develop coronary artery disease in the second decade [322]. Atherosclerosis often affects the aortic valve, leading to life-threatening aortic stenosis. Heterozygotes develop cholesterol xanthomas in adulthood. These are often seen in the Achilles tendons and extensor tendons of the hand. Homozygotes develop xanthomas by the age of 5 years. Xanthelasmas occur commonly in heterozygotes, but are rare in homozygotes. Xanthelasmas are not specific for FH and can appear in subjects with normal lipid levels.

Ophthalmic Manifestations

The most common ocular manifestation of FH is corneal arcus lipoides which may occur in early adolescence. The arcus is comprised of extracellular esterified cholesterol deposits in the collagenous connective tissue of corneal stroma and Descemet's membrane [324]. The deposits tend to start in the peripheral cornea, at 6 and 12 o'clock and fill in until becoming completely circumferential. There is a thin clear section separating the arcus from the limbus known as the lucid interval of Vogt. Because lipid accumulation in the peripheral cornea may reflect the level of cholesterol deposition in blood vessels, many authors have attempted to correlate arcus with lipid levels and degree of atherosclersosis. While some studies have reported lack of correlation between plasma lipid levels and corneal arcus [325], others have shown a positive correlation of arcus with calcific atherosclerosis and xanthomatosis in FH. Patients with more severe arcus tend to have more severe calcific atherosclerosis [326]. Xanthelasma of the eyelids is another ocular complication frequently associated with increased cholesterol levels in the blood.

Diagnosis

Early diagnosis is essential so that patients with FH can be treated early with the hope of preventing or delaying cardiovascular problems. The clinical diagnosis of FH is founded on personal and family history, physical examination, and lipid concentrations. Plasma total cholesterol ≥8 mmol/L (≥310 mg/dL) in adult and ≥6 mmol/L (≥230 mg/dL) in a child or family member(s), premature coronary heart disease in the patient or family member(s), tendon xanthomas and corneal arcus in the patient or a family member, and sudden premature cardiac death in a family member are highly suggestive of FH [322]. A microarray chip for the detection of common point mutations and small deletions in the *LDLR* and *APOB* genes is available and is useful for confirmation. Genetic diagnosis is particularly important in equivocal cases where lipid levels are mildly elevated with no clear external manifestations. Screening of children and adults for FH is recommended if there is a family history of FH, premature coronary heart disease, or sudden premature cardiac death. Secondary causes of hyperlipidemia must be excluded by determining that liver enzymes, renal function, and thyroid hormones are normal and there is no hyperglycemia or albuminuria.

Management

Therapy includes lifestyle management including interventions related to smoking, diet, and physical activity. Diet low in cholesterol and saturated fats is advisable. Dietary supplementation with plant sterols or stanols decrease cholesterol absorption. Statins are required in the majority of heterozygotes, along with bile acid binding resins and cholesterol absorption inhibitors. Niacin can be added as an adjunctive agent to statins. FH homozygotes will eventually require weekly LDL apheresis to lower LDL-C. Liver transplantation could be considered if LDL apheresis cannot be offered.

Disorders of High Density Lipoprotein Metabolism

Tangier Disease

Definition

Tangier disease (familial alpha-lipoprotein deficiency) is a rare autosomal recessive disorder of lipoprotein metabolism that is characterized by virtual absence of high density lipoprotein (HDL) cholesterol (less than 5 % of normal) in the plasma. HDL transports cholesterol and phospholipids from the body's tissues to the liver, where they are removed from the blood. In Tangier disease, mutations in the *ABCA1* gene (9q22-31) encoding the ATP-binding cassette transporter (ABCA1), interfere with cholesterol and phospholipid efflux from cells to nascent HDL particles. This leads to cholesterol and phospholipid accumulation in body tissues including peripheral nerves, spleen, lymph nodes, liver, and the eye, impairing cellular functions and increasing risk of early cardiovascular disorders [327]. The presence of low plasma HDL cholesterol levels is due to a lack of cholesterol efflux and due to increased catabolism of lipid-poor HDL particles. The major clinical manifestations occur in patients with homozygous or compound heterozygous mutations in the *ABCA1* gene. The biochemical phenotype is inherited as an autosomal co-dominant trait [328]. In the heterozygote, half of the normal amount of HDL is sufficient to maintain regular lipoprotein interconversion.

History

Tangier disease was first described by Frederickson in 1961 in two siblings with enlarged and yellowish tonsils. The disease was named after the island off the coast of the Chesapeake Bay in Virginia, USA where the patients lived.

Epidemiology

Tangier disease is a rare disorder with approximately 100 cases reported worldwide [328].

Systemic Manifestations

Peripheral neuropathy, increased risk of myocardial infarction and stroke are the significant consequences of Tangier disease. Cholesterol esters accumulate in peripheral nerves causing neuropathy and in the reticulo-endothelial cells of organs such as spleen, liver, and tonsils causing their enlargement and discoloration. All affected children with Tangier disease present with classic enlarged yellow tonsils, while 50 % of affected adults present with neuropathy. Premature myocardial infarction and stroke has been reported in about 30 % of patients with Tangier disease [328]. Acute onset peripheral neuropathy has been reported as an unusual presentation of Tangier disease. Histopathological examination of the involved nerves reveals axonal degeneration, demyelination, and nerve fiber loss due to lipid infiltration [329]. Some patients with Tangier disease may have an atypical presentation with idiopathic thrombocytopenia purpura due to sequestration of platelets in enlarged spleen [330].

Ophthalmic Manifestation

Diffuse hazy corneal opacification, decreased corneal sensation and lid anomalies are among the common ocular findings. Visual impairment is usually mild. Ectropion and incomplete eyelid closure may precede corneal cloudiness. Visual impairment can develop due to exposure keratopathy [331]. Histopathology studies of corneas from patients with Tangier disease have shown that corneal opacification represents lipid accumulation in the corneal stroma [332]. Confocal microscopy may be of benefit in identifying stromal lipid accumulation that may be missed in regular slit lamp examination [333].

Diagnosis

The biochemical signs of Tangier disease are plasma HDL concentration of less than 5 mg/dl, low total plasma cholesterol (below 150 mg/dl) and normal or high plasma triglycerides. In homozygous disease there is significant reduction of HDL-cholesterol (HDL-C) and ApoA1 (both 10 mg/dL), decreased LDL cholesterol level (40 % of normal) and mild hypertriglyceridemia [334]. In heterozygous disease the HDL-C level is one half of normal individual [327]. Skin or rectal mucosa biopsy reveals foam cells in affected tissues. The diagnosis of Tangier disease can be confirmed by determining the reduced efflux of cholesterol from Tangier fibroblasts in culture medium, or by *ABCA1* gene sequencing.

Management

There is no definite treatment for Tangier disease. Tonsillectomy may be required in case of significant tonsillar enlargement. A low-fat diet helps in reducing liver enlargement and preventing atherosclerosis. New drugs such as cholesterol ester transfer protein (CETP) inhibitors (dalcetrapid and anacetrapid) and reconstituted forms of HDL may be helpful in enhancing cellular cholesterol efflux and reducing cardiovascular and neuropathic complications [328].

Patients with lid ectropion and exposure keratopathy are treated with frequent lubrication and topical antibiotics, and if indicated with lid repair procedures, to prevent subsequent visual loss.

Lecithin Cholesterol Acyltransferase Deficiency

Definition

Lecithin-cholesterol acyltransferase (LCAT) deficiency syndrome is a rare autosomal recessive metabolic disorder. LCAT plays a key role in esterification of free cholesterol, formation of high density lipoprotein (HDL) cholesterol and reverse

cholesterol transport pathway, a process that describes the HDL-mediated removal of excess cholesterol from macrophages in the arterial wall and subsequent delivery to the liver for biliary excretion. There are two LCAT deficiency phenotypes: (1) familial LCAT deficiency characterized by extremely low LCAT activity and (2) Fish Eye Disease (FED) which is characterized by partial LCAT deficiency. Both these conditions are caused by mutations in the *LCAT* gene (16q22.1).

History

In 1967 Gjone and Norum described three Norwegian sisters with anemia, proteinuria, lipid deposits in the cornea, and presence of foamy cells in bone marrow and in the glomerular tuft of the kidney [335]. All three sisters had elevated plasma concentrations of free cholesterol and lecithin, reduced plasma lysolecithin, and deficiency of plasma esterified cholesterol. The enzyme LCAT could not be detected in their plasma.

Epidemiology

The prevalence of LCAT deficiency is below 1:1,000,000. Up to 2012, approximately 70 families with partial or complete LCAT deficiency have been identified worldwide [336].

Systemic Manifestations

Familial LCAT deficiency is systemically characterized by hemolytic anemia, and proteinuria with renal failure. The plasma is turbid or milky in appearance. Renal involvement is a major cause of morbidity and mortality in affected patients. It starts as proteinuria in childhood and progresses to renal insufficiency by the fourth decade. Foam cells are found in the bone marrow and kidney glomeruli, and 'sea-blue histiocytes' are detected both in bone marrow and spleen. In FED, patients are relatively less symptomatic. They usually do not have any systemic manifestations.

Ophthalmic Manifestations

Patients with familial LCAT deficiency and FED develop bilateral corneal opacification due to lipid deposition in the corneal stroma. Corneal opacification is a gradual process which usually starts early in life and often represents the initial symptom of this disease before development of anemia or renal failure, making the ophthalmologist uniquely positioned to make an early diagnosis of this disease [337, 338]. Opacification is most marked in the periphery, simulating an age-related arcus. Unlike the arcus, it tends to extend to the limbus without the sharply demarcated clear interval characteristic of arcus senilis. Although patients may complain of glare, visual acuity is usually not impaired [339]. Some patients may require penetrating keratoplasty. Histopathological evaluation with special staining techniques reveals extracellular deposits of unesterified cholesterol superimposed on the collagenous framework and Bowman's membrane. Amyloid deposits may be detected [338]. In FED, the appearance of the eye, secondary to the dense peripheral cornea1 opacification, resembles the eyes of boiled fish; hence, the name. Cornea1 opacities are the only clinical sign of FED. They are slowly progressive and cause severe visual impairment beginning as early as 15 years.

Diagnosis

The diagnosis of LCAT deficiency is primarily based on clinical manifestations in combination with histological findings from kidney biopsy (glomerulopathy evolving toward sclerosis with lipid deposition). Patients with LCAT deficiency have several abnormalities of their serum lipoproteins including a decrease in the levels of HDL, apo A-I and apoA-II, decrease in LDL, increase in serum levels of free cholesterol and accumulation of lipoprotein X. Patients with FED have a very low level of HDL. The HDL of plasma in FED contains only about 20 % cholesteryl esters relative to total cholesterol as compared to 75–80 % in controls. There is a normal cholesteryl ester percentage in plasma as well as a normal plasma cholesterol esterification rate as a result of the activity of β-LCAT. DNA diagnosis is also available.

Management

Currently, there is no definite treatment for LCAT deficiency. The effect of dietary changes has been investigated. Because high fat diet may exacerbate the renal disease, patients are advised to restrict their fat consumption [340]. The effects of lipid-lowering medications and enzyme replacement therapy on improvement of this disease are being investigated.

Abetalipoproteinemia (ABL; Bassen-Kornzweig Syndrome)

Definition

Abetalipoproteinemia (ABL) is an autosomal recessive disorder that occurs due to mutations in the microsomal triglyceride transfer protein (*MTP*) gene located on chromosome 4q23. MTP catalyzes transfer of triglyceride from the cytosol onto the nascent apoB particle in the endoplasmic reticulum in intestinal and hepatic cells, forming chylomicrons and VLDL, respectively. Mutations in MTP decrease this transfer and therefore decrease the assembly and secretion of chylomicrons from the intestine and VLDL from the liver. This leads to very low plasma concentration of triglycerides, and cholesterol, and apoB containing lipoproteins, namely LDL, VLDL and chylomicrons. Due to inefficient assembly of chylomicrons and VLDL, lipid accumulates in enterocytes and the liver, and patients present with symptoms of fat malabsorption.

History

Bassen and Kornzweig first reported the association of ataxia with atypical retinitis pigmentosa and acanthocytosis in 1950 [341]. Low plasma levels of apoB were found and it was initially believed that ABL occurred due to a genetic defect in the *APOB* gene [342]. Subsequently it was demonstrated that the defect in ABL was in the gene encoding the microsomal protein MTP, involved in lipoprotein assembly [343, 344].

Epidemiology

The incidence of ABL is reported as less than 1 in 1 million [345].

Systemic Manifestations

ABL is characterized by failure to thrive in infancy, developmental delay, oral fat intolerance, steatorrhea, diarrhea, fat malabsorption, deficiency of fat-soluble vitamins, and lipid accumulation in enterocytes and liver cells. Deficiency of vitamin E leads to debilitating neurological problems, which begin in adolescence with dysmetria and spastic gait. Ataxia occurs due to degenerative changes in the cerebellum and dorsal columns of the spinal cord. Unless treated, there is progressive spinocerebellar degeneration, bleeding diathesis due to vitamin K deficiency, anemia (acanthocytosis) and arrhythmias [346]. Acanthocytes inhibit rouleaux formation and result in a low ESR.

Ophthalmic Manifestations

Ocular manifestations in ABL usually appear in childhood: ophthalmoplegia, ptosis, nystagmus, strabismus and angioid streaks have been reported [347–349]. ABL is associated with a progressive and atypical retinal dystrophy with early macular involvement. Age of onset of symptoms of night blindness and visual impairment is variable. Early stages are characterized by subtle changes. Predominant involvement of the posterior fundus with a sharply demarcated white appearance on ophthalmoscopy has been reported with sparing of the peripheral retina. Tigroid appearance, salt-and-pepper retinopathy, and typical retinitis pigmentosa findings of bone spicule pigment clumps have been described in patients with ABL [350]. Histopathological evaluation revealed a loss of photoreceptors, loss or attenuation of the pigment epithelium, preservation of the submacular pigment epithelium with an excessive accumulation of lipofuscin, and invasion of the retina by macrophage-like pigmented cells [351]. Electroretinography is diminished or absent [347, 351]. Vitamin E deficiency has been implicated in its pathogenesis [351].

Diagnosis

The presence of acanthocytosis, in particular spur cells, is strongly suggestive of this diagnosis. Fat malabsorption is also a central feature of this disorder. Plasma total cholesterol and triglyceride concentrations are low. Vitamin E, LDL-cholesterol, and apoB lipoprotein are typically undetectable. Hypobetalipoproteinemia due to *APOB* mutations cannot be differentiated from ABL on clinical grounds.

Management

Appropriate treatment can prevent neurological sequelae; therefore, early treatment is important. Steatorrhea is eliminated when dietary fat intake is reduced to less than 30 % of caloric intake with minimal consumption of long chain and perhaps medium chain fatty acids. Supplementation with high doses of essential fatty acids is essential. High-dose oral fat soluble vitamins are associated with improved clinical outcomes. Early treatment with high dose vitamin A and E can mitigate neuropathy and retinopathy [350, 352].

Sjögren-Larsson Syndrome (SLS)

Definition

SLS is a rare autosomal recessive, inborn error of lipid metabolism characterized by a clinical triad that includes congenital ichthyosis, spasticity and intellectual disability [353]. SLS is caused by mutations in the *ALDH3A2* gene (previously known as *FALDH*) located on chromosome 17p11, that encodes microsomal enzyme fatty aldehyde dehydrogenase (FALDH). Deficient activity of FALDH leads to defective ω-oxidation of leucotriene B_4 (LTB_4) [354]. The SLS phenotype is believed to result from the secondary effects of lipid accumulation in tissues. Recently, mutations of the *ELOVL4* gene have been implicated in the pathogenesis of the SLS phenotype [355].

History

In 1956, Sjögren and Larsson described a series of patients from Northern Sweden who suffered from ichthyosis, mental retardation and spasticity [356]. The underlying enzyme deficiency was discovered in 1988 [357]. It took another 6 years before the genetic defect was unraveled [354].

Epidemiology

The largest population of patients with SLS resides in northern Sweden, in the counties of Vasterbotten and Norbotten. The prevalence of the disease in Vasterbotten is 8.3 per 100,000, whereas in the whole country of Sweden, the prevalence is 0.4 per 100,000 [358].

Systemic Manifestations

The clinical features of SLS develop *in utero*. Most patients (>70 %) are born preterm. Ichthyosis is present at birth and is the first symptom that brings the patient to medical attention. Skin changes are generalized, and progressive. The skin is mildly erythematous early in life, but by 1–2 years of

age, it takes on a brownish yellow discoloration with marked wrinkling and hyperkeratosis. Pruritus is often disabling and helps differentiate SLS from other ichthyotic skin disorders, which are generally non-itching. Spastic diplegia or paraplegia and developmental delay become apparent by 1–2 years of life. Spasticity gradually worsens during the first decades of life, leading to contractures. Seizures occur in 40 % of patients. MRI of the brain shows an arrest of myelination, periventricular signal abnormalities of white matter, and mild ventricular enlargement. Brain MR spectroscopy reveals a characteristic, abnormal lipid peak in myelin [359]. Most patients with SLS live well into adulthood.

Ophthalmic Manifestations

Patients with SLS exhibit bilateral, glistening yellow-white crystalline deposits in the perifoveal region [360]. These appear in the first 2 years of life, and progressively increase with age [361]. Patients are photophobic and have some degree of visual impairment (20/30–20/120) [359]. Mottled hyperfluorescence of the retinal pigment epithelium without leakage is seen on fluorescein angiography [361]. Optical coherence tomography shows focal reflective lesions in the ganglion cell layer and inner plexiform layer corresponding to clinically visible intraretinal crystals, and macular cystic changes [362, 363]. Fundus autofluorescence shows increased autofluorescence in the macular region due to accumulation of lipofuscin granules atrophic changes in the retinal pigment epithelium [363, 364], and reduced levels of macular pigment [365]. ERG and EOG studies are usually normal. VEP may be abnormal [366]. Ichthyosis may involve the lids and periorbital areas.

Diagnosis

Demonstration of elevated plasma fatty alcohols or urinary leukotriene B4 excretion, lack specificity and have not been adopted for routine clinical use. The usual metabolic screening tests (e.g., serum amino acids, urine organic acids, urine metabolic screens) are of no diagnostic value. Routine blood tests (e.g., for electrolytes, transaminases, renal function, CBC count) reveal results within reference ranges. Definitive diagnosis of SLS requires measuring FALDH activity in cultured fibroblasts or mutation analysis of the *ALDH3A2* gene. Genetic and biochemical studies are used for prenatal diagnosis.

Treatment

At present there is no curative therapy, and treatment is largely supportive. Moisturizing skin creams, keratolytic agents, and systemic retinoids are beneficial for cutaneous manifestations. Anti-convulsant medications and surgical procedures for the relief of spasticity may be indicated. Recent reports indicate that inhibition of LTB_4 synthesis with zileuton may be effective in decreasing the severity of the pruritus, and improving behavior [367].

Chanarin-Dorfman Syndrome

Definition

This syndrome is an autosomal recessive disorder of neutral lipid metabolism which results in multisystem, intracellular non-lysosomal triglyceride accumulation. The exact metabolic defect is unknown. The causative gene abnormality involves *CGI-58/ABHD5* gene on 3p21, which is a co-activator of an enzyme called adipose triglyceride lipase (ATGL), that catalyzes the initial step of triglyceride hydrolysis in adipocyte and non-adipocyte lipid droplets [368, 369].

History

Chanarin and Dorfman et al. described this condition in the 1970s in patients with congenital ichthyosis, neurological anomalies, hepatosplenomegaly, and pathognomonic lipid droplets in granulocytes (Jordan anomaly) [370, 371].

Epidemiology

Less than 40 cases have been described. Most affected patients are from families whose origins are in the Mediterranean and Middle-East [368].

Systemic Manifestations

Patients with Chanarin-Dorfman syndrome present with ichthyosis of the non-bullous congenital ichthyosiform erythroderma type. The hair, nails, teeth, and mucous membranes are not affected. Other manifestations include hepatomegaly, ataxia, growth and intellectual retardation, deafness, and myopathy [372]. There is considerable phenotypic heterogeneity among patients. Some patients manifest only ichthyosis, while others have a more wide-spread affectation [368].

Ophthalmologic Manifestations

Neonates may present as colloidion babies with ectropion. Ectropion can persist into the teenage years. Subcapsular cataracts, nystagmus and strabismus have been reported [368, 373, 374]. In one series of 12 patients ranging from 2 to 18 years old, 3 had ectropion, 2 had strabismus, and one 16 year old had bilateral cataract [368].

Diagnosis

Serum measurements of lipid are normal. Observation of lipid vacuoles in neutrophils in peripheral blood smears in patients with ichthyosiform erythroderma is diagnostic [375]. Lipid droplets can also be observed in skin basal

keratinocytes, hepatocytes and muscle cells. On electron microscopy, the cytoplasm has multiple non membrane bound vacuoles. Lipid peaks have been reported in brain MR spectroscopy. Muscle and liver enzymes may be elevated.

Management

Management of patients with Chanarin-Dorfman syndrome includes use of emollients for the ichthyosis and a low-fat, high-carbohydrate diet [376].

Section Seven: Congenital Disorders of Glycosylation (CDGS)

Congenital disorders of glycosylation (CDGs) are a genetically heterogeneous group of predominantly autosomal recessive disorders caused by enzymatic defects in glycosylation of proteins and lipids. Glycans (carbohydrates or sugars), covalently linked to the proteins or lipids by the process called glycosylation, result in different types of glycoconjugates (glycoproteins, glycolipids, glycosylphosphatidylinositol—GPI anchors or proteoglycans). Most extracellular and membrane proteins, and several intracellular proteins undergo post-translational glycosylation, which is a very complex and highly-coordinated process involving more than 250 gene products [377]. Based on their linkage to the protein, the glycans are grouped as N-glycans (linkage to an amide group) or O-glycans (linkage to a hydroxyl group).

Approximately 45 known CDGs have been described, with each CDG named by the mutated gene followed by CDG to denote a congenital disorder of glycosylation, for example, *PMM2*-CDG (*CDG*-Ia), MPI-CDG (*CDG*-Ib) and ALG6-CDG (*CDG*-Ic) [378]. They can be broadly classified into defects of protein (comprised of protein N-glycosylation subtype and protein O-glycosylation subtype) and lipid-glycosylation. Defects in multiple glycosylation pathways and in other pathways comprises another sub-group. In addition there is a rapidly growing group of individuals with yet unidentified glycosylation defects, which are termed as CDGx [378].

Patients with CDG have a broad spectrum of clinical manifestations and may present with involvement of any organ system at any age, often associated with significant morbidity and mortality, especially in early infancy. CDGs should be considered particularly in multi-organ disease with neurological involvement. The expanding field of CDG is a challenge for all specialists. As 1 % of the human genome is involved in glycosylation and it is probable that the majority of CDGs have yet to be discovered, CDG should be considered in every patient with an unexplained syndrome.

History

The first international workshop on CDG was conducted in Leuven in 1999, wherein the previous name of carbohydrate-deficient glycoprotein syndromes was changed to CDG [379]. The first reported CDG was an N-glycosylation defect described and characterized by Jaak Jaeken et al. in 1980 [378]. The report described twin sisters with psychomotor retardation and evidence of a demyelinating process who showed multiple glycoprotein abnormalities. Fifteen years later, deficiency in the enzyme phospho-mannomutase was shown to be the cause.

Epidemiology

Based on the determined frequency of heterozygotes, the estimated incidence of homozygotes for some CDGs is as high as 1:20,000, suggesting the existence of a much higher number of cases than documented [380]. Disorders of N-glycosylation are the most prevalent. *PMM2*-CDG (CDG-Ia) is the most common type of CDG reported, with more than 700 affected individuals [381]. Other frequent CDGs are MPI-CDG (*CDG*-Ib) and ALG6-CDG (*CDG*-Ic) with over 20 case reports of each. The other subtypes are very rare.

Disorders of Protein N-Glycosylation

Sixteen defects of protein N-glycosylation have been detected so far [382].

PMM2-CDG (CDG-Ia)

Definition

PMM2-CDG (CDG-Ia) is the most common disorder of protein *N*-glycosylation and accounts for approximately 80 % of all diagnosed cases [383]. It is caused by mutations in the *PMM2* gene (chromosome 16p13), that encodes phosphomannomutase, an enzyme that transforms mannose-6-phosphate into mannose-1-phosphate. This enzyme has an essential role early in the *N*-glycosylation process and in the synthesis of glycosylphosphatidylinositol (GPI), which is used to anchor proteins to the cell membrane.

Systemic Manifestations

Clinical presentation and course of *PMM2*-CDG is highly variable, ranging from infants who die in the first year of life to mildly involved adults. There are three major types of clinical presentations: infantile multisystem, late-infantile and childhood ataxia-intellectual disability, and adult stable disability. In the first stage, during infancy, systemic symptoms dominate. Patients typically present at birth with

dysmorphism (long fingers and toes, inverted nipples and abnormal fat pads over the buttocks) and multiple organ affectation, with hypotonia, developmental delay, hepatopathy, coagulopathy, hypothyroidism, hypogonadism, pericardial effusions, nephrotic syndrome, renal cysts, and multiorgan failure. The disease evolves into psychomotor retardation, and cerebellar hypoplasia in infancy followed by neuropathy in the first or second decade [381]. Approximately 20 % of the infants die within the first year of life with infection the most common cause of death. The late-infantile and childhood ataxia-intellectual disability has an age of onset between 3 and 10 years, characterized by hypotonia, ataxia, severely delayed language and motor development, inability to walk, IQ of 40–70 and stroke-like episodes. Joint contractures and skeletal deformities have been reported. In the adult form, intellectual disability is stable, peripheral neuropathy is variable, thoracic and spinal deformities progress, and premature aging is observed. Females lack secondary sexual development and males may exhibit decreased testicular volume. Hyperglycemia-induced growth hormone release, hyperprolactinemia, insulin resistance, and coagulopathy may occur.

Ocular Manifestations

PMM2-CDG leads to ophthalmological abnormalities in nearly 80 % of affected patients [384]. The most frequent ocular finding is strabismus which is present at birth or develops in the first year of life, and nystagmus. Other ocular manifestations include delayed visual maturation, myopia, oculomotor apraxia, congenital cataracts, congenital glaucoma and pigmentary retinopathy [384–387]. Pigmentary changes typically appear in late childhood but abnormal ERG responses may be noted as early as 2 years old. Messenger et al. reported a 14 month old infant with PMM2-CDG and nystagmus, esotropia and myopia. Her fundus showed attenuation of retinal vessels, subtle, fine, yellow dots at the macula, general hypopigmentation, and visible choroidal vessels. SD-OCT showed evidence of outer nuclear layer loss throughout the retina including the macula. ERG showed a rod- cone dysfunction with abnormal a-b wave ratios in the scotopic mixed response indicating additional photoreceptor-bipolar synaptic dysfunction. ERG abnormalities typically involving the on-pathway signifying retinal dysfunction at the cone photoreceptor synapse with the on-bipolar cell [388, 389]. A postmortem study of the retina in patients with *PMM2*-CDG showed degeneration and loss of photoreceptors [223]. Andréasson et al. hypothesized that the glycosylation defect involves the photoreceptor glycoprotein opsin and inter-receptor binding protein that encodes the interphotoreceptor matrix proteoglycan [385].

The other *N*-glycosylation defects are rarer and the ophthalmologic features are less well defined. Nystagmus, poor acuity, optic neuropathy, congenital cataracts, congenital glaucoma, and coloboma of the iris or retina have been reported. Strabismus is common in *ALG6*-CDG (CDG Ic) [387].

Diagnosis

Diagnosis of protein *N*-glycosylation disorders relies mainly on isoelectric focusing of serum transferrin, a technique assessing the proportion and the pattern of *N*-glycosylated transferrin. PMM enzyme activity measurement can be performed in fibroblasts or leukocytes to rule out the most common PMM2-CDG defect. In patients with gastrointestinal involvement and bleeding diathesis, phosphomannose isomerase (MPI) should be assayed to exclude or confirm *MPI*-CDG. Enzymatic assays have not been developed for most CDG-related enzymes and confirmation of diagnosis is done through genetic testing. Detection of the genetic defect is essential for genetic counseling and particularly for prenatal testing, as laboratory test results for abnormal glycosylation of fetal serum protein might be false-negatives [390].

Management

With exception of *PMI*-CDG (CDG Ib), no definitive treatment exists for the rest of CDG syndromes. *PMI*-CDG can be successfully treated with oral mannose. By producing mannose-6-phosphate, mannose intake bypasses PMI deficiency. Management of other CDGs is mainly supportive. Early intervention programs and rehabilitation is the mainstay of intervention in children and adults with neurological disease.

Disorders of Protein O-Glycosylation

CDGs related to the defects of protein *O*-glycosylation comprise six disorders, including *POMT1/POMT2*-CDG and POMGNT-CDG (previously known as Walker-Warburg syndrome and muscle-eye-brain disorder, respectively) [382].

Muscular Dystrophy-Dystroglycanopathy (MDDGA; Walker-Warburg syndrome and Muscle-Eye-Brain disease)

Definition

Aberrant O-mannosylation of α-dystroglycan, an external membrane protein expressed in brain, muscle and other tissues, causes a set of heterogeneous disorders called muscular dystrophy-dystroglycanopathies (MDDGA), characterized by severe brain and eye malformations and muscular dystrophy. The most severe disorders include Walker-Warburg syndrome (WWS), muscle-eye-brain disease (MEB), and Fukuyama congenital muscular dystrophy (FCMD). They constitute a spectrum of complex brain and muscle anomalies, with subtypes numbered one to six according to the genetic cause: for example, Walker-Warburg syndrome due

to *POMT1* mutations is referred to as MDDGA1. Lack of consistent ocular abnormalities in FCMD has allowed a clear clinical demarcation of this syndrome, whereas the phenotypic distinction between MEB and WWS has remained controversial.

Walker-Warburg Syndrome (WWS; MDDGA1) is a genetically heterogeneous disease presenting with hydrocephalus, type II lissencephaly, cerebellar malformations and eye abnormalities and congenital muscular dystrophy. Twenty percent of cases are caused by mutations in the protein *O*-mannosyltransferase 1 (*POMT1*) gene; others are caused by mutations in the fukutin (*FKRP*) and *POMT2* genes.

Muscle-eye-brain disease (MEB; MDDGA3) is similar to WWS, but less severe, and with longer survival. It is an autosomal recessive disease caused by mutations in the protein O-mannose beta-1,2-N-acetylglucosaminyltransferase (*POMGnT1*) gene.

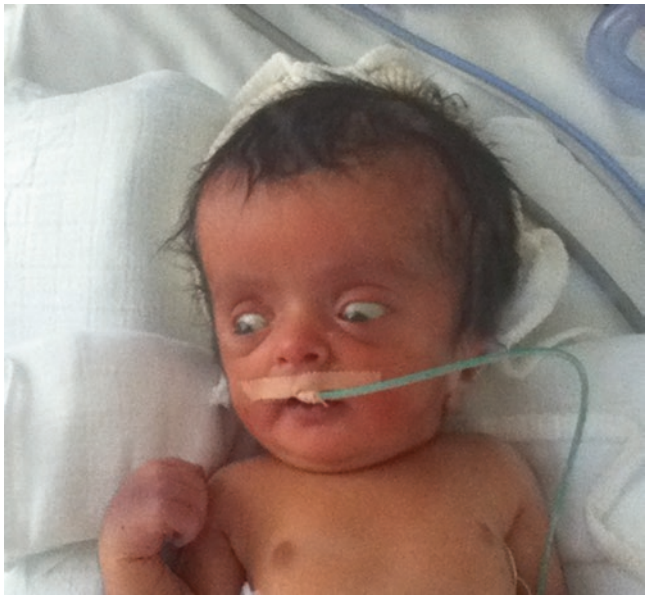

Fig. 13.18 Infant with Walker-Warburg Syndrome. Hydrocephalus resulted in macrocephaly, frontal bossing, and sunset appearance of the eyes. Fundus examination revealed retinal dysplasia. Neuroimaging showed marked severe dilatation of ventricular system, pachygyria, agyria, absent corpus callosum and cerebellar hypoplasia. Serum creatine phosphokinase was markedly elevated 16,754 (normal range: 26–192 IU/L)

History

The coexistence of lissencephaly and eye anomalies was first described by Walker in 1942. Later in 1971, Warburg reported several patients with retinal detachment, hydrocephalus, and lissencephaly [391]. Williams et al. described the coexistence of myopathy [392]. In Finland, Santavuori et al. described an apparently new disorder in which congenital muscular dystrophy, severe brain malformation, and abnormalities of the eyes coexisted. This autosomal recessively inherited condition was given the name muscle–eye–brain disease [393].

Epidemiology

WWS is a rare disease with worldwide distribution. A survey in North-Eastern Italy showed an incidence of 1.2 per 100, 000 live births. MEB is more prevalent in Finland than elsewhere owing to a strong founder effect followed by genetic drift. Only a few patients have been tentatively diagnosed with MEB outside Finland [394].

Systemic Manifestations

Both WWS and MEB are characterized by generalized hypotonia, muscle weakness, developmental delay and, in some children, seizures. Symptoms and signs are already present at birth and early infancy, and occasionally can be detected prenatally with imaging techniques. Affected babies characteristically have cobblestone lissencephaly along with agenesis of corpus callosum and cerebellar hypoplasia, and sometimes encephalocele. This led to the earlier acronym for WWS which was HARD +/− E: hydrocephalus, agyria, retinal dysplasia with/without encephalocele (Fig. 13.18).

The CNS malformations in WWS are often more severe than in MEB. White matter changes are usually not observed after 5 years old in MEB. The facial appearance of a high prominent forehead, prominent eyes and narrow temporal regions has been described as typical for MEB. Survival of children with WWS is usually limited to less than 1 year, whereas patients with MEB often reach adulthood.

Ocular Manifestations

WWS and MEB have distinctive ocular findings involving both anterior and posterior segments with a wide variety of clinical presentations. The anterior segment abnormalities may include microcornea, shallow anterior chamber angle, congenital glaucoma, cataract and microphthalmia. Posterior segment involvement is characterized by high myopia, retinal nonattachment due to retinal dysplasia, optic atrophy or hypoplasia, macular hypoplasia, and optic disc and retinochoroidal coloboma [395]. Zervos et al. described the ocular findings in two siblings with MEB who were born blind with high myopia, strabismus, and retinal and optic nerve anomalies. Postmortem examination of their eyes showed retinal, choroidal and RPE atrophy and optic nerve hypoplasia [396]. The ocular manifestations of MEB are much less profound than those seen in WWS.

Diagnosis

Laboratory investigations usually show elevated creatine kinase, myopathic or dystrophic muscle pathology and hypoglycosylation of α-dystroglycan. Although enzyme activities can be measured in leukocytes or fibroblasts, assays have not

been developed for most CDG-related enzymes and confirmation of diagnosis is done through genetic testing. Antenatal molecular diagnosis is possible in families with known mutations, although antenatal ultrasound can detect hydrocephalus and retinal nonattachment early in gestation [397].

Management

No definitive treatment exists. Management is mainly supportive and includes nutritional support, physiotherapy and medical treatment for seizures. Some patients may require surgical intervention for encephalocele or hydrocephalus. With respect to glaucoma one must assess the retinal and optic nerve prognosis for vision as well as the projected lifespan.

Section Eight: Lysosomal Disorders

Ophthalmic manifestations are important diagnostic and management tools when evaluating patients with lysosomal storage disorders. Some ophthalmic manifestations are highly specific and strongly point towards a specific disorder, thus facilitating early diagnosis. Recognition of these findings are very crucial in targeted diagnostic work up. This section is devoted to lysosomal storage disorders with frequent ocular involvement of high diagnostic value. To avoid redundancy, independent sections will be devoted to disorders that are considered to be prototypes of various forms of ocular involvement.

GM_2 Gangliosidoses

Definition

The G_{M2} gangliosidoses are a group of inherited disorders caused by excessive accumulation of G_{M2} ganglioside and related glycolipids in the lysosomes of neuronal cells. Hydrolysis of the G_{M2} gangliosides requires binding to a substrate specific cofactor, known as the G_{M2} activator. There are three forms of G_{M2} gangliosidosis: (a) Tay-Sachs disease (TSD) and variants, resulting from mutations of the *HEXA* gene, associated with deficient activity of hexoaminidase A enzyme (Hex A) but normal hexoaminidase B enzyme (Hex B); (b) Sandhoff disease and variants, resulting from mutations of the *HEXB* gene, associated with deficient activity of both Hex A and Hex B; and (c) G_{M2} activator deficiency, due to mutation of the *GM2A* gene.

History

Warren Tay, a British ophthalmologist, was the first to describe the clinical characteristics of "infantile amaurotic idiocy" when, in 1881, he observed a cherry-red spot in the retina of a 1 year old child with mental and physical retardation. The American neurologist Bernard Sachs noted the distended cytoplasm of neurons that is characteristic of the disease, and he also recognized the prevalence of the disease in Jews. In the 1930s, the German biochemist Ernst Klenk, identified the storage material in the brains of patients with amaurotic idiocy as a new group of acidic glycosphingolipids. The main neuronal storage compound in Tay-Sachs disease, ganglioside G_{M2} was identified by Svennerholm in 1962.

Prevalence

Before the advent of population-based carrier screening, education, and counseling programs for the prevention of TSD in Jewish communities, the incidence of TSD was estimated to be approximately 1:3600 Ashkenazi Jewish births [398].

Systemic Manifestations

The clinical phenotypes associated with G_{M2} gangliosidosis variants vary widely. They range from infantile-onset, rapidly progressive neurodegenerative disease culminating in death before 4 years old (classical TSD, Sandhoff diseases and G_{M2} activator deficiency) to late, adult-onset, slowly progressive neurologic conditions compatible with long survival with little or no effect on intellect. The clinical phenotypes of the acute infantile form of any of the three genetic G_{M2} gangliosidoses, are essentially indistinguishable. The earliest sign of the disease, often only appreciated in retrospect, is mild motor weakness beginning at 3–5 months old. An exaggerated startle response to sharp, though not necessarily loud sounds is commonly observed at an early stage. Soon regression and loss of already acquired mental and motor skills become obvious. A fundamental aspect of the clinical course of all genetic forms of gangliosidoses is their progressive nature. Progressive weakness and hypotonia, associated with poor head control and with either failure to achieve or loss of gross motor skills are often the features that prompt parents to seek medical attention. Seizures of various forms are rare as the presenting symptom but occur often after several months of other neurologic manifestations. After 8–10 months old, progression of the disease is rapid. Death is usually caused by bronchopneumonia resulting from stasis or aspiration coupled with depressed cough [399, 400].

In late onset forms, involvement of the deeper brain structures is more prominent compared to the overwhelming generalized gray matter involvement in the infantile form. Manifestations include dystonia, other extrapyramidal signs such as ataxia, choreoathetoid movements, the signs of spinocerebellar degeneration and motor neuron disease [401, 402]. Generally, the onset of the subacute disease is heralded by the development of ataxia and incoordination between 2 and 10 years old. Developmental regression and dementia, particularly involving speech and life skills, are prominent

features of this variant. A vegetative state with decerebrate rigidity develops by 10–15 years old, followed within a few years by death, usually due to intercurrent infection. In some cases, described by some as late-infantile G_{M2} gangliosidosis, the disease takes a different course. There is a delayed onset of symptoms, the deterioration is less rapid, and most patients survive to age 60–80 years [403, 404]. Patients with this form of the disease have their clinical onset anywhere from childhood to well into adulthood [405, 406].

Ophthalmic Manifestations

Decreasing visual attentiveness with whitening of the perifoveal macula of the retina with contrasting prominence of the fovea centralis, the cherry-red spot, is seen in virtually all affected children with the acute infantile forms of this type of lysosomal storage disorder (Fig. 13.19).

It is the result of G_{M2} ganglioside accumulation in the retinal ganglion cells, giving the white fundus appearance surrounding the preserved normal tint of the fovea where there are no ganglion cell bodies (The red color comes from the underlying choroid which is seen through the fovea normally. The foveal color may demonstrate variability according to race). As the ganglion cells die, the 'cherry- red spot' fades and optic atrophy becomes apparent. The term "cherry red spot" was used by Bernard Sachs, and although it is a classical sign in patients with Tay Sachs disease, it is also seen in other lysosomal storage disorders including sialidosis, galactosialidosis, G_{M1} gangliosidosis, metachromatic leukodystrophy, Niemann-Pick types A, B, and C, Farber lipogranulomatosis, multiple sulfatase deficiency, and Wolman disease. Table 13.3 summarizes the main clinical findings of the other lysosomal storage disorders where cherry red spots are recognized as a main fundus finding [407–432]. The ERG is normal, but the visual evoked potential is extinguished.

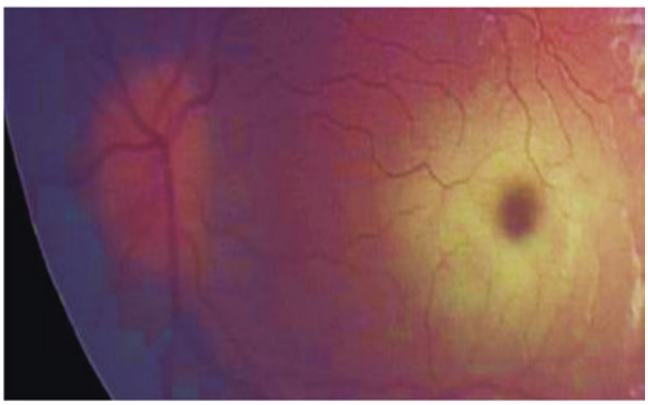

Fig. 13.19 Fundus appearance of cherry red spot seen in an 8 month old child who was developmentally delayed and admitted in an encephalopathic stage. Ocular exam revealed no visual response. Note the intense whitening of the perifoveal macula of the retina. Visual evoked response was negative. Enzyme and genetic studies established the diagnosis of G_{M2} gangliosidosis (Sandhoff's disease)

Patients with late-onset TSD disease show characteristic abnormalities of saccades: saccadic hypometria, transient decelerations, and premature terminations, but normal afferent visual systems [433].

Diagnosis

The availability of biochemical methods for measurement of hexoaminidase enzyme activity enables rapid and reliable diagnostic confirmation in patients suspected to have TSD or Sandhoff disease. The diagnosis of Hex A deficiency relies on the demonstration of absent to near-absent Hex A enzymatic activity in the serum, white blood cells, or other tissues from a symptomatic individual in the presence of normal or elevated activity of the Hex B isoenzyme [434]. In population screening, assay of Hex A enzymatic activity in serum or leukocytes using synthetic substrates provides a simple, inexpensive, and highly accurate method for heterozygote identification. Individuals with two altered *HEXA* alleles, one a pseudodeficiency allele and the second a disease-related mutation, have extremely low or absent Hex A enzymatic activity with synthetic substrates but have no evidence of neurologic abnormality. Molecular genetic testing can be used to identify the two disease-causing mutations when assay of Hex A enzymatic activity is abnormal. This is also important to rule out the presence of pseudodeficiency alleles.

Sandhoff disease and its variants are associated with deficiencies of both Hex A and Hex B enzymatic activity. The enzymatic activity of both Hex A and Hex B is normal in patients with G_{M2} activator defects. G_{M2} ganglioside accumulation occurs because of a deficit of the G_{M2} activator that is required for the degradation of G_{M2} ganglioside. The disorder can be confirmed with demonstration of causative mutations in the *GM2A* gene.

Management

Treatment of G_{M2} gangliosidoses is essentially supportive and directed to providing adequate nutrition and hydration, managing infectious disease, protecting the airway, and controlling seizures. Anti-depressants or anti-psychotics maybe required in older individuals with psychiatric manifestations.

Niemann-Pick Disease Type C

Definition

Niemann-Pick disease is a group of disorders (types A, B, C, and D) in which there is abnormal storage of sphingomyelin. Types A and B are due to mutations in the sphingomyelin phosphodiesterase I gene *SMPD 1*. Clinical subtypes A and B are distinguished by the absence or presence, respectively, of residual catalytic activity of the gene product enzyme. In types C and D ganglioside and sphingomyelin accumulation

Table 13.3 Some lysosomal storage disorders associated with fundus appearance of a cherry red spot

Lysosomal Storage Disorder (LSD)	Systemic manifestations	Ophthalmic manifestations	References
Galactosialidosis	Coarse facies, vertebral changes, foam cells in the bone marrow, and vacuolated lymphocytes	corneal clouding and fundal changes, ranging from a grayish disk to a cherry-red spot	[390–394]
	Three phenotypic subtypes are recognized: (a) early infantile form: fetal hydrops, edema, ascites, visceromegaly, dysostosis multiplex, and early death, (b) late infantile: hepatosplenomegaly, growth retardation, cardiac involvement, and rarely neurologic signs, (c) juvenile/adult form: myoclonus, ataxia, angiokeratoma, mental retardation, neurologic deterioration, no visceromegaly		
G_{M1} gangliosidosis	Infantile form (type 1): developmental arrest is observed a few months after birth, followed by progressive neurologic deterioration and generalized spasticity with psychointellectual dysfunction, facial dysmorphism, hepatosplenomegaly, and generalized skeletal dysplasia	Macular cherry-red spots are of pathognomonic significance. Corneal clouding is often observed. Optic atrophy is present at the late stage of the disease, and the retina becomes edematous	[395–399]
	Late infantile/juvenile form (type 2) or adult/chronic form (type 3): progressive neurologic diseases in children or young adults. Dysmorphic changes are less prominent or absent in these clinical forms		
Niemann-Pick type A	Failure to thrive, hepatosplenomegaly (a constant sign), Neurological examination is normal until 5–10 months of age, then hypotonia & motor regression, pyramidal signs, progressive spasticity, seizures may develop, death between 1.5 and 3 years	Ocular manifestations range from corneal opacification and brown discoloration of the anterior lens capsule to retinal opacification with a macular cherry-red spot in Niemann-Pick Type A	[400–402]
Sialidosis	Type I: mild form, for the first 20–30 years of life, patients are generally normal in terms of development and appearance. Gait abnormalities, reduced visual acuity, or both bring patients to medical attention. Type II: progressively severe, mucopolysaccharidosis-like phenotype, visceromegaly, dysostosis multiplex, and mental retardation	The ocular cherry-red spot, while a consistent finding, is sometimes described as being atypical. Impaired color vision, and/or night blindness in some patients. Punctate lenticular opacities have been described in some patients.	[403–406]
Multiple sulfatase deficiency	The clinical phenotype generally resembles late infantile metachromatic leukodystrophy. Early development may be normal following an often rapid clinical progression, with neurodegeneration leading to early death within a few years of clinical onset. The phenotype may vary according to the deficient sulfatases	Variable corneal clouding Retinal degeneration	[407–409]
		Cherry red spot has rarely been described	
Krabbe disease	85–90% have infantile form: children with this form of the disease appear to be normal for the first few months of life but show extreme irritability, spasticity, and developmental delay before age 6 months; psychomotor regression progresses to a decerebrate state with no voluntary movement. Children with later onset present with weakness and vision loss and may experience intellectual regression	Optic atrophy and sluggish pupillary reactions to light are common	[410–413]
		Macular cherry-red spots rarely described	
Metcahromatic leukodystrophy (MLD)	late-infantile MLD (50–60%): onset between 1 and 2 years, weakness, hypotonia, clumsiness, frequent falls, toe walking, and slurred speech., followed progressive neurodegenerative course	Vision and hearing become compromised over time with slowed sensory evoked potentials and optic atrophy. Patients become eventually blind	[414, 415]
	Juvenile MLD (20–30%): onset age 12–14 years, decline in school performance, followed by abnormal behavior and gait abnormalities	Macular cherry-red spots rarely described	
	Adult MLD (15–20% of cases): intellectual decline, personality changes, peripheral neuropathy, seizures		

occurs due to impaired cellular trafficking of exogenous cholesterol.

History

Albert Niemann published the first description of Niemann-Pick disease, type A. Ludwig Pick described the pathology of the disease in the 1930s. The first recognizable description of Niemann-Pick C appeared in Crocker and Farber's review of Niemann-Pick disease in 1958. Crocker and Farber based their diagnosis of Niemann-Pick disease on the presence of foam cells and increased tissue sphingomyelin. In 1966 Brady and coworkers demonstrated severe generalized sphingomyelinase deficiency in Niemann-Pick A, a finding that was soon extended to type B, but not to types C and D, indicating that the two latter types constituted separate entities [435, 436]. In 1984, observation by Pentchev and coworkers of defective cellular esterification of exogenously derived cholesterol in the murine model of the disease, led to the discovery of an identical lesion in Niemann-Pick C and further demonstration of unique abnormalities of intracellular transport of LDL-derived cholesterol with sequestration of unesterified cholesterol in lysosomes in the disease [437–439].

Epidemiology

Niemann-Pick C is a panethnic disorder. Two genetic isolates have been described, French Acadians in Nova Scotia (formerly Niemann-Pick D) and Spanish-Americans in southern Colorado [440]. A study in Yarmouth County, Nova Scotia found a 1% incidence of Niemann-Pick C and estimated a carrier frequency between 10 and 26% [441]. A prevalence of about 1/150,000 live births has been calculated for France, West Germany, and the United Kingdom [442].

Systemic Manifestations

Niemann-Pick C is a disorder with protean manifestations that can present at any time from intrauterine life to adulthood. The "classic" Niemann-Pick C patient is the product of a normal pregnancy. Approximately 50% of the children have transient neonatal jaundice. Infiltration of the lungs with foam cells may accompany neonatal liver disease or occur as a primary presenting feature. Niemann-Pick C may also present with fetal ascites [443]. Early development is usually normal. The child later becomes clumsy and suffers frequent falls before overt ataxia is recognized. Gelastic cataplexy (sudden loss of muscle tone; drop attacks), seizures and dystonia then follows. The child suffers increasing physical and intellectual disability through late childhood and adolescence, eventually becoming chair-bound. Psychiatric disturbances including psychosis may coincide with the onset of puberty. Severe dysphagia now imperils nutrition, and the upper airway is poorly protected. In many cases, spasticity or rigidity (or both) add to the burden of nursing care. Death from pulmonary complications occurs in the teenage years or early adulthood.

MRI of the brain is usually normal until the late stages of the illness. At that time, marked atrophy of the superior/anterior cerebellar vermis, thinning of the corpus callosum, and mild cerebral atrophy may be seen. In as many as 10% of Niemann-Pick C cases, terminal hepatic failure without neurologic symptoms occurs [444, 445]. Some children present with hypotonia and delayed motor development before 2 years old. These children invariably have hepatosplenomegaly, usually do not learn to walk, develop intention tremor and generalized spasticity, and die between 3 and 5 years old [446]. Insidious onset and slow progression characterize late or adult onset cases. Cognitive and psychiatric disturbances are prominent, and may overshadow other findings [447, 448].

Ophthalmic Manifestations

Vertical supranuclear gaze palsy is the ocular hallmark of this disease. It has been present in all juvenile and adult cases [449, 450]. Increase in saccadic latency, followed by subtle slowing of vertical saccades (upward or downward) begins in childhood, and may be accompanied by blinking or head thrusting. Voluntary vertical gaze is completely paralyzed in the late stages of the illness, and horizontal eye movements may also be affected. Oculocephalic reflexes are preserved. Saccades should always be examined in addition to pursuit movements. Recent studies suggest that vertical supranuclear gaze palsy in Niemann-Pick C most likely reflects selective dysfunction of vertical burst neurons in the brain stem [451, 452].

A faint cherry red spot may be seen in Niemann-Pick C. Niemann-Pick A and B patients manifest "macular haloes" or "cherry-red spot". Macular halos are seen by age 12 months in all patients with NP-A, but in only one-third of type B patients [453]. The macular haloes in Niemann-Pick disease patients rarely exceed three mm in outer diameter. Spectral domain OCT may reveal a layer of hyper-reflective retinal tissue at the shoulders of the foveal depression [454].

Diagnosis

Definitive diagnosis of Niemann-Pick C requires demonstration of abnormal intracellular cholesterol homeostasis in cultured fibroblasts [438]. These cells show reduced ability to esterify cholesterol after loading with exogenously derived LDL-cholesterol. Filipin staining demonstrates an intense punctate pattern of fluorescence concentrated around the nucleus, consistent with the accumulation of unesterified cholesterol. Oxysterol measurement is likely to replace skin biopsy and will likely prove to be a robust first line screening and diagnostic test for Niemann-Pick C in the future [455, 456]. Although rarely done now for the purpose of diagnosis, bone marrow, spleen, and liver may contain foamy cells (lipid-laden

macrophages); sea-blue histiocytes may be seen in the marrow in advanced cases. Mutations in two genes *NPC1* and *NPC2* are known to cause Niemann-Pick C.

Management

Clinical management guidelines for Niemann-Pick C have been published [457]. No curative therapy exists. Symptomatic therapy may be at least partially effective in the management of seizures, dystonia, and cataplexy. Chest physical therapy with aggressive bronchodilation and antibiotic therapy for inter-current infection appears beneficial. Individuals whose mobility is compromised should have a regular bowel program to prevent severe constipation, which may present as increased seizure frequency or increased spasticity in some impaired individuals with Niemann-Pick C. Physical therapy is indicated to maintain mobility as long as possible. Miglustat, an inhibitor of glycosphingolipid synthesis has been shown to delay onset and prolong survival in both murine and feline models of Niemann-Pick C. Subsequent clinical studies have supported a role of this drug in stabilizing Niemann-Pick C. The agent has been approved for the management of neurologic manifestations of Niemann-Pick C in several countries, not including the United States.

Gaucher Disease

Definition

Gaucher disease is an autosomal recessive inborn error of glyolipid catabolism caused by deficiency of the lysosomal enzyme, β-glucosidase (also known as glucocerebrosidase). This results in multisystem accumulation of glucosylceramide (glucocerebroside) and other glucosphingolipids that are intermediates in the catabolism of globoside and gangliosides. There are three major clinical types (1, 2, and 3) and two subtypes (perinatal-lethal and cardiovascular) of Gaucher disease.

History

In his 1882 doctoral thesis, Phillipe Charles Ernest Gaucher provided the first description of the disease, which was named Gaucher's disease by Brill in 1905. Oberling and Woringer recognized the similarities between the visceral pathologies of Gaucher disease and a rapidly progressive fatal infantile disease involving the CNS, later termed the acute neuronopathic form, now type 2, of the disease (3). In 1959, Hillborg described the Norrbottnian form of slowly progressive neuronopathic Gaucher disease, now type 3, in Swedes descending from an isolate above the Arctic circle [458]. The familial occurrence of Gaucher disease was recognized in 1901, but its inheritance pattern was clarified much later. The metabolic nature of Gaucher disease was appreciated by Marchand in 1907. The enzymatic defect in Gaucher disease was shown to be due to impaired glucosylceramide hydrolysis by Brady et al. and Patrick [459, 460]. The lysosomal localization of the enzyme was demonstrated by Weinreb et al., establishing Gaucher disease as a member of the lysosomal storage disease family [461]. The gene encoding acid β-glucosidase was mapped to 1q21 [462, 463]. De Duve proposed in 1964 that lysosomal enzyme deficiencies might be effectively treated by enzyme infusions [463]. Achord et al. proposed that this might be useful in directing enzyme to macrophages in the treatment of Gaucher disease [464]. These principles were subsequently applied in developing enzyme therapy for Gaucher disease [465–467].

Epidemiology

A study from Australia reported a disease frequency of 1:57,000 [468]. A similar study from the Netherlands reported 1.16:100,000 [469]. Non-neuropathic Gaucher disease (type 1) is more common in the Ashkenazi Jewish population, with a disease prevalence of 1:855 and an estimated carrier frequency of 1:18.

Systemic Manifestations

Gaucher disease encompasses a spectrum of clinical findings from a perinatal-lethal form to an asymptomatic form. Three major clinical types are delineated by the absence (type 1) or presence (types 2 and 3) of primary central nervous system involvement. Clinical or radiographic evidence of bone disease occurs in 70–100 % of individuals with type 1 Gaucher disease. Bone disease ranges from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis [470]. Acute bone pain manifests as bone crises: episodes of deep bone pain that are usually confined to one extremity or joint [471]. Conventional radiographs may reveal undertubulation (Erhlenmeyer flask configuration) noted in the distal femur and endosteal scalloping as a sign of bone marrow infiltration. MRI reveals the extent of marrow involvement and the presence of fibrosis and/or infarction. Neurologic complications such as spinal cord or nerve root compression may occur secondary to bone disease (e.g., severe osteoperosis with vertebral compression; emboli following long bone fracture), or coagulopathy (e.g., hematomyelia) [472]. Hepatosplenomegaly is typically seen in patients with Gaucher disease, with the enlargement of the spleen being massive. Cytopenia is almost universal in untreated Gaucher disease. Anemia, thrombocytopenia, and leukopenia may be present simultaneously or independently [473]. Interstitial lung disease, alveolar or lobar consolidation and pulmonary hypertension maybe seen.

Previously, affected individuals were classified into type 2 or type 3 Gaucher disease based on the age of onset of neurologic signs and symptoms and the rate of disease progression. Children with onset before 2 years old with a rapidly

progressive course, limited psychomotor development, and death by 2–4 years old were classified as having type 2 Gaucher disease. Individuals with type 3 Gaucher disease may have onset before 2 years old but often have a more slowly progressive course, with life span extending into the third or fourth decade in some cases.

Neurological involvement in Gaucher disease may include bulbar involvement, pyramidal signs, seizures, dementia or ataxia. Gaucher disease is now better thought of as representing a phenotypic continuum, ranging from abnormalities of horizontal ocular saccades at the mild end to hydrops fetalis at the severe end [474].

A perinatal-lethal form is associated with hepatosplenomegaly, pancytopenia, and microscopic skin changes and may present clinically with ichthyosiform or collodion skin abnormalities or as nonimmune hydrops fetalis [475]. The cardiovascular form is characterized by calcification of the aortic and mitral valves, and mild splenomegaly.

Ophthalmic Manifestations

Saccade initiation failure (ocular motor apraxia, supranuclear gaze palsy) is often the earliest neurological sign in patients with Gaucher disease. This sign can be difficult to detect clinically, but is readily revealed as missed quick-phases during induced optokinetic and vestibular nystagmus. Optokinetic and vestibular nystagmus show marked paucity of quick-phases making the eyes "lock up" at the limit of gaze, thus indicating saccade initiation failure [476]. Cherry-red spots may occasionally be seen in Gaucher disease, but the perifoveal halo is more gray than white. In occasional patients, scattered white spots in and on the retina may be observed. These white spots consist of clusters of swollen histiocytes (Gaucher cells) [477–479]. White deposits in the conjunctiva, corneal epithelium, anterior chamber angle, ciliary body, and pupil margin have also been reported [480].

Diagnosis

The most efficient and reliable method of establishing the diagnosis of Gaucher disease is the assay of β-glucosidase (glucocerebrosidase) enzyme activity in peripheral blood leukocytes or other nucleated cells. Molecular genetic testing and the identification of two disease-causing mutations in *GBA* provide an alternative means of confirming the diagnosis. Bone marrow examination, although not necessarily needed for the diagnosis, reveals the presence of lipid-engorged macrophages (Gaucher cells).

Management

Supportive care for all affected individuals may include: transfusion of blood products for severe anemia and bleeding, analgesics for bone pain, joint replacement surgery for relief from chronic pain and restoration of function, and oral bisphosphonates and calcium for osteoporosis. Enzyme replacement therapy (ERT) has changed the natural history of Gaucher disease and eliminated the need for splenectomy in individuals with hypersplenism. Individuals with type 1 Gaucher disease report improved health-related quality of life after 24–48 months of ERT [481, 482]. Although bone marrow transplantation (BMT) had been undertaken in individuals with severe Gaucher disease, primarily those with chronic neurologic involvement (Gaucher disease type 3), this procedure has been largely superseded by ERT. Individuals with Gaucher disease type 2 and pyramidal tract signs are not likely to respond to ERT, perhaps because the underlying neuropathology is cell death rather than lysosomal storage of GL1 [483]. Individuals with Gaucher disease type 3 appear to derive some benefit from ERT, although long-term prognosis remains to be defined for this heterogeneous group [484]. In patients with Gaucher disease type 1 in whom ERT is not feasible due to problems like difficult venous access or hypersensitivity, miglustat may be considered [485, 486].

VIII.4. α-Galactosidase A Deficiency: Fabry Disease

Definition

Fabry disease is an X-linked recessive inborn error of glycosphingolipid catabolism caused by deficiency of the lysosomal enzyme, α-galactosidase (GLA). This results in multisystem accumulation of systemic deposition of glycosphingolipids with terminal α-galactosyl moieties, predominantly globotriaosylceramide (GB3). Although heterozygous females have an attenuated form of the disease and are usually asymptomatic, they can rarely be as severely affected as hemizygous males. Variation in clinical manifestations in heterozygous females is attributed to random X-chromosome inactivation.

History

The first patients with first patients with angiokeratoma corporis diffusum were independently described by two dermatologists, Anderson in England, and Fabry in Germany. The characteristic corneal opacities and the vascular abnormalities in the conjunctiva and retina were first described by Weicksel and Franceschetti [487]. In postmortem examination of two affected brothers who died of renal failure, Pompen and coworkers described the presence of abnormal vacuoles in blood vessels throughout their bodies suggesting that the disease was a generalized storage disorder [488]. Subsequently, Scriba defined the lipid nature of the storage material. In 1963, Sweeley and Klionsky isolated and characterized two neutral glycosphingolipids from the kidney of a Fabry hemizygote obtained at autopsy [489]. In 1967, Brady et al. demonstrated that the enzymatic defect was in

ceramide trihexosidase, a lysosomal galactosyl hydrolase required for the catabolism of glycosphingolipids [490]. The gene was subsequently identified [491].

Systemic Manifestations

In males with classic Fabry disease, the onset of symptoms usually occurs in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesias). Angiokeratomas are often one of the earliest manifestations of Fabry disease. They appear as appear as clusters of individual punctate, dark red to blue-black angiectases in the superficial layers of the skin. Acroparesthesias occurring as episodic crises of agonizing, burning pain in the distal extremities most often begin in childhood or early adolescence and signal clinical onset of the disease. Anhidrosis, or more commonly hypohidrosis, is an early and almost constant finding [492]. Cardiac and/or cerebrovascular disease is present in most males with the classic phenotype by middle age. Cardiac disease is the major cause of morbidity and mortality in those who have not undergone dialysis or transplantation for treatment of end stage renal disease (ESRD). Myocardial deposition may cause left ventricular hypertrophy. Echocardiography demonstrates an increased thickness of the interventricular septum and the left ventricular posterior wall [493]. Cerebrovascular manifestations result primarily from multifocal small vessel involvement and may include thrombosis, transient ischemic attacks (TIA), basilar artery ischemia and aneurysm, seizures, hemiplegia, hemianesthesia, aphasia, labyrinthine disorders, or frank cerebral hemorrhage [494]. Progressive glycosphingolipid accumulation in the kidney interferes with renal function, resulting in azotemia and renal insufficiency. Gradual deterioration of renal function and the development of azotemia usually occur in the third to fifth decade of life, although ESRD has been reported in the second decade. Other clinical manifestations include episodic diarrhea, nausea, vomiting, bloating, cramping abdominal pain, and/or intestinal malabsorption [495]. Several affected individuals have had pulmonary involvement, manifest clinically as chronic bronchitis, wheezing, or dyspnea [496]. High-frequency hearing loss, tinnitus, and dizziness have been reported [497]. The clinical manifestations in heterozygous females range from asymptomatic throughout a normal life span to as severe as affected males.

A cardiac variant of the disease is also recognized. Screening of males with "late-onset" hypertrophic cardiomyopathy found that 6.3 % who were diagnosed at or before age 40 and 1.4 % of males who were diagnosed before age 40 had low α-Gal A enzyme activity and GLA mutations [498]. Renal variants were identified among Japanese individuals on chronic hemodialysis in whom ESRD had been misdiagnosed as chronic glomerulonephritis [499].

Ophthalmic Manifestations

Fabry disease may involve the cornea, lens, conjunctiva, and retina. A characteristic corneal opacity, termed cornea verticillata and observed only by slit-lamp examination, is found in affected males and most heterozygous females. The earliest corneal lesion is a diffuse haziness in the subepithelial layer. With time, the opacities appear as whorled streaks extending from a central vortex to the periphery of the cornea. The whorl-like opacities are typically inferior and cream colored, but may vary in color from white to golden brown [500]. Lenticular changes are present in approximately 30 % of affected males and include a granular anterior capsular or spider-like subcapsular deposit (the "Fabry cataract"). The corneal and lenticular opacities usually do not interfere with visual acuity. Aneurysmal dilatation and tortuosity of conjunctival and retinal vessels also occur; while not specific for Fabry disease, vessel tortuosity is observed more frequently in individuals with a higher disease severity score [501, 502].

Diagnosis

For males clinically suspected to have Fabry disease, the diagnosis can be confirmed by demonstration of deficient α-Gal A enzyme activity in plasma and/or isolated leukocytes. Molecular genetic testing that identifies a *GLA* mutation provides additional confirmation of the diagnosis. For suspected heterozygous females, demonstration of markedly decreased α-Gal A enzyme activity in plasma and/or isolated leukocytes confirms the carrier state. Females with enzyme activity in the normal range should undergo molecular genetic testing, as heterozygous females may have normal enzyme activity.

Management

The management of patients with Fabry disease relies on symptomatic treatment and enzyme replacement therapy. Diphenylhydantoin and carbamazepine may reduce the severity and frequency of painful crisis, while gabaptentin may improve pain [503]. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers should be used in patients with evidence of renal involvement, especially to reduce proteinuria. Clinical trials involving recombinant or gene-activated human α-Gal A enzyme led to the approval of Fabrazyme® (algalsidase beta; Genzyme Corp) and Replagal™ (algalsidase alpha; Shire Human Genetic Therapies, UK) by the European Agency for Evaluation of Medical Products; only Fabrazyme® was approved by the FDA for use in the US in 2001. Only Fabrazyme® was approved by the FDA for use in the US [504]. A panel of physician experts have recommended that enzyme replacement therapy (ERP) be initiated as early as possible in all males with Fabry disease, including children and those with end stage renal disease undergoing dialysis and renal

transplantation, and in female carriers with significant disease [505, 506].

Glycogen Storage Disease Type II: Acid A-Glucosidase (Acid Maltase) Deficiency and Danon Disease

Definition

Glycogen storage disease type II or Pompe disease is an autosomal recessive disorder of glycogen metabolism resulting from defects in activity of the lysosomal hydrolase acid α-glucosidase in all tissues of affected individuals. The disorder is caused mutations involving the *GAA* gene. In contrast to the other glycogen storage disorders, Pompe disease is also a lysosomal storage disease, and intralysosomal accumulation of glycogen may be observed in numerous tissues. Danon disease is an X-linked recessive disorder, that causes similar clinical features to those seen in Pompe disease [507]. Danon disease is caused by mutations in the lysosome-associated membrane protein 2 (*LAMP2*) gene, encoding the LAMP2 protein. Reduction in LAMP2 disrupts intracytoplasmic trafficking and leads to accumulation of autophagic material and glycogen in skeletal and cardiac muscle cells [508].

History

More than 50 years ago, Pompe described a 7 month old female child who died suddenly with idiopathic hypertrophy of the heart. Over the next two decades, additional clinical manifestations of idiopathic cardiomegaly associated with storage of glycogen were defined. The Coris' investigations led to the classification of what was then called Pompe disease as glycogen storage disease type II (GSDII), the most severe of the glycogen storage disorders. Danon disease was first described in boys presenting with cardiomyopathy, skeletal myopathy, and varying degrees of intellectual disability [507]. In 2000, Nishino et al. identified the genetic defects in *LAMP2* [508].

Epidemiology

The combined incidence of Pompe disease varies from 1:14,000 in African Americans to 1:100,000 in individuals of European descent.

Systemic Manifestations

Classic infantile-onset Pompe disease may be apparent *in utero* but more often presents in the first 2 months of life as hypotonia, generalized muscle weakness, feeding difficulties, failure to thrive, and respiratory distress. Hearing abnormalities are common [509, 510]. Without treatment by ERT, the cardiomegaly and hypertrophic cardiomyopathy that are often identified at birth by echocardiography progress to left ventricular outflow obstruction [511, 512]. Cardiomegaly can be seen with or without left ventricular outflow obstruction; it is not a major source of clinical morbidity [513]. Progressive deposition of glycogen results in conduction defects as seen by shortening of the PR interval on ECG. The non-classic variant of infantile-onset Pompe disease usually presents within the first year of life predominantly with motor delays and/or muscle weakness.

Pseudohypertrophy of the calf muscles and a Gower sign (inability to get from supine to standing without "crawling up" oneself) simulate Duchenne muscular dystrophy, but these findings typically occur at an earlier age in Pompe disease than in Duchenne muscular dystrophy.

Late-onset Pompe disease can present at various ages with muscle weakness and respiratory insufficiency. Progression of the disease is often predicted by the age of onset, as progression is more rapid if symptoms present in childhood. Cardiomegaly is not typically seen but progressive muscle weakness resulting in motor delays, swallowing difficulties, and respiratory insufficiency usually occurs as in the infantile form, but at a slower rate. In patients with Danon disease, major clinical features include skeletal and cardiac myopathy, cardiac conduction abnormalities, mild intellectual difficulties, and retinal disease. Men are typically affected earlier and more severely than women.

Ophthalmic Manifestations

Strabismus, ophthalmoplegia, and ptosis have all been reported in patients with Pompe disease [514]. Ophthalmoplegia and ptosis were observed in adults with late-onset Pompe disease. Strabismus was noted in children with infantile and juvenile forms of Pompe disease. In the infantile form, deposits of lysosomal glycogen have been observed in virtually every ocular tissue with the exception of the retinal pigment epithelium [514–516].

A number of ocular findings have been described in patients with Danon disease. These include diffuse choriocapillary ocular atrophy, peripheral pigmentary retinopathy, and near-complete loss of pigment in the retinal pigment epithelium [516, 517]. Predominantly central fundus abnormalities (a "bull's-eye maculopathy"), severe color vision disturbances, and a cone-rod pattern of amplitude reduction in the full-field ERG has also been described [518].

Diagnosis

Serum creatine kinase (CK) concentration is uniformly elevated (as high as 2000 IU/L; normal: 60–305 IU/L) in classic infantile-onset Pompe disease and in the childhood and juvenile variants, but may be normal in adult-onset disease [518]. Elevation of a specific urinary glucose tetrasaccharide (Glcα1-6Glcα1-4Glcα1-4Glc (Glc(4)); a glycogen-derived limit dextrin) is highly sensitive in Pompe disease but is also seen in other glycogen storage diseases [519]. It correlates

with the extent of glycogen accumulation in skeletal muscle [520]. Muscle biopsy reveals glycogen storage in the lysosomes of muscle cells as vacuoles of varying severity that stain positively with periodic acid-Schiff [521]. Acid alpha-glucosidase (GAA) enzyme activity can be performed on dried blood spots. DNA testing is also available.

Management

Enzyme replacement therapy should be initiated as soon as the diagnosis of Pompe disease is established. The FDA approved use of Myozyme® (alglucosidase alfa) for infantile Pompe disease in 2006. Studies on later-onset forms of Pompe disease have been completed, and Lumizyme® was approved by the FDA in 2010Treatment of patients with Danon disease is largely supportive.

Neuronal Ceroid Lipofuscinoses (NCL)

Definition

NCL are a group of autosomal recessive, lysosomal storage disorders characterized by the accumulation of autofluorescent material in the brain and other tissues. Collectively, they constitute the most common neurodegenerative disorders of childhood. They are progressively disabling, blinding and fatal. Depending on the electron microscopy appearance of the storage material and age of onset, four major clinical forms of NCL are recognized: infantile, late-infantile, juvenile, and adult NCL (Table 13.4) [522]. They are genetically heterogeneous with over 14 different NCL subtypes identified depending on locus heterogeneity.

History

NCL have been historically known by the eponym Batten disease after Sir Frederick Batten who first described the juvenile form of the disease in the 1900s. Zeman and Dyken (1969) referred to these conditions as the neuronal ceroid lipofuscinoses to describe the storage of ceroid and lipofuscin in neuronal cells [523].

Systemic Manifestations

The NCL are a group of neurodegenerative disorders with the major effects seen in the brain resulting inseizures, cognitive decline, visual loss, and premature death. The clinical manifestations of the major groups of NCL are generally distinguished by the age of onset. Children with *infantile NCL (INCL)* have normal development until the age of 6–12 months [524]. Children present with arrest of development, hypotonia and ataxia by 12–18 months old. Microcephaly is seen in almost all patients. Children also develop mycolonic jerks, although generalized seizures are uncommon. Loss of signal intensity in the thalamus and cerebral atrophy are commonly seen. Classical *late INCL* presents between 2 and 4 years old [525]. Affected children present with severe myoclonic seizures and they slowly progress to blindness. The progressive disease may damage the internal circadian timing system and cause sleep disturbances in patients with variant late INCL [522]. EEG shows large amplitude irregular slow activity and polyphasic spikes that are elicited with photic stimulation [526]. The most common form of NCL is *juvenile NCL* (JNCL). Children present with progressive visual failure between the ages of 4–9 years [527]. This is followed by cognitive decline that is usually noted in school. Motor dysfunction caused by extrapyramidal movements, cerebellar dysfunction and Parkinson-like rigidity are seen later. The clinical course of the disease is variable [527]. It takes an average of 3 years for JNCL patients who present with visual loss to develop neurologic symptoms. Affected patients usually die by the third or fourth decade of life. *Adult NCL* (Kufs disease) is distinguished from the other

Table 13.4 Classification of neuronal ceroid lipofuscinosis (NCL)

Age of onset (y = years)	Eponym	Gene	Deficient protein	Locus	Ultrastructure
Congenital	–	CLN10	Cathepsin D	11p15	GRODs
Infantile	Haltia-Santavuori	CLN1	Palmitoyl protein thioesterase 1 (PPT1)	1p32	GRODs
Birth—37 years					
Late Infantile	JanskyBielschowsky	CLN2	Tripeptidyl-peptidase 1 (TPP1)	11p15	Curvilinear profiles
2–10 years	Finnish variant	CLN5	Soluble lysosomal protein	13q22	Rectilinear/curvilinear/Fingerprint
	Gypsy/Indian	CLN6	ER transmembrane	15q21	Rectilinear/curvilinear/Fingerprint
	Turkish variant	CLN7	protein	4q28	Fingerprint profiles
	Northern Epilepsy	CLN8	MFSD8,lysosomal protein	8q23	
			–		
Juvenile	Spielmeyer Vogt-Sjogren	CLN3	Lysosomal transmembrane protein	16p12	Fingerprint profiles
4–10 years					
Adult	Parry	CLN4	Cysteine string protein	20q13	Rectilinear profiles
15–50 years	Kufs A	CLN6	ER transmembrane protein	15q21	Rectilinear/curvilinear/Fingerprint

NCL types by the absence of visual failure and an onset at around 30 years of age.

All of the NCL show accumulation of autofluorescent storage material in various tissues as demonstrated on light microscopy. The cerebral cortex is disproportionately affected. The appearance of the storage material under the electron microscope is highly characteristic for each of the major NCL types: granular osmiophilic deposits (GROD) in INCL, curvilinear profiles in classical late INCL, and fingerprint profiles in juvenile neuronal ceroid lipofuscinosis (JNCL). Variant forms of LINCL usually show a mixture of curvilinear and fingerprint profiles. Adult onset (Kufs) disease shows fingerprint profiles in most cases, but GROD in others.

Northern epilepsy is a specific phenotype caused by a particular mutation in *CLN8*, and is characterized by epilepsy with tonic-clonic or complex-partial seizures, slow intellectual deterioration, and motor dysfunction. Vision problems are rare.

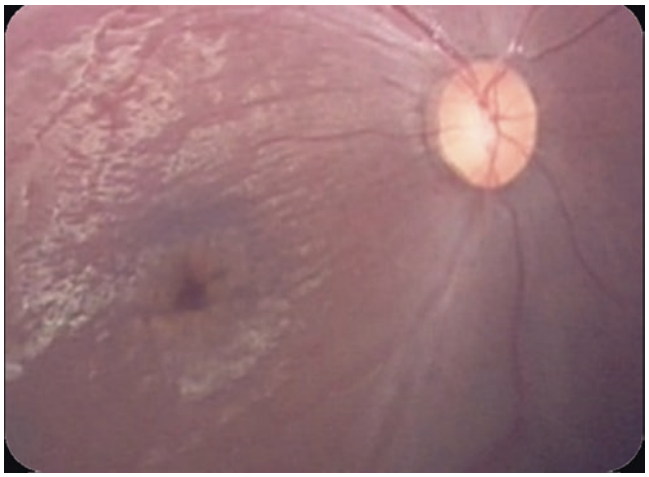

Fig. 13.20 Bull's eye maculopathy in a 6-year-old child with late infantile neuronal ceroid lipofuscinosis. Electroretinogram showed a profound loss of amplitude in this child with neuroregression and visual impairment

Ophthalmic Manifestations

Progressive visual deterioration is a characteristic feature of NCL; it is the presenting feature in JNCL, with legal blindness developing within 1–2 years of presentation [528–531]. Children are commonly noted to have eccentric viewing or overlooking holding the eyes in a raised position when trying to fixate [529, 531]. This observation is attributed to the loss of central and inferior visual field. Rotary nystagmus may be seen in all fields of gaze [532]. Patients with INCL have optic atrophy, pigmentary changes in the macula more than the retinal periphery, and a reduced or absent ERG and VEP. Visual deterioration starts by the age of 12 months, resulting in blindness by the age of 24 months. In the late infantile form there is a bull's-eye maculopathy first (Fig. 13.20).

In JNCL, early on, foveal atrophy with loss of foveal reflexes and subtle granularity of the retina may be seen, although a bull's eye maculopathy is classically described. Later on, optic nerve atrophy, vascular attenuation and pigment accumulation in the peripheral retina is seen. Compared to other retinal degenerations, the rate of progression is generally rapid [528, 529, 531, 533, 534]. The rapid progression of a retinal dystrophy and vision loss in a young child, especially when associated with neurologic deterioration and/or sleep dysfunction, should always raise the possibility of NCL. Electroretinogram (ERG) generally shows profound loss of amplitude at presentation, particularly under scotopic conditions. The loss of b-wave amplitude is greater than the decrease in a-wave amplitude, creating an electronegative configuration [529, 535]. Loss of b-wave amplitude is rapidly progressive [536].

Diagnosis

Schulz et al. provided a diagnostic algorithm for patients with NCL [537]. The diagnosis of infantile NCL is based on the combination of rapid psychomotor retardation in infancy, loss of memory, behavioral changes, dementia, and evidence of retinal degeneration. A recent onset of nightmares, scholastic failure disproportionate to the visual impairment, or behavioral changes and lability in a child with a retinal dystrophy should prompt an investigation for JNCL. Generalized cerebral and cerebellar atrophy seen on MRI are observed. The demonstration of GROD on electron microscopy of a biopsy of rectal mucosa or in peripheral blood leukocytes confirms the diagnosis. Patients with CLN3 show vacuolated lymphocytes. Skin or conjunctival biopsies can help confirm the presence and nature of lysosomal storage material (fingerprint or curvilinear profiles or granular osmiophilic deposits) [538]. Occasionally, a biopsy may fail to reveal the lysosomal inclusions, which are seldom extensive or widespread but might be seen in a repeat skin or conjunctival biopsy, and therefore should be undertaken if other findings are supportive [539]. Measurement of palmitoyl-protein thioesterase 1 (PPT1) and tripeptidyl-peptidase 1 (TPP1) in white blood cells or skin fibroblasts provides a direct way of confirming of confirming the diagnosis in patients with infantile or late infantile NCL caused by mutations in their respective genes. With the advantage of next generation sequencing, the diagnosis of NCL is now largely established on molecular genetic testing.

Management

Treatment is currently symptomatic and palliative only. Antiepileptic drugs should be selected with caution. Benzodiazepines may help control seizures, anxiety, and spasticity. Trihexyphenydate may improve dystonia and sialorrhea. Individuals with swallowing problems may benefit from placement of a gastric tube.

Acid Ceramidase Deficiency: Farber Disease

Definition

Farber lipogranulomatosis, also known as lysosomal acid ceramidase deficiency or Farber disease is a rare lysosomal storage disease. Farber disease is an autosomal recessive lipid storage disorder that is caused by mutations in the gene encoding for lysosomal acid ceramidase (*ASAH1*). Acid ceramidase is a soluble lysosomal enzyme responsible for synthesis and degradation of ceramide [540]. Deficiency of this enzyme results in progressive accumulation of ceramide in body tissues. Early- onset subcutaneous nodules, progressive deformities in body joints, hoarseness of voice and central nervous system dysfunction are among the most common manifestations of the disease.

History

Farber disease was first described by Sidney Farber in 1957 [541].

Epidemiology

Given the limited number of cases identified so far, the disorder is probably rare, and it is of unknown prevalence yet. The true incidence of the disorder likely exceeds current estimates, given the newly recognized phenotypes and difficulty in establishing diagnosis.

Systemic Manifestations

Depending on the severity and pattern of tissue involvement, seven clinical phenotypes are now recognized.

Type 1 (classic Farber disease): Classic Farber disease presents most commonly during the first few months after birth systemic with a triad of clinical manifestations including: (1) painful joints with progressive joint deformities, (2) subcutaneous nodules, and (3) progressive hoarseness of voice consistent with laryngeal involvement. Hypotonia, severe and progressive delayed psychomotor development, and seizures are recognized clinical manifestations in this phenotype. The illness is progressive and often leads to death during the first few years [542–544].

Types 2 & 3: These types are characterized by less severe neurological involvement, and longer survival periods compared to type 1 [545–547].

Type 4 (Neonatal/visceral form): These patients are extremely ill during the neonatal period with severe hepatosplenomegaly. The most severely involved patient presented hydrops fetalis and died on the third day [548]. At this early age, the classic clinical features of Farber disease are not seen and diagnosis relies on enzymatic and biochemical assays [547].

Type 5 (Neurologic progressive): this type begins between the age of 1 year to 2.5 years and characterized by significant neurological dysfunction, quadriplegia, loss of speech, myoclonic seizures and mental retardation. In contrast to classic disease viscera are spared, and connective tissues involvement and subcutaneous nodules are usually milder [549, 550].

Type 6 (combined Farber and Sandhoff disease): this phenotype may have represented co-segregation of two different alleles in the consanguineous family described by Fusch and colleagues [551, 552].

Type 7: is a rare phenotype and it is the result of combination of deficiency of glucocerebrosidase, galactocerebrosidase and ceramidase due to a mutation of prosaposin, the precursor protein for two sphingolipid activator proteins. The first patient who was described with this phenotype had a clinical picture resembling type 2 Gaucher disease [553].

Ophthalmic Manifestations

Cogan and colleagues reported a diffuse, grayish opacification of the retina about the foveola with a cherry-red center but without disturbance of visual function [554]. This abnormality, which resembles that seen in metachromatic leukodystrophy, is subtler than the cherry-red spot of Tay-Sachs disease. Macular cherry-red spot was also reported in another patient described by Nowaczyk et al [555]. A second eye abnormality reported was a granulomatous lesion of the conjunctiva. One patient showed corneal opacity and another lenticular opacity.

Diagnosis

In patients with the classic clinical triad of subcutaneous nodules, joint and laryngeal involvement, a clinical diagnosis can be made on the spot. Demonstration of deficient acid ceramidase activity, which is less than 6% of control values, measured in cultured skin fibroblasts, white blood cells or amniocytes confirms the diagnosis. Biopsy of the lesions show typical histopathologic features, showing granulomas with macrophages containing lipid cytoplasmic inclusions in subcutaneous nodules or other tissues [541]. Determination of ceramide accumulation in tissues by chromatography or mass spectrometry is also an established diagnostic test for Farber Disease.

Management

Current management for patients with Farber Disease is largely supportive, and it has therefore focused on pain therapy, physical therapy, surgical correction of severe contractures and anti-inflammatory medications. Hematopoetic stem cells transplantation (HSCT) from a healthy donor can be a source of a sufficient amount of enzyme and thus abolishes or at least decreases or stabilizes symptoms of disease

in some patients. However HSCT may not be appropriate for patients with CNS involvement as ceramide neurotoxicity may not be reversible by stem cell transplantation. HSCT provides a promising although limited approach for Farber Disease patients without neurological involvement [556–558].

Mucolipidosis Type IV

Definition

Mucolipidosis type II (MLII; I-Cell Disease; pseudo Hurler disease), and mucolipidosis type III (ML III) are autosomal recessive diseases of lysosomal enzyme trafficking. They are caused by deficiency of *N*-acetylglucosamine-1-phosphotransferase which phosphorylates carbohydrate residues on *N*-linked glycoproteins. MLII and III are caused by homozygous or compound heterozygous mutations in the *GNPTAB* gene (chromosome 12q23). Mucolipidosis Type IV (ML IV) is an autosomal recessive inborn error of intracellular membrane trafficking that is associated with lysosomal inclusions in a variety of cell types.

History

The first patient with this disorder, a 5 month old Ashkenazi Jewish boy who presented with cloudy corneas and mild developmental delay, was described in 1974 [559]. The term mucolipidosis was chosen due to the corneal clouding and the presence of multilamellar cytoplasmic inclusions in the liver, conjunctiva, and fibroblasts, similar to those seen in the sphingolipidoses, as well as the presence of single-membrane fibrogranular bodies that are often seen in the mucopolysaccharidoses [559]. Early on it was noted that the pathognomonic intracytoplasmic inclusions were present in virtually every cell in the brain, eye, and other organs. The uniform presence of constitutive achlorhydria in ML IV patients was described in 1998 [560]. In 2000, three groups independently identified the *MCOLN1* gene [561–563].

Prevalence

The combined carrier frequency of the two Ashkenazi Jewish mutations ranges from 1:100 to 1:127 in individuals of Ashkenazi Jewish descent [564, 565].

Systemic Manifestations

ML II or "I cell" disease presents at an early age with neurologic degeneration, joint stiffening, facial coarsening, and kyphoscoliosis. Death occurs in childhood. ML III is milder, with a slowly progressive course and survival to adulthood [566]. ML IV is a neurodevelopmental disorder that is also neurodegenerative in about 15 % of individuals. The most common presentation in patients with typical ML IV is severe psychomotor delay by the end of the first year of life. Psychomotor development is usually limited to few or no words and poor hand use [567]. Most individuals do not achieve independent walking [567]. Neurologic examination typically reveals severe dysarthria or anarthria, slow chewing, slow eating and swallowing, and spastic diplegia or quadriplegia [568] Epileptiform discharges are common but are infrequently associated with clinical seizures [568]. Iron deficiency occurs in about 50 % and iron deficiency anemia, which is usually well tolerated, occurs in about 10 % of individuals [567]. The achlorhydria is asymptomatic.

Individuals with atypical ML IV are less severely affected than individuals with typical ML IV or have one organ system disproportionately affected [567]. Some individuals attain the ability to walk independently. They develop slowly progressive ataxia, have mild eye abnormalities, and are usually of non-Ashkenazi Jewish descent.

Ophthalmic Manifestations

Patients with MLII manifest retinal degeneration and corneal clouding. Ophthalmic features in MLIII include corneal clouding, hypermetropic astigmatism, optic disk swelling, retinal vascular tortuosity, and maculopathy (Fig. 13.21a, b) [569].

Individuals with typical mucolipidosis IV have superficial corneal clouding that is bilateral, symmetric, and most visible in the central cornea [570]. On occasion, corneal clouding is the feature that prompts medical evaluation. Painful episodes consistent with corneal erosions are common, but appear to decrease in frequency and severity with age. Vision may be close to normal at a young age but over the first decade of life, progressive retinal degeneration with varying degrees of vascular attenuation, retinal pigment epithelial changes, and optic nerve pallor result in further decrease in vision. Virtually all individuals with mucolipidosis IV develop severe visual impairment by their early teens as a result of the retinal degeneration [567, 571] Other ocular findings are strabismus (>50 % of individuals), nystagmus, ptosis, and cataract [572].

Diagnosis

Plasma gastrin concentration is elevated in virtually all individuals with mucolipidosis IV (mean 1507 pg/mL; range 400–4100 pg/mL) (normal 0–200 pg/mL) [560]. Biopsy of skin or conjunctiva shows accumulation of abnormal lamellar membrane structures and amorphous cytoplasmic inclusions in diverse cell types. The diagnosis is confirmed with demonstration of biallelic causative mutations in the *MCOLN1* gene.

Management

Management of patients with ML IV is largely supportive. Speech therapy and physiotherapy are advised. Seizures are usually treated with standard anti-epileptic therapy. Topical lubricating eye drops, artificial tears, gels, or ointments maybe required for management of the intermittent

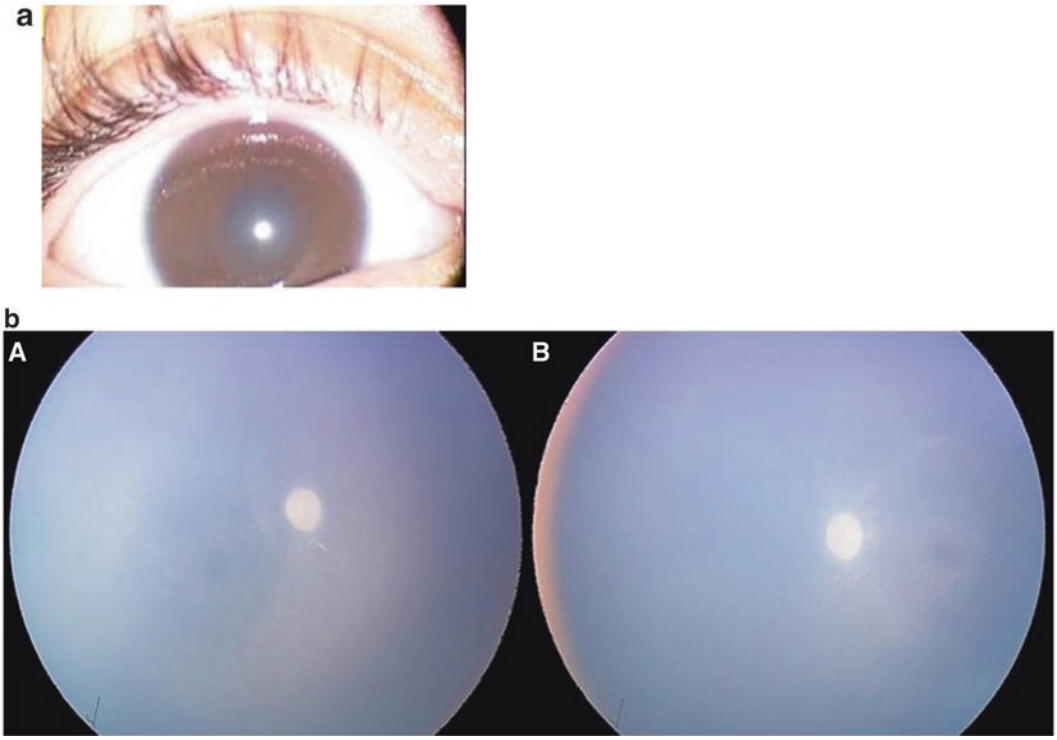

Fig. 13.21 Mucolipidosis IV. (**a**) Diffuse corneal haze and (**b**) pigmentary retinopathy in a 3-years-old boy with psychomotor delay, spasticity, and photophobia. Fundus photos show a pale disc with attenuated vessels. The details are unclear due to the corneal haze. Vision was reduced to finger counting level. High serum gastrin, low iron and ferritin, microcytic hypochromic anemia, structural brain anomalies on neuroimaging and a mutation in the *MCOLN1* gene established the diagnosis of mucolipidosis IV

Table 13.5 Classification of mucopolysaccharidoses

MPS type	Defective enzyme	GAG affected	Gene (Locus)	Inheritance
MPS IH (Hurler)	α-L-iduronidase	DS,HS	*IDUA* (4p16)	AR
MPS IH/S (Hurler/Scheie)	α-L-iduronidase	DS,HS	*IDUA* (4p16)	AR
MPS IS (Scheie)	α-L-iduronidase	DS,HS	*IDUA* (4p16)	AR
MPS II (Hunter)	Iduronate-2-sulfatase	DS,HS	*IDS* (Xq28)	X-linked
MPS IIIA (Sanfilippo A)	Heparan N-sulfatase (sulfamidase)	HS	*SGSH* (17q25)	AR
MPS IIIB (Sanfilippo B)	N-acetyl- α-D-glucosaminidase	HS	*NAGLU* (17q21)	AR
MPS IIIC (Sanfilippo C)	Acetyl-CoA: α-glucosaminidase			
	N-acetyltransferase	HS	*HGSNAT* (8p11)	AR
MPS IIID (Sanfilippo D)	N-acetylglucosamine-6-sulfatase	HS	*GNS* (12q14)	AR
MPS IVA (Morquio A)	N-acetylgalactosamine-6-sulfatase	KS	*GALNS* (16q24)	AR
MPS IVB (Morquio B)	β-galactosidase	KS	*GLB1* (3p21)	AR
MPS VI (Maroteaux-Lamy)	N-acetylgalactosamine-4-sulfatase	DS	*ARSB* (5q11)	AR
MPS VII (Sly)	β-D-glucuronidase	DS,HS,CS	*GUSB* (7q11)	AR
MPS IX (Natowicz)	Hyaluronidase	CS	*HYAL 1* (3p21)	AR

ocular irritation seen frequently in younger children. Some patients require surgical correction of strabismus. Iron supplementation is indicated for treatment of iron deficiency anemia.

Mucopolysaccharidoses

Definition

The mucopolysaccharidoses (MPSs) are a group of seven inherited metabolic disorders (Table 13.5) caused by deficient lysosomal enzymes involved in the metabolism of glycosaminoglycans (GAGs). The disorders are all characterized by intracellular accumulation of the incompletely cleaved compounds. MPSs result from mutations in genes coding for the different lysosomal enzymes [573] All except MPS II (Hunter) which is X-linked recessive, are inherited in an autosomal recessive manner. Multiple organ systems are affected including the skeletal, nervous, ocular, cardiac, respiratory, and gastrointestinal systems. The main systemic and ocular features seen in the MPSs are summarized in Table 13.6 [573].

Table 13.6 Manifestations MPS

MPS type	Ocular manifestations	Systemic manifestations
MPS IH (Hurler)	Corneal clouding +++, retinopathy++ optic disc swelling and atrophy ++ glaucoma++	Relative macrocephaly, coarse facies, macroglossia, hernias, hepatosplenomegaly, dysostosis +++, joint stiffness, deafness, recurrent respiratory infections, cardiac disease+++, CNS disease+, mental subnormality+++. Early death due to cardio-respiratory failure
MPS IH/S (Hurler/Scheie)	Intermediate between Hurler and Scheie	Intermediate between Hurler and Scheie, mental subnormality+
MPS IS (Scheie) span	Mild variant of Hurler	Mild variant of Hurler, normal intelligence, normal stature and life
	Optic disc swelling and atrophy +	Mild skeletal deformities+ (early onset carpal tunnel syndrome)
MPS II (Hunter)	Corneal clouding±, retinopathy++ optic disc swelling and atrophy ++ glaucoma+	Coarse facies, macroglossia,dyostosis+, cardiac disease++ hernias, hepatosplenomegaly, respiratory difficulties, CNS disease+, ivory colored skin, normal intelligence, early death due to cardio-respiratory failure
MPS IIIA (Sanfilippo A)	Corneal clouding±, retinopathy++ (hyperactivity),	Mental subnormality+++, behavioral abnormalities+++
	Glaucoma+	Somatic disease are mild, leading to late diagnosis
MPS IIIB (Sanfilippo B)	Same as MPS IIIA	Same as MPS IIIA
MPS IIIC (Sanfilippo C)	Same as MPS IIIA	Same as MPS IIIA
MPS IIID (Sanfilippo D)	Same as MPS IIIA	Same as MPS IIIA
MPS IVA (Morquio A)	Corneal clouding+, retinopathy+ glaucoma+	Distinctive skeletal deformities (gibbus)+++, odontoid hypoplasia. CNS disease ++ (myelopathy), cardiac disease+
MPS IVB (Morquio B)	Same as MPS IVA	Same as MPS IVA
MPS VI (Maroteaux-Lamy)	Corneal clouding+++ glaucoma++, retinopathy+ optic atrophy++	Clinically like MPS IH but normal intelligence, dysostosis+++, CNS disease+, cardiac disease+
MPS VII (Sly)	Corneal clouding++ optic atrophy++	Dysostosis++, mental subnormality++ cardiac disease++ (fetal hydrops)

MPS I (Hurler; Hurler/Scheie; Scheie)

Definition

MPS I considered the prototypic MPS, occurs due to deficiency of the lysosomal enzyme alpha-L-iduronidase (IDUA). The accumulation of GAGs dermatan and heparan sulfate result in three major clinical entities: Hurler (MPS IH), Scheie (MPS IS), and Hurler/Scheie (MPS IH/S) syndromes. MPS 1H and MPS 1S syndromes represent phenotypes at the severe and mild ends of the MPS I clinical spectrum, respectively and the MPS1H/S syndrome is intermediate in phenotypic expression. MPS I is caused by homozygous or compound heterozygous mutation in the gene *IDUA* (chromosome 4p16).

Epidemiology

Although MPS 1H is most common type of MPS 1 and comprises at least 80 % of affected individuals, MPS 1H/S or MPS 1S patients make up a larger fraction of individuals with MPS I due to increased longevity. MPS I is seen in all populations at a frequency of approximately 1:100,000 for the severe form and 1:500,000 for the attenuated form.

History

MPS 1 was first described in 1919 by pediatrician Gertrude Hurler in two infants with gibbus, corneal clouding and mental retardation. Brante classified MPS 1H as a mucopolysaccharidosis, after he isolated dermatan sulfate from the liver of patients with MPS 1H [574, 575].

Systemic Manifestations

Children with MPS 1H appear normal at birth, but may have inguinal or umbilical hernias and suffer from recurrent respiratory tract infections in infancy. A slight coarsening of the facial features at 3–6 months old is usually the first abnormality detected. The head is large with prominent frontal bones, and the skull is often scaphocephalic secondary to premature closure of the metopic and sagittal sutures. The nasal bridge is depressed with broad nasal tip and anteverted nostrils, and cheeks are full. The lips are enlarged and the mouth is usually held open, with glossoptosis. The pejorative term "gargoylism" is no longer applied but referred to these "coarse" facial features (Fig. 13.22).

Chronic 'rhinitis' with noisy mouth breathing is virtually universal. During the second year of life developmental progress slows, and physical manifestations become more apparent. Scoliosis, gibbus deformity, other bony abnormalities including joint contractures, short stature, facial and body hypertrichosis, dental abnormalities, hearing loss, cardiac disease (coronary insufficiency, valvular incompetence, and/or cardiomyopathy), and hepatosplenomegaly develop with time. The disease has a chronic and progressive course. Death usually occurs in childhood (median 5 years) due to respiratory or cardiac failure, with only rare survivors beyond the first decade.

If development is normal at age 24 months and if moderate somatic involvement is evident, the patient is classified as having intermediate MPS IH/S. Mental function is often preserved, but some patients have intellectual decline with age. More than 85 % of persons with MPS IH/S have dysostosis,

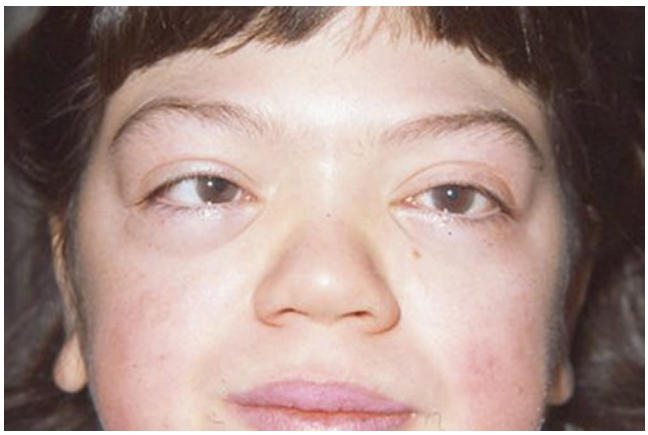

Fig. 13.22 Coarse facies in a patient with Mucopolysaccharidosis IH. The head is large with prominent frontal bones. The nasal bridge is depressed with broad nasal tip and anteverted nostrils, and cheeks are full. The lips are enlarged and the mouth is usually held open, with glossoptosis

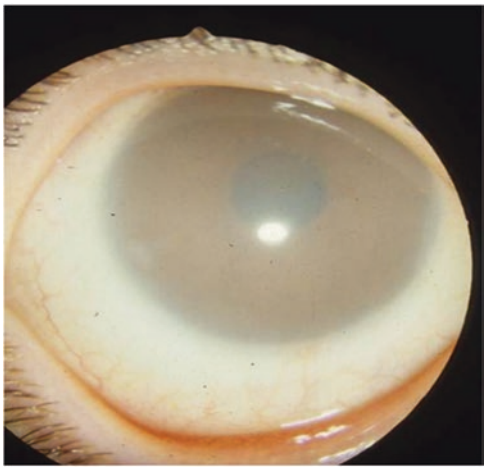

Fig. 13.23 Ground-glass appearance of the cornea due to glycosaminoglycan deposition in the stroma in a patient with Mucopolysaccharidosis IH

primarily in the vertebrae and femur. The manifestations of MPS IS are so mild that the diagnosis is often not considered until adulthood. Stiff joints, and aortic regurgitation are common features. Joint involvement is marked in the hand with a claw-hand deformity. The face is normal in MPS IS without the coarsening seen in MPS IH and IH/S. Survival to adulthood is typical in MPS IH/S and MPS IS.

Ophthalmic Manifestations

Progressive corneal opacification (ground-glass appearance) due to abnormal GAG deposition in the corneal stroma with resultant photophobia and visual impairment is a prominent feature of patients with MPS I and IH/S (Fig. 13.23).

Corneal clouding in MPS IS is seen in adults and more commonly involves the peripheral cornea. GAG deposition which results in an increased corneal thickness which correlates with the degree of corneal opacification [576]. This must be kept in mind and accounted for at the time of measuring IOP in patients with MPS 1. The adjustment factor for increased corneal thickness secondary to GAG deposition may differ from the adjustment factor for normal collagen fibers, and might require taking into account both the central corneal thickness and hysteresis [577]. Elevated IOP may occur due to GAG accumulation in the angle of the anterior chamber, leading to outflow obstructive glaucoma (open-angle glaucoma) or due to secondary angle-closure glaucoma caused by thickening of the anterior segment structures, in particular by the peripheral cornea in all types of MPS I [578]. Retinal pigmentary degeneration, optic disc swelling, and optic atrophy may occur in all MPS I subtypes [579]. Corneal opacification often impedes evaluation of the posterior segment. ERG reveals a rod-cone dystrophy with no distinct differentiation from that seen in MPS II and III. There is a wide variability in severity. Although the retinal dystrophy is progressive, there is no apparent correlation between severity and age [580]. The ERG changes are often much worse than the retinal appearance, with mild RPE changes often being the only visible changes. A normal retinal appearance does not rule out the presence of retinal dystrophy.

Diagnosis

Measurement of urinary GAG levels is a sensitive but non-specific screening test for MPS. GAG electrophoresis helps determine the specific type of GAG excreted. False-negative results may occur, especially if the urine is too dilute (specific gravity of <1.015 g/mL). A definitive diagnosis of MPS is based on deficient enzyme activity in fibroblasts, leukocytes, serum, or blood spots. Enzyme assay alone cannot predict the severity of MPS I. Large cells containing acid MPS can be seen in conjunctiva suggesting the role for conjunctival biopsy in diagnosis. Identification of the *IDUA* mutations confirms the diagnosis. Prenatal diagnosis is possible on both cultured amniotic fluid cells and chorionic villus biopsies.

Management

Therapy is provided by an interdisciplinary team approach and includes special education for developmental delays, cardiac valve replacement as needed, physical therapy, orthopedic surgery as needed (joint replacement, atlanto-occipital stabilization, median nerve decompression for carpal tunnel syndrome); tonsillectomy and adenoidectomy for upper airway obstruction and surgical intervention for cervical myelopathy. Hematopoietic stem cell (HSC) transplantation, which provides a continuous source of enzyme produced by the blood cells of an unaffected individual, and ERT that ensures delivery of exogenous enzyme (laronidase, Aldurazyme®) are now considered standard procedures for definitive management of MPS IH and IH/S and IS when

symptoms are moderately severe. In addition to bone marrow and peripheral blood, unrelated umbilical cord blood is an effective HSC source [581]. To be effective, HSC transplantation and ERT have to be performed early, well before evidence of CNS involvement [582]. Early diagnosis is necessary for optimal outcomes. Bone marrow transplantation can prolong life with some survivors well into their teenage years [583]. Their effect on visual acuity, corneal clouding and optic nerve and retinal function is controversial. Most studies report persistence of visual impairment, progressive corneal clouding and decline of retinal function [576, 583, 584]. A number of promising therapeutic approaches are currently under investigation. Intrathecal ERT delivered to the brain via an implanted device has shown strong promise in animal models of MPS I, and this modality is being tested in MPS I, II and IIIA patients.

Corneal transplantation can improve vision, and should be considered in patients with MPS [585]. Replacement of all three corneal layers may not be required in cases where disease is limited mostly to the stromal and epithelial layers. Deep anterior lamellar keratoplasty (DALK) has been recommended over penetrating keratoplasty for patients with MPS [586]. Preserving the host endothelium eliminates the risk of endothelial rejection. Visual recovery may be compromised despite successful keratoplasty due to coexisting retinopathy, optic nerve dysfunction, glaucoma, and cortical visual impairment. Careful preoperative evaluation and selection of patients for surgical intervention is essential.

MPS II (Hunter Syndrome)

Definition

MPS II is an X-linked recessive disorder due to deficiency of lysosomal enzyme iduronate-2-sulfatase (IDS) leading to accumulation of heparan and dermatan sulfate in tissues. It is caused by mutations in the *IDS* gene (Xq28).

History

Charles Hunter first reported two brothers with what was then referred to as gargoylism, in 1917 [587], although the enzymatic defect would not be elucidated until decades later in 1968 by Neufeld et al. [588].

Epidemiology

The incidence is 1 in 34,000–140,000 depending on the population studied.

Systemic Manifestations

Age of onset, disease severity, and rate of progression vary significantly. In those with severe disease, CNS involvement (progressive cognitive deterioration), progressive airway disease, and cardiac disease usually result in death in the first or second decade of life. In those with attenuated disease, the CNS is not (or is minimally) affected, and survival into the early adult years with normal intelligence is common. Ever since Hunter's first description, the classic coarse facial appearance and hair, skeletal dysplasia with short stature and joint contractures, cranial vault abnormalities, and hepatosplenomegaly have been well recognized. Hearing loss and dental anomalies may also occur. The appearance of newborns with MPS II is normal, and coarse features generally do not manifest until between ages 18 months and 4 years in the severe form and about 2 years later for those with the attenuated form.

Ophthalmic Manifestations

Corneal clouding is not a typical feature of MPS II. Discrete corneal lesions that do not affect vision may be discovered by slit-lamp examination. A retinal dystrophy and ERG findings similar to those described above for MPS I may be present. Optic nerve head swelling and optic atrophy has been reported.

Diagnosis

A definitive diagnosis of MPS in a male proband is based on deficient enzyme activity in fibroblasts, leukocytes, serum, or blood spots [589]. Identification of the *IDS* mutations confirms the diagnosis in a patient with an unusual phenotype.

Management

Supportive therapy is as for MPS I. No controlled clinical studies of HSCT have been performed. ERT with idursulfase (idursulfase; Elaprase®), a recombinant form of human iduronate 2-sulfatase approved for clinical use that is beneficial if started early [590]. A number of promising therapeutic approaches are currently under investigation. Intrathecal ERT delivered to the brain via an implanted device has shown strong promise in animal models of MPS I, and this modality is being tested in MPS I, II and IIIA patients.

MPS III (Sanfilippo Syndrome)

Definition

The Sanfilippo syndromes are characterized by impaired degradation and systemic accumulation and urinary excretion of heparan sulfate. There are 4 subtypes, each due to the deficiency of a different enzyme: heparan N-sulfatase (type A); alpha-N-acetylglucosaminidase (NAGLU; type B); acetyl CoA:alpha-glucosaminide acetyltransferase (type C); and N-acetylglucosamine 6-sulfatase (type D). Clinically, the four types MPS IIIA-D are indistinguishable. The genes encoding these four enzymes have been characterized and various mutations have been reported (Table 13.5).

History

MPS III was described in 1963 by a pediatrician named Sylvester Sanfilippo in children with a form of mental retardation associated with excretion of GAG in the urine, but with less pronounced visceral and skeletal manifestations than reported in previously described MPS patients. Kresse et al. recognized different forms of Sanfilippo syndrome by co-cultivation experiments on fibroblasts [591]. Kresse and Neufeld identified heparan sulfatase as the enzyme deficient in this disorder [592].

Epidemiology

MPS III is the most frequently occurring type of the mucopolysaccharidoses. The incidence is 1 in 20,000–325,000 depending on the population studied. Given the early mild phenotype and the possibility of a missed diagnosis, the true incidence may be higher. Sanfilippo syndrome type A is probably the most frequent subtype.

Systemic Manifestations

Unlike the other MPSs that present with extensive somatic involvement, patients with MPS III typically present with mainly cognitive and neurological signs and symptoms. Symptoms usually appear at 2–6 years old often beginning with attention deficits, hyperactivity and progressive developmental delay with loss of milestones all being the harbingers of progressive cerebral atrophy throughout childhood resulting in eventual aphasia, vasomotor instability, seizures, and dementia. Facial dysmorphism, although frequently mild and easily missed, is detected in most Sanfilippo patients. Patients show hirsutism and progressive coarsening of the facial features. A vegetative state is the end stage with death occurring in the second or third decade. However, milder phenotypes can occur and there may be marked intrafamilial variability. Hepatosplenomegaly is mild or absent. Joint involvement and short stature are not marked. The presentation may be divided into three stages [593].

Stage 1: 1–4 years old, isolated developmental delay
Stage 2: 3–4 years old, severe behavioral problems, sleep disturbances, progressive mental deterioration leading to severe dementia
Stage 3: 10 years old, improved behavior, but motor retardation and problems with ataxia, swallowing, seizures and spasticity

Sleep disturbances consist of settling difficulties, early waking and frequent nocturnal waking. Some patients even show a complete reversal of their day–night rhythm. The clinical course in Sanfilippo type A is more severe, with earlier onset, more rapid progression of symptoms and shorter survival [594, 595].

Ophthalmic Manifestations

A retinal dystrophy may be present and the ERG findings similar to those described above for MPS I [580]. However, less variability in the range of severity is observed as compared to MPS I and II [580]. Corneal opacification is insignificant in MPS III [596]. Optic atrophy and disk swelling can occur, but is infrequent compared to MPS I [579].

Diagnosis

The probable diagnosis of all MPS III subtypes is based on increased concentration of heparan sulfate in the urine. Enzymatic assays in leukocytes and/or fibroblasts confirm the diagnosis and allow for discrimination between the different subtypes. Molecular genetic testing can be offered. Prenatal diagnosis is possible for all four subtypes.

Management

Current treatment options are limited to supportive care. Antipsychotic drugs may be required. The behavioral problems respond poorly to standard stimulant-based medications or behavior-based interventions. Bone marrow transplantation is not very successful in this form of MPS [597]. A number of promising therapeutic approaches are currently under investigation. Intrathecal ERT delivered to the brain via an implanted device has shown strong promise in animal models of MPS I, and this modality is being tested in MPS I, II and IIIA patients. In a pilot study in children with MPS IIIA and B, improvements were demonstrated after 12 months of oral treatment with a genistein-rich isoflavone extract (substrate reduction therapy). Treated patients showed a decrease in urinary GAG levels and improvement [598], but the drug failed to ameliorate clinical disease in patients in a placebo-controlled crossover study [599]. Higher doses are being studied and these might be more effective clinically.

MPS IV (Morquio Syndrome)

Definition

Morquio syndrome is characterized by systemic accumulation of keratan sulfate and chondroitin-6-sulfate. There are 2 subtypes, each due to the deficiency of a different enzyme: N-acetylgalactosamine-6-sulfatase (GALNS; type A) and β-galactosidase (type B). The genes encoding these two enzymes have been characterized and various mutations have been reported. The two subtypes have overlapping clinical features, but type IVB is milder than IVA.

History

In 1929, the Uruguayan pediatrician Luis Morquio described a form of "familial skeletal dystrophy" affecting four of five

children born to consanguineous parents from Swedish descent. Urinary excretion of keratan sulfate was noted. Nelson et al. proposed the division of MPS IV into subgroups based on severity in 1988 [600].

Epidemiology

The incidence of MPS IVA in the general population ranges from 1 in 76,000 live births to 1 in 640,000 live births in multiple countries. MPS IVB is very rare.

Systemic Manifestations

Clinical presentations of MPS IVA reflects a spectrum of progression from a severe "classical" phenotype to a mild "attenuated" phenotype. Accumulation of chondroitin-6-sulfate and keratan sulfate manifests predominantly as short stature and skeletal dysplasia (dysostosis multiplex), including atlantoaxial instability and cervical cord compression. Kyphosis and pectus carinatum are often present before the first year with gibbus observable before 2 years old in patients with a classical phenotype. Children with severe MPS IVA show a reduced growth rate beginning at approximately 18 months old and growth will stop at approximately 7 or 8 years old; although, some patients with attenuated MPS IVA may continue growing into adolescence and exceed 140 cm in height. Ligamentous laxity and joint hypermobility are distinctive features of MPS IVA, and are rare among other storage disorders. Abnormalities in the auditory, cardiovascular, and respiratory systems also occur. With disease progression, cardiac and pulmonary complications typically arise, even in cases categorized as mild. It is believed that the dental findings are pathognomonic for MPS IVA. Patients usually have widely spaced anterior teeth, tapered posterior teeth with pointed cusp tips, pitted and grayish enamel with decreased thickness, and frequent caries [601]. The central nervous system is not believed to have significant manifestations of GAG accumulation and normal intelligence appears to be preserved. Patients have a high risk of developing neurological complications due to odontoid hypoplasia, and incomplete ossification of the anterior and posterior rings of the atlas. This results in atlantoaxial subluxation and spinal cord compression with cervical myelopathy, consequential quadriparesis or even death. The average age of death for a MPS IVA patient is 25 years with respiratory failure as the main cause of death (63 %).

Patients with MPS IVB have a milder disease than MPS IVA and show normal or near normal stature with normal neck development and absence of hearing loss or hepatomegaly. In some cases β-galactosidase deficiency leads to accumulation of GM1 ganglioside, causing the neurodegenerative disease GM1 gangliosidosis [602].

Ophthalmic Manifestations

Mild corneal clouding, and retinopathy may be observed in MPS IV patients. Pseudoexophthalmos may be seen secondary to shallow orbits. No cases of optic nerve swelling or atrophy were found in 29 MPS IV patients [579], but optic atrophy may ensue due to progressive retinopathy. Cataracts may occur but are usually clinically insignificant. Punctate lens opacities have been reported in three siblings with MPS IV [603, 604].

Diagnosis

Diagnosis of MPS IV is made by evaluating urinary GAG, and enzymatic activity in blood cells or fibroblasts. Gene sequencing is often used to confirm enzyme results.

Management

Bone marrow transplantation is not very successful in this form of MPS. ERT for MPS IVA is considered ideal due to lack of neurologic deterioration in these patients, and is currently under investigation.

MPS VI (Maroteaux-Lamy Syndrome)

Definition

This autosomal recessive disorder is caused by a deficiency of lysosomal N-acetylgalactosamine-4-sulfatase also known as arylsulfatase B (ASB), leading to accumulation of dermatan sulfate in tissues. The gene encoding ASB, *ARSB* (5q11-13), has been characterized.

History

Maroteauxet al first described this disorder as a novel dysostosis associated with increased urinary excretion of chondroitin sulfate in 1964 [605].

Epidemiology

Birth prevalence of MPS VI is between 1 in 43,261 and 1 in 1,505,160 live births. The incidence is 1 in 76,000–300,000 depending on the population studied.

Systemic Manifestations

The clinical presentation of MPS VI varies with respect to age of onset and rate of disease progression. Affected children typically exhibit short stature, bony dysplasia (dysostosis multiplex), coarse facies, hearing loss, hernias, hepatosplenomegaly joint stiffness, and cardiac disease. Morbidity includes recurrent respiratory tract disease sometimes necessitating tracheostomy, spinal cord compression and obstructive hydrocephalus often requiring shunting procedures. Intelligence is usually not affected. Patients with the rapidly progressing form frequently die from heart failure in the second or third decades.

Ophthalmic Manifestations

Full thickness corneal clouding is a characteristic finding. Vision can be reduced to hand motions as a result of corneal

involvement. Corneal transplantation has been performed but mucopolysaccharide accumulation in the donor graft may occur. Microscopic examination of the host tissue reveals thickening of the corneal epithelium, loss of Bowman's layer, and positive staining (Alcian blue or colloidal iron) for acid mucopolysaccharide in the epithelium, anterior stroma, and cytoplasm of keratinocytes and endothelial cells. Intraocular pressure may be elevated due to a secondary angle closure and/or trabecular outflow obstruction from GAG deposition. Optic disc swelling or atrophy may also occur. Retinopathy is usually not seen in patients with MPS VI.

Diagnosis

Diagnosis of MPS VI is made by evaluating urinary GAG, and enzymatic activity in blood cells or fibroblasts. Gene sequencing is often used to confirm enzyme results. Prenatal diagnosis is based primarily on reduced/low ASB activity with optional support of mutational analysis.

Management

ERT with galsulfase (Naglazyme®), a recombinant form of human N-acetylgalactosamine-4-sulfatase, is approved for clinical use and is beneficial if started early [606]. Visual impairment, progressive corneal clouding and decline of retinal function may not resolve following ERT [583]. There is one report of resolution of papilledema and improvement in visual acuity after ERT [607]. Bone marrow transplantation has been used in MPS VI. Although leukocyte ASB enzyme level and urinary GAG improve, skeletal abnormalities remain difficult to stabilize or correct.

Management of ocular complications is similar to that of patients with MPS I. DALK can be successful in the short term management of visually significant corneal opacification in ML VI [608].

MPS VII (Sly Syndrome)

Definition

β-glucuronidase (GUSB) is a lysosomal enzyme which catalyzes the hydrolysis of β-glucuronide residues as part of the sequential degradation of the GAGs chondroitin sulfate, dermatan sulfate, and heparin sulfate. The autosomal recessive disorder known as MP VII is due to deficiency of this enzyme. The clinical manifestations are due to the accumulation of incompletely degraded GAGs in secondary lysosomes in many tissues. The gene for β-glucuronidase has been cloned and over 50 mutations have been identified. A pseudo deficiency is also known in which enzyme levels are reduced (but ≥3%), yet the phenotype is normal with no abnormal urinary excretion [609].

History

The first patient was described by Sly in 1973 [610].

Epidemiology

Less than 50 cases have been reported. The incidence of the severe neonatal form is estimated at approximately 1 per 300,000 live births. Milder forms are even more uncommon.

Systemic Manifestations

MPS VII may be categorized as mild, moderate, or severe or as neonatal, infantile, and juvenile. Although MPS VII is perhaps more likely than other mucopolysaccharidosis to be detected at birth, some individuals with mild disease may not present until childhood or even early adulthood. The more common and severe form presents often as lethal neonatal hydrops fetalis [609, 611]. Other features of the moderate and severe type of MPS VII include short stature, coarse facies, bone and joint abnormalities (dysostosis multiplex), kyphoscoliosis with gibbus deformity, sternum deformity, congenital hip dislocation, recurrent respiratory disease, umbilical and inguinal hernia, hepatosplenomegaly, and mild to severe mental retardation which is usually non progressive [612]. Other less common findings include hypertrophic cardiomyopathy.

Reduced life span is seen in the more severe forms, often with neonatal or infant death. Survivors beyond the neonatal period with moderate to severe disease experience multiple skeletal problems with difficulties ambulating and recurrent respiratory infections. A mild form of MPS VII presents after 4 years old with variable severity of skeletal involvement, normal intelligence, and normal facies [613]. Mild MPS VII can also present as isolated fixed thoracic kyphosis [614].

Ophthalmic Manifestations

Oculofacial features of the characteristic facies may include epicanthus, mid facial hypoplasia, and telecanthus. The most common ocular abnormality is progressive corneal clouding which is usually mild and not noted until the end of the first decade but may be observed in some infants and younger children [615]. The cornea is clear in the milder forms of MPS VII and usually in the first 5 years of life even in more moderate disease. There are very few reports in the literature regarding other ocular findings although retinal dystrophy, optic atrophy, and papilledema may occur. Optic atrophy is usually a late manifestation in survivors beyond the neonatal period. Abnormal storage of GAGs in retinal pigmented epithelium, ciliary body epithelium, and corneal endothelium has been observed in animal models.

Diagnosis

The biochemical diagnosis requires high urinary excretion of GAGs and large oligosaccharides. Metachromatic granular inclusions (Alder-Reilly bodies) are observed in leukocytes. Abnormalities can also be seen in some leukocytes of obligate carriers or pseudo deficiency patients. Light and electron microscopy of fibroblasts, lymphocytes, neurons, conjunctiva,

muscle fibers, renal cells, gingiva or hepatic cells show cytoplasmic inclusions representing partially degraded GAGs in secondary lysosomes. Inclusions are also found in corneal stromal keratocytes. The definitive diagnosis is based on the presence of low leukocyte or fibroblast ß-glucuronidase enzyme activity (0–2 %). Gene mutation analysis is confirmatory.

Management

ERT has been unsuccessful. Variable success has been reported with bone marrow transplantation. There are currently multiple animal trials of gene therapies including viral mediated gene transfer and artificial neo-organ implantation. Some success has been observed in mice with gene therapy techniques resulting in partial resolution of eye disease following intravitreal injection of recombinant adenovirus. Penetrating or lamellar keratoplasty is the treatment of choice for visually significant corneal clouding, although visual gain may be limited by retinal and/or optic nerve disease.

Section Nine: Peroxisomal Disorders

Peroxisomes are intracellular organelles that catalyze a range of essential metabolic functions, mainly related to lipid metabolism. Like lysosomes, they are present in all cells and are particularly abundant in the liver, kidney and the developing brain; but unlike lysosomes they possess anabolic and catabolic functions. Peroxisomes are formed *de novo* by budding off from the endoplasmic reticulum and by division of preexisting peroxisomes. Peroxisomal proliferation and the formation and incorporation of the peroxisomal matrix and membrane proteins are regulated by about 13 *PEX* genes which encode proteins (peroxins) required for peroxisomal biogenesis [616]. Peroxisomal disorders are a heterogeneous group of multi-organ dysfunction disorders, which fall into three main categories—peroxisome biogenesis disorders, single peroxisome enzyme/protein deficiencies, and contiguous deletion syndromes (Table 13.7).

History

Johannes Rhodin discovered the peroxisome in a rat kidney in 1954, and called it a ‘microbody’ [617]. For more than 20 years after their original description, peroxisomes were thought to have only a limited role in mammals. The first demonstration of a more significant role was provided by Lazarow and Duve who found that these structures oxidized certain substrates by utilizing molecular oxygen and producing hydrogen peroxide, leading them to designate this organelle the “peroxisome” [618]. Study of the peroxisomal disorders has contributed to understanding the expanded physiologic roles of this organelle [616, 619–622].

Peroxisomal Biogenesis Disorders

Peroxisomal biogenesis disorders are characterized by malformation or complete absence of peroxisomes in cells and multiple enzyme deficiencies.

Zellweger Spectrum

Definition

The Zellweger spectrum includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease, which have overlapping features with Zellweger syndrome being the most severe and infantile Refsum disease the least severe of peroxisomal biogenesis disorders. This group of diseases is characterized by generalized loss of peroxisomal functions including impaired β-oxygenation of very long-chain fatty acids (VLCFA), impaired oxygenation of phytanic acid and pipecolic acid, decreased plasmalogen synthesis, and abnormal bile-acid metabolism. Clinically they are characterized by neurologic dysfunction, typical craniofacial dysmorphism of varying severity, hepatic and gastrointestinal dysfunction and ocular abnormalities.

Epidemiology

The incidence of Zellweger syndrome is 1 in 50,000–100,000 live births.

Systemic Manifestations

Affected individuals present at birth with a typical facial appearance characterized by a high forehead, large anterior fontanelle with widely spaced sutures, low and broad nasal bridge, micrognathia, high arched palate, external ear deformity, and redundant skin folds in the neck. The neurological picture is dominated by severe hypotonia with resultant poor feeding, depressed neonatal and deep tendon reflexes, seizures and developmental delay [623]. The most prominent organ abnormalities are severe brain malformations, hepatic fibrosis, renal cysts, and abnormal calcific stippling of multiple joints [623]. Death usually occurs in early infancy in Zellweger syndrome secondary to progressive apnea or respiratory compromise from infection. Brain MRI demonstrates diffuse cortical (microgyria and pachygyria) and white matter abnormalities (dysmyelination). Neonatal adrenoleukodystrophy (NALD) is a slightly milder phenotype; some patients survive to mid-childhood, although they become deaf, blind, and profoundly retarded. NALD and infantile Refsum disease differ from Zellweger syndrome in the extent of central nervous system changes, and the absence of chondrodysplasia punctata and renal cysts. Patients with NALD demonstrate atrophy of the adrenal cortex, but rarely manifest adrenal insufficiency [624]. Patients with infantile Refsum disease may have no neuronal migration disorder. Neonatal seizures are present in both Zellweger syndrome

Table 13.7 Classification of peroxisomal disorders

#	Disorder	Main systemic manifestations	Main ocular manifestations	Biochemical Derangements	Gene/s
Disorders of peroxisome biogenesis					
1. Zellweger Spectrum					
1.1	Zellweger syndrome (ZS)	Infancy	– Early onset pigmentary retinopathy (leopard-spot retina)	Elevated plasma	*PEX 1, 2 3, 4, 5, 6, 10,12, 13, 14, 16,19, 26*
		– Characteristic face with large fontanelles	– Optic atrophy	– VLCFA (highest in ZS)	
		– Severe hypotonia	– Unrecordable ERG	– Bile acid intermediates	
		– Seizures	– Anterior segment abnormalities in ZS corneal clouding, cataract, glaucoma	Di/Tri hydroxycholestanic acid	
		– Sensorineural deafness		Elevated/Normal	
		– Hepatocellular dysfunction failure to thrive		– Phytanic acid	
				– Pristanic acid	
				– Pipecolic acid	
1.2	Neonatal adrenoleukodystrophy	– Neonatal/early infantile hypotonia		Low eryhthrocyte plasmalogens (lowest in ZS)	
1.3	Infantile Refsum disease	Infancy			
		– Mild external features of ZS			
		– Spectrum from learning disability to severe global developmental delay			
		– Deafness			
		– Growth failure			
		– Hyperoxaluria			
2	Rhizomelic chondrodysplasia punctate (RCDP) type 1	Infancy	– congenital cataracts	– Elevated phytanic acid	*PEX7*
		– Skeletal abnormalities (rhizomelia, contractures)		– Low erythrocyte plasmalogens	
		– Short stature			
		– Intellectual disability			
		– Seizures			
		– Congenital heart disease			
Single peroxisomal enzyme deficiency					
3	X-linked Adrenoleukodystrophy (X-ALD)	Onset infancy—adulthood	– Optic atrophy	Elevated plasma	*ABCD1*
		– Neurodegeneration		– VLCFA	
		– Cognitive decline			
		– Seizures			
		– Spasticity			
		– Behavioral changes			
		– Hearing loss			
		– Adrenal insufficiency (Addison disease)			
4	Refsum disease	Onset first to third decade	– Pigmentary retinopathy	Elevated in fluids/tissues	*PHYH*
		– Deafness	– Cataracts	– Phytanic acid	*PEX7*
		– Anosmia	– Miosis (dysautonomia)	Decreased	
		– Cardiomyopathy		– Phytanic oxidase activity	
		– Ichthyosis			
		– Peripheral sensorimotor neuropathy			
		– Ataxia			
5	Primary hyperoxaluria	Onset in childhood	– Pigmentary retinopathy (black parafoveal ringlets)	– Hyperoxaluria	*AGXT*
		– Calcium oxalate nephrolithiasis, nephrocalcinosis, renal failure	– Optic atrophy	– Hyperoxalemia	
		– Pathological fractures	– Choroidal neovascularization	– Hyperglycolic aciduria	
		– Heart block		– Calcium oxalate deposits in tissues	
		– Peripheral vascular insufficiency		– Metabolic acidosis	
		– Acrocyanosis, calcinosis cutis			
6	Mulibrey Nanism	Onset in childhood	– Pigmentary retinopathy (yellow dots)		*TRIM37*
		– Short stature	– diffuse chorio-retinal atrophy		
		– Dysmorphism			
		– Cardiomyopathy			
		– Nevi flaemmei			
		– Hepatomegaly			
		– Hypotonia			
		– Wilms tumor			

and NALD, but not in infantile Refsum disease. Patients with infantile Refsum disease often survive to the second decade. Older children manifest progressive deafness and visual impairment. Children with infantile Refsum disease may also experience episodes of hemorrhage, including intracranial hemorrhage associated with low serum levels of vitamin K [625].

Ophthalmic Manifestations

Ocular findings in peroxisomal biogenesis defects include shallow orbital ridges, upslanting palpebral fissures, epicanthal folds, retinal degeneration, and optic atrophy [618, 626, 627]. Retinal dystrophy is universal. A leopard-spot retinal pigmentation (small, round, discrete, evenly pigmented, and spaced pigment clumps) is characteristically seen in Zellweger syndrome, NALD and infantile Refsum disease during the first year or two of life [628]. The flecked appearance fades with time and retina assumes characteristic appearance of advanced retinitis pigmentosa with chorioretinal atrophy and pigment clumps. The flecks possibly represent VLCFA deposits in the RPE or outer retinal layers [629]. Prominent macular involvement has been reported in infantile Refsum disease. Several children with NALD and infantile Refsum disease have ocular findings suggestive of Leber congenital amaurosis [630, 631]. The ERG is often isolelectric early. Corneal clouding, cataracts, and glaucoma have been reported in Zellweger syndrome, but the anterior segment seems to be unaffected in NALD and infantile Refsum disease [626, 627, 632, 633]

Diagnosis

Biochemical abnormalities seen in peroxisomal biogenesis disorders include increased plasma levels of VLCFA, phytanic acid and pipecolic acid, and reduced levels of a polyunsaturated fatty acid, docosahexaenoic acid (DHA), and plasmalogens (ether-phospholipids). These altered lipid levels are among the diagnostic markers for peroxisomal biogenesis disorders. Zellweger syndrome is biochemically distinct in having the highest VLCFA accumulation and lowest level of plasmalogens. Decreased cellular peroxisomes in liver and kidneys is a hallmark of peroxisomal biogenesis disorders. Complementation studies on fibroblasts could be performed to identify the specific defective protein but molecular analysis of the *PEX* gene is more practical. All these disorders can be diagnosed prenatally, even during the first trimester.

Treatment

There is no definitive treatment for Zellweger spectrum disorders. The focus is on symptomatic therapy. Monitoring for hyperoxaluria to prevent stone formation and renal failure is indicated.

Rhizomelic Chondrodysplasia Punctata (RCDP) Type 1

Definition

RCDP type 1 is a multisystem, disorder in which peroxisomes are present, but they lack a specific group of proteins. There are 3 genetic subtypes of RCDP. RCDP type 1 caused by mutations in the PEX7 gene, is the most common type. RCDP type 2 and 3 are single enzyme deficiencies in the plasmalogen biosynthesis pathway [634].

Epidemiology

The prevalence of RCDP1 is estimated to be lower than 1:100,000. The disorder is pan ethnic. The high frequency of the p.Leu292X allele is secondary to a founder effect in individuals of Northern European descent [635].

Systemic Manifestations

Patients with RCDP type 1 have a disproportionately short stature, characterized by symmetric proximal shortening of the humerus and to a lesser degree the femur (rhizomelia), with congenital contractures. Epiphyseal and extra-epiphyseal punctate calcification (chondrodysplasia punctata) are seen. Stiffness and painful joints results in irritability in infancy. Radiological studies may also show absent femur head nucleus, coronal clefts of vertebrae, increased intravertebral disc spaces, cupping of dorsal ribs, and a barrel-formed thorax. Calcific stippling is seen in most patients by 18 months old, and disappears in older patients.

Cartilaginous structures of the face are also affected, leading to a typical facial appearance characterized by frontal bossing, and a broad nasal bridge. Other dysmorphic features include epicanthus, high-arched palate, dysplastic external ears, and micrognathia. Severe intellectual disability is always seen [623]. Most children develop seizures. Birth weight, length, and head circumference are often at the lower range of normal; postnatal growth deficiency is profound with resultant dwarfism. Routine brain imaging is normal or shows cerebral and cerebellar atrophy with enlargement of the ventricles and CSF spaces. Neuronal migration defects are not seen in RCDP type 1. Most patients die in the first decade of life. Other less frequent features include ichthyotic skin changes that are found in less than one third of patients, clefting of the soft palate. Congenital heart disease, with pulmonary hypoplasia, are the main causes of neonatal deaths in RCDP type I.

A milder phenotype in which all affected individuals have congenital cataracts and mild epiphyseal changes is now recognized. These patients have variable rhizomelia, and milder intellectual disability and growth deficiency.

Ophthalmic Manifestations

Bilateral cortical cataracts develop in virtually all affected individuals. They are present at birth or appear in the first few months of life and may be progressive. Other anterior segment anomalies reported include glaucoma and Axenfeld spectrum [636, 637]. Retinal degeneration is not a characteristic feature, but has been reported occasionally [638]

Diagnosis

Biochemical abnormalities common to peroxisomal biogenesis disorders are seen in RCDP type 1. These include elevated plasma phytanic acid and reduced levels of a polyunsaturated fatty acid and docosahexaenoic acid (DHA). Red blood cells show deficient plasmalogens (etherphospholipids). These changes are seen in cultured fibroblasts as well. However, plasma levels of VLCFA and pipecolic acid are normal as β-oxidation is not impaired. Additionally, unlike the peroxisome biogenesis disorders, peroxisomes are present but may be abnormal. Molecular studies identifying mutations in the *PEX7* gene are confirmatory.

Management

Management is supportive and limited by the multiple handicaps present at birth and poor outcome. Cataract extraction is more likely to restore some vision in patients with RCDP type 1, when compared to Zellweger spectrum where retinal degeneration limits the gain from cataract surgery.

Single Peroxisomal Enzyme Deficiency

The peroxisomal matrix contains over 50 enzymes mainly related to lipid metabolism, of which 10 single peroxisomal enzyme deficiencies have been identified. The clinical manifestations and pathological changes seen in this group of disorders resemble those seen in peroxisomal biogenesis disorders, from which they may be distinguished on the basis of biochemical assay of peroxisomal functions and demonstration of structurally intact peroxisomes. Various peroxisomal enzyme deficiencies with resulting disease state, clinical manifestations, and diagnostic tests are mentioned in Table 13.7. Of these, X-linked adrenoleukodystrophy, Refsum disease, hyperoxaluria, and Mulibrey nanism are described in detail.

X-Linked Adrenoleukodystrophy (X-ALD)

Definition:

The leukodystrophies are a group of inherited neurodegenerative disorders affecting the integrity of myelin in the brain and peripheral nerves. X-linked recessive adrenoleukodystrophy (X-ALD) is caused by mutations in the *ABCD1* gene located at Xq28, which codes for a protein called ALDP involved in the uptake of VLCFA across the peroxisomal membrane. This results in defective peroxisomal β-oxidation of saturated VLCFA in tissues and plasma. Over 100 mutations have been reported most of which are private to individual kindreds. X-ALD demonstrates almost full penetrance in hemizygote males and 60 % penetrance in heterozygote females.

There are several phenotypic categories and more than one phenotype may be observed within the same family [639]. The cause of this markedly variable expression is unknown and no clear phenotype-genotype correlations are known [639]. Currently there are six known phenotypes ranging from the severe childhood cerebral form to asymptomatic persons: (1) childhood cerebral form: onset between 5 and 10 years old, rapidly progressive; (2) adolescent cerebral form: onset 10–21 years old; (3) adrenomyeloneuropathy: onset after 19 years old, slowly progressive; (4) adult cerebral form: onset after 21 years old, rapidly progressive; (5) Addison disease only: primary adrenocortical insufficiency; (6) heterozygotes; and (7) asymptomatic.

History

X-ALD was first described in 1923 as a disorder that manifested adrenal hypofunction and cerebral demyelination. As affected children appeared tanned due to adrenal dysfunction, and their post-mortem brains and spinal cords showed demyelination with gliosis, the condition was called "bronzed sclerosing encephalomyelitis." The full range of phenotypes was not appreciated until the 1970s when adrenal glands of affected patients were found to contain lipid inclusions, leading to the appreciation that X-ALD is a metabolic disorder [640]. The name adrenoleukodystrophy was introduced based on the striking association of a leukodystrophy with adrenal insufficiency. The X-ALD locus was mapped to the terminal segment of the long arm of the X-chromosome, Xq28 by Migeon et al. in 1981 [641]. A mixture of unsaturated fatty acids erucic and oleic acids, was found to inhibit elongation of saturated fatty acids, and normalize plasma VLCFA levels within 4 weeks, and led to development of "Lorenzo's oil" [642]. However Lorenzo's oil was found to be of limited clinical benefit to patients [643].

Epidemiology

X-ALD is the most common single peroxisomal disorder with an incidence of 1:21,000 males in the USA [644], and 1:15,000 males in France [645].

Systemic Manifestations

X-ALD is a neurodegenerative disease characterized clinically by progressive motor, auditory, visual and mental impairment. Cerebral forms of the disease are associated with an inflammatory response in white matter of the central nervous system

and demyelination. The disease severity is correlated with the degree of inflammatory demyelination. The childhood progressive cerebral form is the most severe form, causing severe rapid behavioral, cognitive, and motor deterioration leading to vegetative state by 3 years and death usually in the first decade. The adolescent cerebral form has a similar rapid deterioration despite its later onset. Adreno-myeloneuropathy manifests as progressive spastic paraparesis, has a later onset and is a more slowly progressive disease. This form of the diseases is characterized by a distal axonopathy involving the long tracts in the spinal cord with mild or absent cerebral inflammatory response. Adult form is characterized by dementia, behavioral disturbances, and focal deficits. White matter inflammatory response is present, and progression parallels that of the childhood cerebral form. In all forms, hypoglycemia and/or salt losing episodes with increased skin pigmentation reflect adrenal insufficiency. Patients with Addison only form of the disease present with primary adrenal insufficiency without apparent neurologic involvement. Onset is common before 7.5 years. Addison disease in young males should prompt consideration of ALD as the underlying abnormality. Most eventually develop adreno-myeloneuropathy [646].

Approximately 40–60 % of women heterozygous for X-ALD develop adrenomyeloneuropathy like symptoms in middle age or later due to non-random X inactivation favoring the mutant allele in heterozygous cells [647]. Cerebral involvement and adrenocortical insufficiency are however, rare. The mean age of onset is in the fourth decade. Some patients with the genetic defect of X-ALD are free of adrenal insufficiency and neurologic disability despite the presence of highly elevated saturated VLCFA levels (asymptomatic X-ALD). These patients are still at high risk of eventually developing neurologic symptoms.

Ophthalmic Manifestations

Visual loss due to demyelination of the visual pathway is a prominent feature of childhood forms of X-ALD [648]. Adrenomyeloneuropathy is associated with color vision deficits which have been attributed to the red/green color pigment genes being closely linked to the gene for X-ALD on chromosome Xq28 [649–651]. Other reported findings include exotropia, esotropia, ocular motility disturbance suggesting ocular motor apraxia, optic nerve atrophy and macular pigmentation. ERG and EOG is often normal with borderline to abnormal visual evoked response [648]. The diagnosis of X-ALD should be considered in all boys presenting with unexplained visual loss, dementia, and adrenal dysfunction.

Diagnosis

The initial diagnosis of X-ALD is based on the clinical presentation, brain imaging and biochemical analyses of VLCFA. The principal biochemical abnormality in X-ALD is elevated plasma VLCFA. The accumulation of saturated VLCFA in the nervous system white matter and adrenal cortex is demonstrated by imaging. Most childhood patients show symmetric cerebral lesions on MRI brain scans with confluent loss of myelin in the parietal or occipital lobes. The majority of patients have laboratory evidence of adrenal insufficiency. Adrenal function should be assessed in all suspected cases. Mutation analysis of the *ABCD1* gene has shown many different, often novel mutations. Mutation analysis is the most reliable technique for heterozygote identification. Although prenatal testing may be available, it is impossible to predict the degree of phenotypic severity based on a given mutation.

Management

Therapies include adrenal steroid replacement therapy and dietary restriction of fatty acid intake. “Lorenzo’s oil” can reduce the levels of VLCFA but cannot reverse neurological impairment, probably because the oil cannot cross the blood brain barrier. Lorenzo’s oil may reduce risk of disease progression when administered to asymptomatic boys with X-ALD who have normal brain MRI results [652]. Allogenic bone marrow transplantation has been reported to reverse neurological deficits and brain MRI when performed at a very early stage of the disease [653]. It is hypothesized that transplanted marrow cells cross the blood–brain barrier and supply the missing peroxisomal functions. Gene therapy through HSCT strategy of transplanting autologous lentivirally corrected cells (*ex vivo*) was shown to be beneficial in patients with X-ALD and is a promising approach for future X-ALD therapy [654].

Refsum Disease (Hereditary motor and sensory neuropathy IV)

Definition

Refsum disease is an autosomal recessive disorder of lipid metabolism classically characterized by a tetrad of clinical abnormalities, namely retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and elevated CSF protein. It is caused by defective alpha oxidation of phytanic acid due to mutations in the *PHYH* gene located on chromosome 10p13 which encodes the enzyme phytanoyl-coenzyme A hydroxylase (PAHX). A subset of patients have a mutation in the *PEX7* gene. Inability to degrade phytanic acid results in its accumulation in neuronal and other body tissues [655]. It differs from other peroxisomal disorders in that it responds to dietary treatment.

History

Refsum disease was first delineated as a distinct clinical entity by Sigvald Refsum in the 1940s in patients with night blindness, pigmentary retinopathy, hearing loss, peripheral

neuropathy and ataxia and noted the hereditary aspect. He called the disorder 'heredopathia-atactica-polyneuritiformis' [656]. The accumulation of phytanic acid in Refsum patients was discovered in the early 1960s [657].

Epidemiology

The prevalence of Refsum disease is very low. In the literature, no estimates of its prevalence have been reported. It is probably highest in the United Kingdom and Norway.

Systemic Manifestations

The clinical picture of Refsum disease is often that of a slowly developing progressive peripheral neuropathy manifested by severe motor weakness and muscular wasting. Affected individuals typically present in adolescence, with night blindness and anosmia. This is invariably followed by peripheral polyneuropathy, cerebellar ataxia, ichthyosis, progressive sensory-neural hearing loss, cardiomyopathy, and cardiac conduction defects [658]. Anosmia is perhaps the earliest and most constant feature after pigmentary retinopathy. Skeletal abnormalities of the metacarpals and metatarsals, including a characteristic shortening of the fourth toe, have been reported. Cognitive function is usually normal. The clinical course is variable. Without treatment, patients show a gradually progressive deterioration. Exacerbations may occur with acute illness, fasting, rapid weight loss, or surgery.

Ophthalmic Manifestations

Retinitis pigmentosa (RP) is present in all patients with Refsum disease but the pigmentation is atypical. Retinopathy is characterized by optic atrophy, narrowed arterioles, granular pigmentation, degenerative maculopathy relatively early in the disease, and ERG abnormalities indicating diffuse rod-cone dystrophy [657]. Patients may have cataracts, miosis and poor pupillary dilation; the latter occurring because of high lipid levels in the iris or consequent to generalized dysautonomia [659].

Diagnosis

The diagnosis is made clinically and confirmed by elevated plasma concentration of phytanic acid. The degree of elevation of plasma and tissue phytanic acid is much greater in Refsum disease than in any of the disorders of peroxisomal biogenesis. Other laboratory features include elevated CSF protein concentration without an increase in cells. Nerve conduction studies typically show slowed conduction velocity. Peripheral nerve biopsy reveals hypertrophic changes with onion bulb formation and paracrystalline inclusions on electron microscopy. PAHX activity is reduced in fibroblasts. DNA diagnosis is available.

Management

Treatment consists of dietary restriction to achieve a dietary intake of phytanic acid to less than 10 mg daily. Phytol (unbound form of phytanic acid) containing foods, such as meat or fats, baked goods containing animal fats, and dairy products are eliminated from the diet. Rapid weight loss or fasting conditions that simulate lipolysis which will result in release of endogenous phytanic acid from the body fat stores must be avoided. Strict reduction in dietary phytanic acid intake may be associated with a significant improvement in peripheral neuropathy, ataxia, ichthyosis and cardiac conduction defect, but the visual and hearing impairments are less responsive to treatment [659, 660]. Phytanic acid concentration can also be reduced by plasmapheresis, which is resorted to when rapid reduction is required [661]. Plasmapheresis, however, cannot deplete phytanic acid in neural tissue, and so cannot reverse neurologic abnormalities. Supportive treatment includes hydrating creams for ichthyosis and medical therapy for cardiac arrhythmias and cardiomyopathy.

Primary Hyperoxaluria (PH) type 1

Definition

There are two types of genetically determined primary hyperoxaluria. Primary hyperoxaluria Type I (PH1) is an autosomal recessive disorder which results from an endogenous overproduction of oxalic acid and its accumulation within the body. It occurs due to a deficiency of the pyridoxal phosphate dependent enzyme alanine:glyoxylate aminotransferase (AGT) which catalyzes conversion of glyoxalate to glycine in the hepatic peroxisome. Deficiency of AGT results in an accumulation of glyoxalate, its conversion to oxalate, and increased urinary excretion of oxalate and glyoxalate. Oxalate can be removed from the body only by the kidney, and when production of oxalate exceeds renal clearance capabilities, there is systemic precipitation of the relatively insoluble calcium oxalate salt, particularly in the kidneys and eyes. Primary hyperoxaluria Type 2 (PH2) results from a deficiency of D-glyceric dehydrogenase and is not a peroxisomal disorder.

PH1 differs from other peroxismal disorders in that lipid metabolism is not affected, and peroxisomes are quantitatively and morphologically normal [662]. PH1 is caused by mutations in the *AGXT* gene on chromosome 2q36, which encodes the enzyme AGT.

History

Activities of alanine:glyoxylate aminotransferase in the livers of two patients with primary hyperoxaluria type I were substantially lower than those found in five control human livers. Detailed subcellular fractionation of one of the hyperoxaluric livers, compared with a control liver, showed that there was a complete absence of peroxisomal alanine:glyoxylate aminotransferase. This led to identification of primary hyperoxaluria type I as a peroxisomal disorder [663].

Epidemiology

PH1 has an incidence of 1:60,000–1:120,000 live births in Europe [664]. In Kuwait, PH1 is responsible for 10.4 % of end stage renal disease [665].

Systemic Manifestations

Individuals with PH1 are at risk for recurrent nephrolithiasis due to deposition of calcium oxalate in the renal pelvis or urinary tract, nephrocalcinosis due to deposition of calcium oxalate in the renal parenchyma, or end-stage renal disease. Over 90 % of cases present with loin pain, hematuria, urinary tract infection, growth delay and anemia. Bone is a major compartment of the insoluble oxalate pool. Oxalate osteopathy has been reported and may result in erythropoietin-resistant anemia and pathological fractures [666]. Renal failure leads to death either in adulthood in the chronic variant or much less frequently in infancy or childhood.

Age at onset of symptoms typically ranges from 1 to 25 years. Approximately 19 % of affected individuals present before the age of 4–6 months with severe disease, often associated with failure to thrive, nephrocalcinosis, and rapid progression to end stage renal disease due to early oxalate load and immature glomerular function. Approximately 54 % of affected individuals present in late childhood or early adolescence, usually with symptomatic nephrolithiasis [667]. The remainder of affected individuals present in adulthood with recurrent renal stones. Increased intracranial pressure, perhaps due to poor CSF circulation as a result of high oxalate concentration, may occur.

Ocular Manifestations

PH1 causes a distinctive retinal pigmentary disturbance secondary to deposition of oxalate. In the largest series of patients studied for ophthalmologic features, Small et al. found a characteristic pattern of black parafoveal ringlets with a bright white or yellow center. Advanced cases show similar intensely black macular lesions with dense white sub-retinal fibrous tissue plaque in the center [668]. Despite this striking macular abnormality, visual acuity remains quite good (20/20–20/60). The black pigmented lesions of PH1 are believed to represent retinal pigment epithelium hypertrophy and or hyperplasia in response to irritation by oxalate crystal deposition [669]. Minute, round, white flecks in the perifoveal area have been described in PH1 in the early stages of the disease [670]. Some patients develop optic atrophy and this is associated with a worse visual prognosis. The pathogenesis of optic atrophy is unclear. It may result following papilledema. Optic atrophy has also been reported in the absence of elevated intracranial pressure, and may be secondary to retinal arteriolar occlusion or primary retinal axonal loss secondary to oxalate deposition in the retinal vessels or inner retina respectively [668]. Ocular manifestations in PH1 are correlated with infantile onset of the disease, poorer renal status at presentation, worse renal prognosis, and decreased life span [668].

Diagnosis

The diagnosis of PH1 is suspected in an individual with an elevated oxalate to creatinine ratio in urine and an elevated plasma oxalate concentration. AGT deficiency in PH1 is confined to hepatic peroxisomes; definitive diagnosis therefore depends on enzyme assay in specimens obtained by percutaneous hepatic needle biopsy. Mutation analysis may provide confirmation of diagnosis without liver biopsy. Prenatal diagnosis has been accomplished by assaying the enzyme in biopsied fetal liver tissue and through mutation analysis.

Management

As pyridoxine is converted to a cofactor for AGT, a minority of patients may respond to pharmacologic doses of pyridoxine [662]. Conservative measures to reduce oxalate production and increase solubility of calcium oxalate should be started as soon as the diagnosis is suspected. Maintenance of high fluid intake, and use of potassium or sodium citrate, pyrophosphate-containing solutions to reduce renal stone formation is recommended. Until recently, the mainstay of treatment has been renal dialysis or transplantation. In the last 3 years, several patients have been successfully cured using liver transplantation [662].

Mulibrey Nanism (MUscle-LIver-BRain-EYe nanism)

Definition

Mulibrey nanism is an autosomal recessive disorder characterized by severe growth failure of prenatal onset, pericardial constriction, muscle, liver, brain, and eye abnormalities [671]. It is caused by mutations in the *TRIM37* gene on chromosome 17q22, encoding the peroxisomal protein TRIM37 [672]. TRIM37 is expressed in many tissues and is located in the peroxisomes. However, is function and the pathogenic mechanisms underlying Mulibrey nanism are unknown.

History

Mulibrey nanism was first described and named by Perheentupa et al. in 1973 in 23 Finnish patients, who manifested progressive growth failure, dysmorphism, a peculiar voice, hepatomegaly and retinal abnormalities [673].

Epidemiology

More than 80 % of previously reported cases of this rare disease are Finnish.

Systemic Manifestations

Patients have an intrauterine onset of growth failure (dwarfism) and characteristic facial features, with a triangular facies, high and broad forehead, low nasal bridge, and occipitofrontal bossing. Patients lack post-natal catch up growth and display progressive growth failure, slender build, a small bell shaped thoracic cage, and thin and proximally short limbs [671]. Constrictive pericarditis with restrictive cardiomyopathy, when present, dominate the clinical state as well as the prognosis [674]. A weak, high-pitched voice, insulin resistance with type 2 diabetes, and an increased risk for malignant tumors including Wilms tumor [675], thyroid cancer, and benign vascular lesions (cutaneous naevi flammei), most commonly in the lower limbs are characteristic [676]. Adult males have a unique disorder of testicular function with small testes, elevated FSH and LH, low inhibin B and severely compromised fertility [677]. Lack of major neurological manifestations and mental retardation are the most notable differences between Mulibrey nanism and other peroxisome disorders with which Mulibrey nanism shares many features. Radiological evaluation reveals slender long bones with thick cortex and narrow medullary channel and a low, shallow (J shaped) sella turcica in nearly all patients. More than half of the patients had true orbital hypertelorism. Fibrous dysplasia is present in 15 % of the patients, mostly in the lower limbs [671].

Ophthalmic Manifestations

Retinal pigment abnormalities with patches of diffuse chorioretinal atrophy and hypopigmentationn mid-peripheral retina may be noted [678, 679]. Yellow dots in the retinal midperiphery have also been reported [671]. Areas of focal choroidal hypoplasia may be seen on fluorescein angiography. Choroidal changes are believed to represent one further manifestation of mesodermal tissue affectation in these patients [678]. True orbital hypertelorism is seen on radiological evaluation.

Diagnosis

Diagnostic criteria have been proposed for Mulibrey nanism, and include major (growth failure; characteristic radiological findings of slender long bones with thick cortex and narrow medullary channels; low and J-shaped sella; characteristic craniofacial features; characteristic ocular findings; and Mulibrey nanism in a sibling) and minor (peculiar high pitched voice, hepatomegaly, cutaneous naevi flammei, and fibrous dysplasia of long bone) signs. Three major with one minor sign, or two major with three minor signs are required for the diagnosis [671]. Identification of a disease causing mutation in the *TRIM37* gene is diagnostic.

Management

Therapy is supportive and includes management of cardiac dysfunction. Pericardiectomy may be indicated for restrictive cardiomyopathy. Growth hormone can have a good short term effect, with a modest impact on adult height. Hormone replacement therapy may be indicated for delayed puberty.

Section Ten: Disorders in the Metabolism of Vitamins

Disorders of Cobalamin Metabolism (Cobalamin C Disease)

Definition

Cobalamin C (CblC) disease, an autosomal recessive disease, is an inborn error of intracellular metabolism of vitamin B_{12} (cobalamin). It is characterized by the impaired conversion of cobalamin into its two active forms, methylcobalamin and adenosylcobalamin. Methylcobalmain (methyl-Cbl) is the cofactor for methionine synthase, which catalyzes the conversion of homocysteine into methionine; cblC disease therefore leads to decreased methionine synthesis and homocysteinemia. Adenosylcobalamin (adenosyl-Cbl) is the cofactor for methylmalonyl-CoA mutase, which converts methylmalonyl-CoA into succinyl-CoA; CblC disease therefore leads to methylmalonic aciduria (Fig. 13.24).

Mutations in the *MMACHC* gene on chromosome 1p34.2 are responsible for the disease [680].

History

In 1969, Mudd et al. described a previously unrecognized abnormality involving altered vitamin metabolism with defective synthesis of the active coenzymes derived from vitamin B_{12} [681]. A protein encoded by the *MMACHC* gene was found to act as a "trafficking chaperone" for cobalamins [682].

Epidemiology

The incidence of cblC disease has been estimated as approximately 1:100,000 live births. CblC deficiency is the most common cause of methylmalonic aciduria and homocysteinemia. A rarer form is cobalamin F (CblF) deficiency due to defective lysosomal transport of cobalamin.

Systemic Manifestations

CblC disease has been classified into early-onset (infantile) and late-onset (noninfantile) forms. Although manifestations of cblC disease can arise *in utero,* infantile presentation is the most frequently recognized form of the disease. Patients with the infantile form of the disease present in infancy with severe systemic involvement, characterized by hypotonia, failure to thrive, irritability, restlessness, recurrent diarrhea, microcephaly, seizures or myoclonic jerks, microangiopathy, pancytopenia, and developmental delay [683–685]. Patients

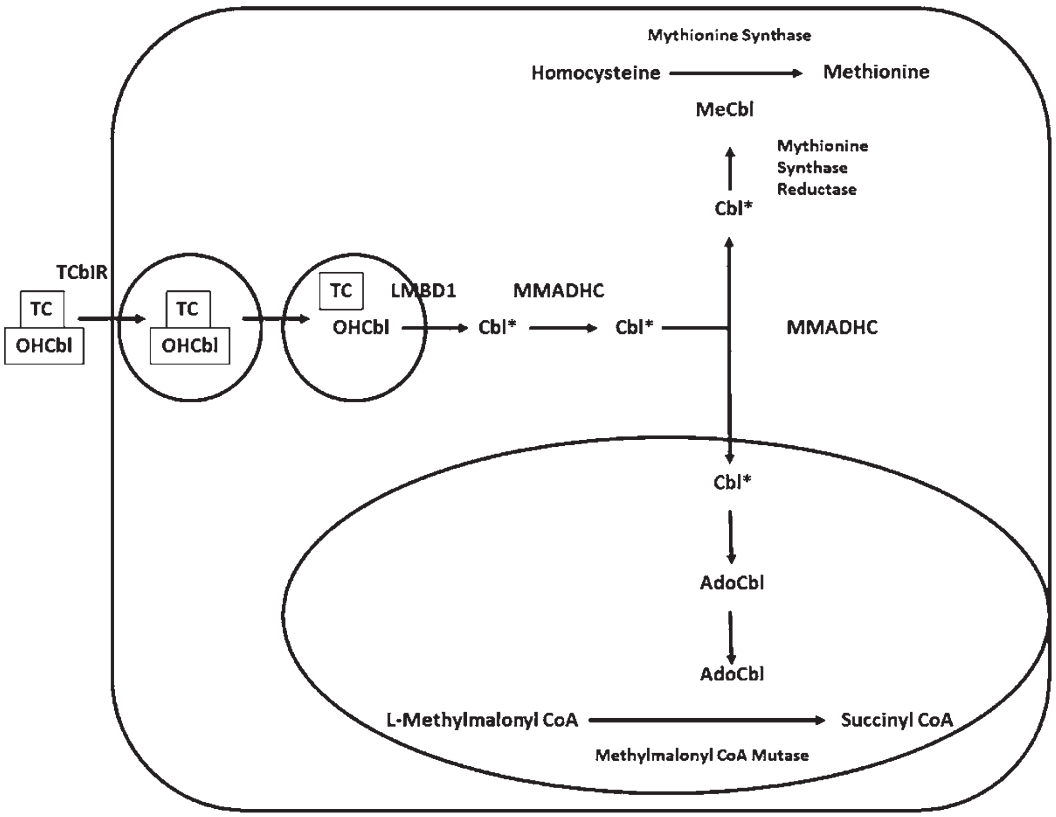

Fig. 13.24 Cobalamin transport and metabolism. Hydroxycobalamin [OHCbl] enters the cell bound to transcobalamin (TC). The hydroxycobalamin-transcobalamin complex is broken down inside the lysosome, and the enzyme cobalamin C (MMACHC) removes the hydroxyl group to generate free cobalamin (Cbl), which is synthesized via additional steps into methyl-cobalamin (MeCbl) and adenosyl-cobalamin (AdoCbl). MeCbl is the cofactor for methionine synthase, which catalyzes the conversion of homocysteine into methionine. AdoCbl is the cofactor for methylmalonyl-CoA mutase, which converts methylmalonyl-CoA into succinyl-CoA

with the late-onset form of the disease can present in any decade of life with neurological regression, cognitive decline, behavioural disturbances, progressive encephalopathy, subacute combined degeneration of the spinal cord dysfunction and pancytopenia [686]. Some patients show dysmorphism including a "hatchet shaped head," high arched palate and arachnodactyly, as well as hyperpigmented skin macules [683, 684]. Congenital structural heart defects, hydrocephalus, and renal failure are less common findings [684].

Ophthalmic Manifestations

Poor visual acuity, strabismus, nystagmus, maculopathy, pigmentary retinopathy, and optic atrophy have been described in patients with early-onset disease [33, 683, 684, 687, 688]. The progression of ophthalmologic complications seems to invariably lead to blindness in the first decade of life [689]. Although late onset disease is usually not associated with ophthalmologic complications, some reports describe visual impairment in patients with late-onset disease [34]. Retinal findings range from peripheral pigmentary retinal changes to central macular atrophy with or without bull's eye lesions [32, 34, 688, 690, 691]. These ophthalmic findings are useful, sometimes critical elements for the diagnosis of cblC disease. Macular thinning on optical coherence tomography, and decreased scotopic and photopic responses on ERG have been reported [32, 690]. There appears to be no correlation between funduscopic appearance and the type of photoreceptor dysfunction on ERG [33]. Optic atrophy is typically mild and may be seen in the absence of retinal findings [34, 687, 692]. Although patients with cblC disease have homocysteinemia, dislocation of the lens has not been reported in the literature. This contrasts with classical homocystinuria, caused by deficiency in cystathionine β-synthase in which ectopia lentis is a key clinical finding.

Diagnosis

The presence of both homocysteinemia and methylmalonic aciduria, in the presence of reduced methionine levels is suggestive of cblC deficiency since both metabolic pathways rely on vitamin B_{12} as an enzyme cofactor. Vitamin B_{12} levels are normal and should always be measured initially to rule out nutritional deficiency, congenital disorders of the absorption of vitamin B_{12} and cblF disease. Total plasma homocysteine is the preferred homocysteine parameter to monitor in patients with cblC disease [693]. Complementation studies on skin fibroblasts with failure of correction of the defects in adenosyl-Cbl and methyl-Cbl synthesis when complemented with cells from other cblC patients is confirmatory. Sequencing of the *MMACHC* gene is clinically available and is more cost-effective and less time-consuming than

complementation analysis. Gene sequencing has a 95 % chance of identifying causative mutations in affected individuals [680]. Early prenatal diagnosis of cblC disease is possible by molecular analysis of chorionic villus cells or cultured amniocytes, or by measuring and monitoring metabolites in the amniotic fluid and maternal urine.

Treatment

The goals of systemic treatment of cblC disease are to improve clinical manifestations, normalize serum methionine and lower both homocysteinemia and methylmalonic aciduria as soon as possible. Therapy typically includes hydroxycobalamin, folinic or folic acid, betaine, vitamin supplementation, and carnitine. It is recommended that treatment with hydroxycobalamin and betaine be initiated as soon as there is a suspicion for cblC disease, after determining baseline plasma metabolites and vitamin B_{12} levels, without waiting for confirmatory testing. Patients with cblC disease respond to parenteral hydroxycobalamin with a considerable improvement in biochemical parameters, resolution of hematological abnormalities, some improvement in neurologic manifestations, growth parameters, and amelioration of vascular complications [693]. Normalization of visual evoked potentials and brain stem auditory potentials has also been reported [683]. However, despite therapeutic measures, sometimes started soon after initial presentation or even prenatally, the long-term outcome is often unsatisfactory [694].

Retinal dysfunction may progress despite metabolic control [688, 690]. Knowledge and awareness of visual dysfunction in patients with cblC disease allows initiation of appropriate early vision intervention programs and support [33, 34].

Disorders of Biotin Metabolism: Biotinidase Deficiency

Definition

Biotin is a water-soluble vitamin needed by enzymes called biotin-dependent carboxylases which break down fats, proteins, and carbohydrates. Under normal conditions, biotinidase cleaves biotin from biocytin to produce free biotin, restoring free biotin to continue its cofactor enzymatic activity. Biotinidase deficiency or absence, also known as late-onset multiple carboxylase deficiency, leads to a free biotin deficiency which results in decreased metabolic activity of the biotin-dependent carboxylases, and buildup of potentially toxic compounds in the body. Biotinidase deficiency is autosomal recessive, and occurs due to mutations in the *BTD* gene (chromosome 3p25). Profound biotinidase deficiency results when the activity of biotinidase is reduced to less than 10 % of normal. Partial biotinidase deficiency occurs when biotinidase activity is reduced to between 10 and 30 % of normal.

History

The role of biotin to treat carboxylase deficiencies was first recognized in the 1970s [695]. Wolf et al. reported a newborn infant with multiple carboxylase deficiency whose neurologic and metabolic status improved markedly within a few days of administration of pharmacologic doses of oral biotin. His EEG, and extensive computed tomography scan changes resolved with biotic therapy over 2 months [695].

Epidemiology

In 1991, Wolf published the findings of neonatal screening for biotinidase deficiency, conducted in 14 countries from 1984 to 1990 with involvement of 8,532,617 newborns. The estimated incidence of profound biotinidase deficiency was found to be 1:112,271 and the incidence of partial deficiency 1:129,282. The incidence of combined profound and partial deficiency was 1:60,089 newborns. The estimated frequency of the allele for biotinidase deficiency was 0.004. An estimated 1 in 123 individuals are heterozygous for the disorder [696].

Systemic Manifestations

Profound biotinidase deficiency typically presents within the first 6 months of life. The clinical presentation is characterized by metabolic acidosis. Ketolactic acidosis, organic aciduria and hyperammonemia can be life threatening and result in permanent neurological impairment if biotin is not administered in time [697]. Other manifestations include neurological abnormalities such as hypotonia, seizures, ataxia, developmental delay, hearing loss, respiratory problems such as hyperventilation, laryngeal stridor, and apnea and dermatological manifestations such as alopecia and erythematous skin lesions with skin scaling that spreads over the whole body but is more predominant in the diaper and intertriginous areas. In some cases, the skin rash may not be typical and may resemble seborrhoeic dermatitis or icthyiosis. Late onset presentations are nonspecific and include motor limb weakness and spastic paraparesis. Individuals with partial biotinidase deficiency may develop symptoms only when stressed, such as during infection. Brain MRI reveals cerebral edema, low attenuation of white matter signal, cerebral atrophy, and compensatory ventricular enlargement. CT scan is more useful to demonstrate bilateral basal ganglia calcifications.

Ophthalmic Manifestations

Salbert et al. studied 78 children with biotinidase deficiency and found that 30 % present with ocular infections (mostly conjunctivitis), 13 % with optic neuropathies and visual disturbances, 13 % with motility disturbances, 4 % with retinal pigments changes and 1 % with pupillary abnormalities [698]. Patients may be asymptomatic until adolescence, when they develop sudden loss of vision with progressive optic neuropathy and spastic paraparesis. Hayati et al. reported a child with biotindase deficiency and bilateral optic neuritis [699].

Diagnosis

Urine organic acid analysis shows elevated excretion of 3-hydroxyisovaleric, lactic and 3-hydroxypropionic acids, and 3-methylcrotonylglycine. However, these metabolic abnormalities are variable, and affected children, whether symptomatic or asymptomatic, do not always exhibit ketoacidosis or organic aciduria.

Neuroimaging is helpful. The finding of low enzyme (biotinidase) activity in lymphocytes is confirmatory. Molecular genetic testing of *BTD* is warranted when the results of enzymatic testing are ambiguous. With development of reliable biotinidinase assay on serum or dried blood spots, diagnosis of biotinidase deficiency has become easier, and is part of newborn screening in many jurisdictions.

Management

Children with biotinidase deficiency should be provided with lifelong daily supplement of biotin (oral dose 5–10 mg). Raw eggs should be avoided as they contain avidin, an egg-white protein that binds biotin and decreases the bioavailability of the vitamin. Once vision problems, hearing loss, and developmental delay occur, they are usually irreversible, even with biotin therapy.

Section Eleven: Disorders of Copper Metabolism

Copper is an essential component for a number of metalloenzymes. Its absorption in the intestine, delivery to various organs including the brain, and excretion by the liver are tightly regulated to maintain adequate serum levels. This balance is disturbed in two inborn errors of copper transport caused by a deficiency of copper transporting proteins: Menkes disease and Wilson disease. Absorption of copper from the small intestine and efflux into the blood stream is mediated by a specialized transporter protein, the Menkes ATPase (ATP7A). ATP7A also mediates copper transport across the placenta and the blood brain barrier. In the portal blood absorbed copper is loosely bound to plasma albumin and amino acids, and taken to the liver where most of it is incorporated into the copper-containing protein ceruloplasmin, and transported to peripheral tissues. The majority of serum copper is bound to ceruloplasmin. Specialized transporters return excess unused copper from peripheral tissues to the liver for additional storage or biliary excretion. The Wilson ATPase (ATP7B) is responsible for ceruloplasmin biosynthesis, delivery of copper to the secretory pathway of hepatocytes, and for endosome formation prior to biliary secretion. Although copper has no effect on the rate of synthesis or secretion of ceruloplasmin, failure to incorporate this metal results in secretion of an apoprotein that is rapidly degraded in the plasma. Thus in Wilson disease there is a marked decrease in ceruloplasmin in the serum of affected patients.

Menkes disease is caused by mutations in the *ATP7A* gene and Wilson disease is caused by mutations in the *ATP7B* gene. The differences in disease manifestations are related to the tissue-specific expression of *ATP7A* and *ATP7B* with Menkes disease resulting in copper deficiency and Wilson disease resulting in copper toxicity due to excess free copper.

Copper metabolism disorder not linked to ATP7A (MNK or Menkes protein), ATP7B (Wilson protein) has been reported with improvement in symptoms and complete restoration of cytochrome-c oxidase activity in skeletal muscle with copper histidinate supplementation. The authors concluded that there might be as yet undiscovered genes involved in copper metabolism [700].

Menkes Disease (Kinky Hair Disease)

Definition

Menkes disease is an X-linked recessive disorder wherein mutations in the *ATP7A* gene result in failure of copper efflux from intestinal cells, with resultant deficiency of copper in the serum, liver and brain. Without copper, several copper-dependent enzymes including those involved in neurological function and with the formation of collagen, elastin, keratin, and melanin display decreased activity.

History

Menkes et al. described five male infants in a family of English-Irish heritage in 1962, who were affected with a distinctive syndrome of neurological degeneration, peculiar hair, and failure to thrive [701]. In 1972, Danks et al. recognized that the unusual hair of infants with Menkes disease appeared similar in texture to the brittle wool of sheep raised on copper-deficient soil in Australia, and found very low serum copper in seven Menkes disease patients [702].

Epidemiology

The incidence is 1:100,000–298,000 live births [703, 704]

Systemic Manifestations

The distinct clinical manifestations of Menkes disease appear around the 2–3 months old. The earliest manifestations include hypothermia, failure to thrive, seizures, profound hypotonia, and developmental regression with loss of milestones. The diagnosis of Menkes disease is made when these manifestations are seen in children with characteristic changes of the hair (short, sparse, coarse, twisted, often lightly pigmented) and face (sagging cheeks, frontal bossing, and sparse eyebrows). Patients are often blonde with fair complexion. Other findings include skin laxity, hypermobile joints, vascular

tortuosity, and bladder diverticula due to defective collagen cross-linking. They are present in virtually all patients Untreated, patients rarely survive beyond 3 years old [705]. Neuroimaging reports have described intracranial vessel tortuosity and white matter changes. Cerebral infarctions in the deep gray matter due to underlying vasculopathy may play a significant role in the neurodegeneration of children with Menkes disease [706]. Subdural hematomas consequent to intracranial vasculopathy, and bony changes (rib and long bone fractures) are classical features of Menkes disease, and may lead to a mistaken diagnosis of child abuse [706, 707]. Search for typical features of Menkes disease, absence of cutaneous injury, and retinal hemorrhage should enable the correct diagnosis.

Some patients (10–15 %) have a mild phenotype, with the occipital horn syndrome being the mildest. Mild Menkes disease is characterized by moderate developmental delay and cerebellar ataxia. Patients with occipital horn syndrome exhibit slightly subnormal intelligence along with autonomic dysfunction. These patients have cranial exostoses in the occipital region (hence the name of the syndrome). Survival into mid adulthood is seen.

Ophthalmic Manifestations

In the largest reported series specifically designed to examine eye findings (20 patients: 18 classic, 2 mild), 40 % showed severe visual dysfunction including no response to light presumably due to cortical visual impairment. Myopia up to –5.50D and strabismus (exotropia more than esotropia) are common [708]. Although aberrant eyelashes (25 %), blue sclera, and anterior iris stromal hypoplasia (35 %) have been reported [708, 709], structural malformations of the eye are not common. The iris may show transillumination (15 %) and over 90 % of patients have blue irides [708]. Peripheral retinal hypopigmentation may also be observed [708]. These pigmentary abnormalities may be related to the copper dependence of tyrosinase. Visual function is usually impaired early in infancy and deteriorates with disease progression. Optic atrophy is uncommon and nystagmus may be present [708]. The ERG is consistent with a rod-cone dystrophy with severe depression of scotopic responses and absent oscillatory potentials in the first year of life [709]. All of these ocular abnormalities except for the visual dysfunction may occur in mild Menkes disease [708].

Diagnosis

Patients with Menkes disease demonstrate low serum copper and ceruloplasmin, but these findings are not specific since normal infants usually have low levels of copper and ceruloplasmin. Deficiency of dopamine β-hydroxylase causes elevation of catecholamines in plasma and CSF, resulting in abnormal ratio of catecholamine metabolites. Reduced urinary excretion of deoxypyridinoline (collagen metabolism) seems to be specific for Menkes disease [710, 711]. The diagnosis is confirmed by fibroblast copper uptake studies (increased accumulation and reduced efflux). Final diagnosis requires identification of the gene mutation. Prenatal diagnosis is done by mutation analysis. Since the success of treatment in this disorder depends heavily on early diagnosis and treatment, newborn screening for Menkes disease based on biochemical findings from dried blood spots, or via high throughput molecular assays, is desirable.

Treatment

Ideally, affected infants are identified and treatment commenced within 10 days of birth. Although oral copper supplementation is not useful, treatment with small molecule copper complexes such as parenteral copper-histidine can halt deterioration and prolong life [712]. However, the best effect is only achieved if treatment is started in the first month and even then, connective tissue effects such as vascular complications are not well prevented and may ultimately lead to death [704]. In addition to copper replacement, antithrombotic therapy may be effective in preventing neurological damage. However, the risk of catastrophic hemorrhage from anticoagulant therapy must be considered. Treatment outcome depends on the causative mutation and how early the treatment was started [713, 714]. Severe mutations are associated with poor prognosis even when treatment is started early.

Wilson Disease (Hepatolenticular Degeneration)

Definition

Wilson disease is autosomal recessive and characterized by decreased incorporation of copper into ceruloplasmin, and reduced excretion of copper into the bile, leading to copper excess despite low circulating levels of ceruloplasmin. The increase in serum non-ceruloplasmin-bound copper results in elevated urinary copper excretion, and gradual copper deposition in the liver and various tissues, including the brain, kidney, cornea, muscle, bone, and joint. Excess of copper exerts toxicity by generating free radicals, and causes cellular damage via oxidative stress. Additionally, intracellular copper deposits impede inhibitor of apoptosis proteins (IAPs), leading to apoptotic cell death [715]. Wilson disease is caused by mutations in *ATP7B* gene located on chromosome 13q14, which results in an abnormal copper-transporting protein ATP7B in the liver, where its major function is incorporation of copper into ceruloplasmin and excretion of hepatic copper into the circulation and the biliary tract [716]. Impaired incorporation of copper into ceruloplasmin leads to secretion of ceruloplasmin peptide that is folded differently than normal. The abnormal protein has

a shorter half-life in the circulation, thereby reducing steady state circulating levels of this protein.

History

The clinical condition was first described in 1912 by Wilson, an American-born neurologist working in England. In 1930 Horowitz and Luethy noted an increased concentration of copper in the liver and brain of affected patients. Twenty-six years later, therapy with copper chelation by penicillamine was introduced by Walshe, a British physician working in Boston [717].

Epidemiology

Wilson disease has an incidence of 1 in 30,000 newborns.

Systemic Manifestations

The clinical presentation varies from predominantly hepatic to predominantly neurologic and shows great heterogeneity regarding severity, age of onset and initial symptoms. Patients with hepatic symptoms generally present earlier between 8 and 20 years old. While liver disease is acute, rapidly progressive, and results in fulminant hepatic failure in some patients, in others it is chronic in nature. Transaminases, although raised, generally are much lower than in autoimmune or viral hepatitis. Neurologic signs typically present in the 2nd or third decade of life, but sometimes manifest in childhood. They follow two general patterns—movement disorders (dysarthria, dysphagia, tremor), or rigid dystonia (mask-like facies, rigidity, gait disturbance). In some patients psychiatric symptoms predominate, ranging from behavioral disturbances to frank psychosis. Structural changes in the brain of Wilson's disease patients have been well documented by MRI, which has revealed lesions of the basal ganglia, midbrain, pons and cerebellum and widespread cortical atrophy and white matter changes [718]. Wilson disease results in severe disability and death if untreated.

Ophthalmic Manifestations

Deposition of copper in peripheral Descemet's membrane leads to golden brown pigmentation, known as the Kayser-Fleischer (K-F) ring. Identification of a K-F ring remains an important clinical sign for the diagnosis of Wilson disease. Slit-lamp examination reveals these rings in 95 % of patients with neurologic presentations [719], but they are often absent in children presenting with liver disease. About 40 % of patients with hepatic, and 20 % with neurological symptoms show no K-F rings [720]. The density of a K-F ring correlates with the severity of Wilson disease [721]. The ring reduces in intensity with treatment, but may even be seen in asymptomatic Wilson disease patients [721, 722]. Sunflower cataracts may be observed occasionally on slit lamp examination due to copper deposition on the anterior lens capsule. The corneal and lens involvement in Wilson disease do not affect vision. Retinopathy may occur as a result of dysregulation of copper levels. Retinal degeneration and visual pathway involvement in Wilson disease have been quantified by optical coherence tomography, ERG and VEP [723–725]. By providing useful information about ongoing neuronal degeneration these tools may be useful to monitor patients. Abnormal saccadic eye movements with preservation of pursuit movements has been reported and may reflect pathology of the descending fronto-bulbar neural pathway [726]. Oculogyric crises has been reported as an initial manifestation of Wilson disease [727, 728]. Patients with Wilson disease may also develop an upgaze palsy and loss of accommodation.

Diagnosis

The diagnosis of Wilson disease can be confirmed by the demonstration of ceruloplasmin concentrations of <20 mg/dl, low serum copper, elevated urinary copper (>100 μg/day), Kayser-Fleischer rings, and a hepatic copper concentration by biopsy of more than 250 μg/g of dry tissue [729]. These laboratory tests should be interpreted in combination [729]. The diagnosis is confirmed by the detection of biallelic *ATP7B* mutations. Prenatal diagnosis has been performed [730].

Management

Treatment with copper chelating agents (penicillamine or trientine) or zinc, should be initiated as soon as possible, as it can reduce hepatic, neurologic, and psychiatric findings in many symptomatic individuals. Delay in initiating treatment adversely affects prognosis [731]. Treatment is life-long. Copper chelating agents increase urinary excretion of copper. Pyridoxine must be given along with penicillamine. Given the side effects of penicillamine, trientine is now the preferred method of treatment [729]. Tetrathiomolybdate is a relatively new copper chelating agent. It has a unique mechanism of action developed for patients with neurological Wilson disease. Tetrathiomolybdate treatment does not result in serum copper spikes typically observed with penicillamine and trientine, which may explain why neurological worsening is rare with its use compared to other chelating agents. High-dose oral zinc interferes with absorption of copper from the gastrointestinal tract and is most effective after initial therapy with a chelating agent [732]. Antioxidants, such as vitamin E, may be used with a chelator or zinc to prevent tissue damage, particularly to the liver. Restriction of foods very high in copper (liver, brain, chocolate, mushrooms, shellfish, and nuts) is recommended. Liver transplantation may be considered for patients who fail to respond to or cannot tolerate medical therapy.

Section Twelve: Disorders of Membrane Transport

Cystinosis

Definition

Cystinosis is an autosomal recessive metabolic disorder in which cystine, a disulfide of the amino acid cysteine, accumulates within cellular lysosomes. As cystine is poorly soluble, crystals form in virtually all tissues, resulting in functional damage, and the clinical manifestations of the disorder. Cystinosis has been classified into a severe nephropathic form and a milder non-nephropathic form that is also called ocular cystinosis. Nephropathic cystinosis is further divided into infantile (classic) and intermediate (juvenile-onset) cystinosis. All three types of cystinosis are caused by mutations in the *CTNS* gene on chromosome 17p13, which encodes a transporter protein called cystinosin [733]. Deficient cystinosin leads to abnormal cystine egress from the lysosomes, where it is formed as a result of protein degradation (Fig. 13.25).

History

Cystinosis was first described in 1903 by Abderhalden who found cystine crystals in the spleen and liver at autopsy in a child with severe growth failure in infancy. In 1924, Lignac noted that children with cystinosis often present with profound rickets, and in 1931, Fanconi linked cystinosis with a renal tubulopathy. In 1957, Cogan et al. reported the first case of ocular cystinosis in an adult patient [734]. In the 1960s, cystinosis was revealed for the first time to be a cystine storage disease due to a defect in efflux of free cystine from lysosomes [735].

Epidemiology

Cystinosis affects approximately 1 in 100,000–200,000 newborns worldwide [736]. The incidence is higher in the province of Brittany, France, where the disorder affects 1 in 26,000 individuals. It is estimated that there are 30–40 new cases each year in the US [736]. It is also more common in Menonite and Amish populations.

Systemic Manifestations

Nephropathic cystinosis in untreated children is characterized by Fanconi proximal renal tubular syndrome (polyuria, polydipsia, dehydration, and acidosis), poor growth, hypophosphatemic rickets, and accumulation of cystine crystals in almost all cells, leading to cellular destruction and tissue dysfunction. Patients appear normal at birth, but failure to thrive and signs of renal tubular dysfunction become apparent by 6 months old. Episodes of fever, probably related to dehydration, are commonly noted. Caucasian patients often have blond hair and a fair complexion. This has been attributed to abnormal pigment formation in melanosomes. Progressive impairment of glomerular function results in renal failure by 10 years old [737]. Nearly half of all cystinosis patients are also thyroxine deficient by 10 years old [738].

Prior to renal transplantation and cystine-depleting therapy for patients with cystinosis, the life span in nephropathic cystinosis was about 10 years. With these therapies, affected patients survive at least into the mid-forties or fifties with satisfactory quality of life. After renal transplantation, nonrenal tissues continue to accumulate cystine, and a variety of complications such as distal vacuolar myopathy, swallowing difficulty, pancreatic endocrine insufficiency [739, 740], central nervous system deterioration [741] and primary male hypogonadism [742] have been reported.

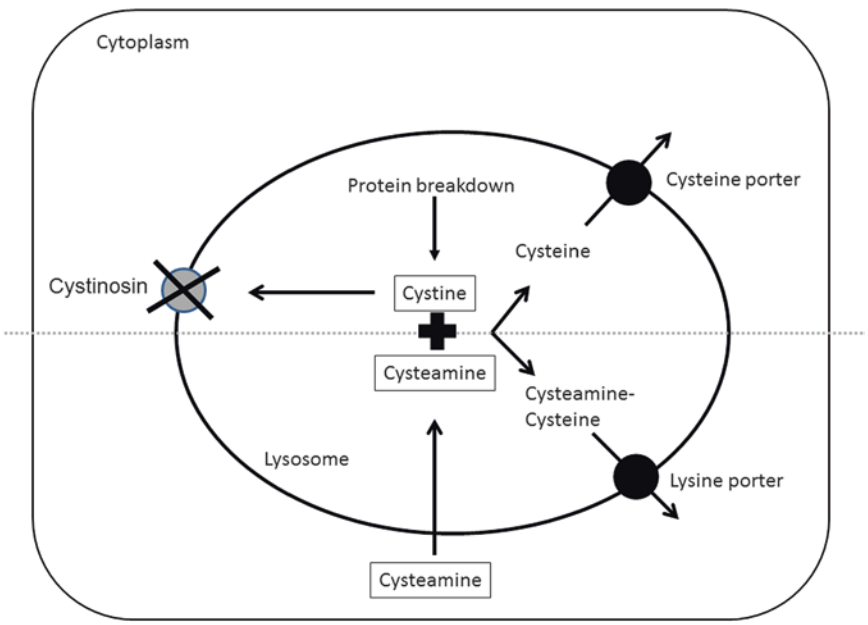

Fig. 13.25 Lysosomal porters for cystine and related metabolites: Cystinosin deficiency leads to progressive accumulation of cystine within the lysosomes. Cyseamine, used in the therapy of cystinosis, enters the lysosome, combines with cystine to produce (1) cysteine that can be transported through the cysteine porter or (2) cysteamine-cysteine disulfide that is transported out of the lysosome through the lysine porter

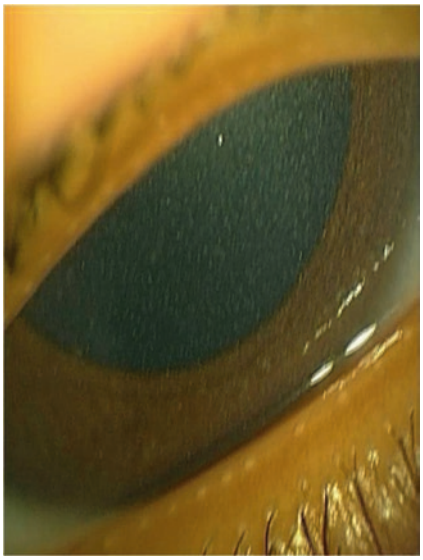

Fig. 13.26 Cysteine deposits in the cornea of a child with nephropathic cystinosis

Intermediate or juvenile-onset cystinosis is characterized by all the typical manifestations of nephropathic cystinosis, but onset is at a later age and it has a slower rate of progression. The non-nephropathic form of cystinosis is characterized only by ocular manifestations.

Ophthalmic Manifestations

Ocular involvement in cystinosis is characterized by cysteine deposition in the conjunctiva, cornea, iris, anterior lens capsule, retina, and choroid. Corneal involvement leads to photophobia, which usually appears around the 2 years old. The corneal crystals are numerous needle-shaped, and highly refractile and are easily seen on slit-lamp examination. These findings are so characteristic that they often establish the diagnosis of cystinosis (Fig. 13.26).

Cystine crystals are initially concentrated in the superficial layers of corneal periphery but with time spread to involve all layers of the cornea including the endothelium. Crystal deposition increases with age. The corneal crystals usually do not reduce acuity, so decreased acuity should prompt investigation of other causes. Other corneal findings in long-standing cases include superficial punctate keratopathy, painful recurrent erosions, filamentary keratitis, and band keratopathy. Posterior segment involvement, with progressive retinal degeneration also have been described in infantile nephropathic cystinosis [743]. Patches of depigmentation in the peripheral retina with pigmentary mottling constitute the most commonly described ophthalmoscopic abnormalities, and may be seen as early as 6 months old [744]. With time degenerative changes in the outer retinal layers with focal destruction of the photoreceptor outer segments is seen [744]. These changes are associated with moderate to severe constriction of the visual fields and reduction in rod- and cone-mediated ERG responses [744].

Diagnosis

The diagnosis of cystinosis is established by noting the typical cysteine crystals in the cornea on slit lamp examination in a patient with renal tubular Fanconi syndrome which results in increased urinary losses of electrolytes (sodium, potassium, bicarbonate), minerals (calcium, phosphate, magnesium), glucose, amino acids, carnitine, and water. Patients have a 50–100-fold elevation of cystine levels in leukocytes. Serum cysteine levels are normal. Identification of bialelic mutations in the *CTNS* gene, is confirmatory. Prenatal diagnosis can be accomplished either via cystine assay or molecular genetics.

Management

The treatment of nephropathic cystinosis is both supportive and specific. Early detection and prompt treatment are critical in slowing the development and progression of symptoms. Oral cystine-depleting agents such as cysteamine begun just after birth or as soon as the diagnosis is made, can preserve renal function and improve growth rates [745]. The odor and taste of cysteamine make compliance potentially difficult. Supportive therapy includes restoration of fluid and electrolyte balance, and vitamin D and carnitine supplementation. Hormone replacement therapies with L-thyroxine, insulin, growth hormone, and/or testosterone may be required. Renal transplant is a mainstay of management.

Oral cysteamine does not have any effect on corneal crystal accumulation, and topical administration is required to promote dissolution of corneal crystals and alleviate the ocular symptoms [746]. Cysteamine eyedrop therapy has been shown to be effective in reducing corneal deposits in several single-center and one multi-center trial. This is true even if therapy is started at a later age [747, 748]. The recommended regimen is a 0.55 % (50 mM) cysteamine hydrochloride solution with benzalkonium chloride 0.01 % as a preservative, used 10–12 times per day [746, 749]. This dosing schedule may lead to noncompliance to treatment, especially in childhood. Dark glasses and lubricants may be useful to reduce photophobia. Early initiation of oral cysteamine therapy can reduce the frequency of posterior segment complications in cystinosis patients [744]. But retinal changes that have already occurred are irreversible.

Sialic Acid Storage Disorders

Salla Disease; Infantile Sialic Acid Storage Disease (ISSD)

Definition

Sialic acid storage diseases are caused by a defective lysosomal sialic acid transport mechanism resulting in storage of free sialic acid within lysosomes and a 100-fold increase in urinary excretion. These disorders are autosomal recessive,

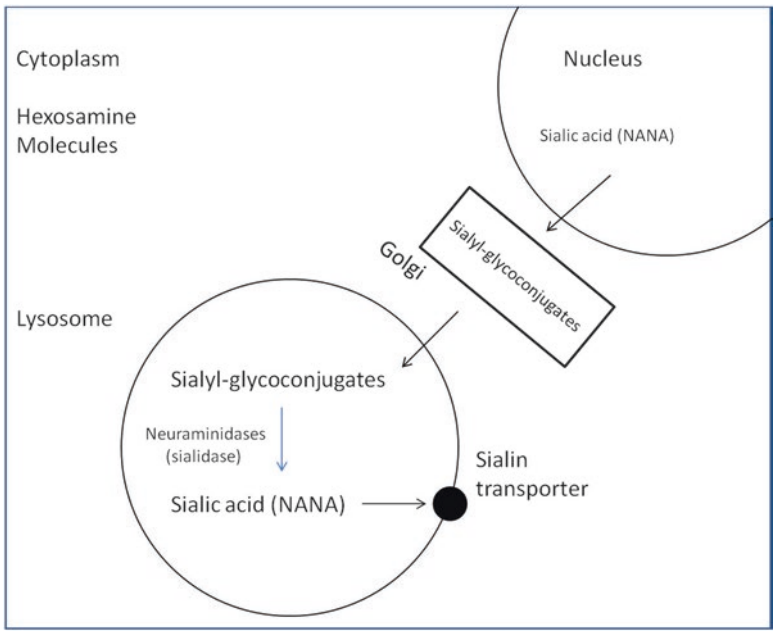

Fig. 13.27 Sialic acid metabolism pathway. Sialic acid (N-acetyl neuraminic acid; NANA) synthesis starts in the cytoplasm and then sialic acid is activated in the nucleus. Activated sialic acid is transported to Golgi for conjugation. These sialylated conjugates are cleaved by neuraminidases (sialidase) found in the lysosomes, and then transported out of the cell

characterized by neurodevelopmental delay and learning difficulties, and may present as a severe infantile form (infantile sialic acid storage disease; ISSD) or a slowly progressive adult form referred to as Salla disease. Mutations in the *SLC17A5* gene (chromosome 6q14-15) are responsible for these disorders. The gene encodes an amino acid transporter, sialin, which appears to be needed for transport of acid monosaccharides across lysosomal membranes [750]. Sialidosis and galactosialidosis are characterized by lysosomal storage of sialyl-oligosaccharides, due to a deficiency of the enzyme sialidase (Fig. 13.27).

History

In 1979, Aula et al. studied 4 adults in 2 related sibships from an institution for disabled people in Finland and observed features of a new lysosomal storage disease [751]. The disease was named Salla disease for the geographic area in Finland where the patients lived.

Epidemiology

Most cases of Salla disease are found particularly in residents in this northeastern part of Finland. All Finnish patients have the same missense mutation, $\text{Salla}_{\text{FIN}}$ (C115T/R39C) in exon 2 (founder effect). Few cases are known outside of Finland. Unlike Salla disease, ISSD has no particular ethnic prevalence and do not have the $\text{Salla}_{\text{FIN}}$ mutation [752].

Systemic Manifestations

Patients with ISSD exhibit coarse facial features, fair complexion, cutaneous telangiectasias, hepatosplenomegaly, cardiomyopathy, and failure to thrive. Early death (usually within the first 2 years of life) is common [753]. The clinical picture of Salla disease is less severe than the infantile form and is characterized by slowly progressive psychomotor retardation, hypotonia, and ataxia all usually beginning in the first year of life. MRI reveals progressive cerebellar atrophy, white matter abnormalities, and thinning of the corpus callosum [754]. Intermediate cases have been reported who lack the neonatal manifestations typical of ISSD but are more severely affected than patients with Salla disease. They were found to be compound-heterozygotes, with the founder mutation R39C, in only one allele [752].

Ophthalmic Manifestations

Dysmorphic features include epicanthal folds, ptosis and downslanting palpebral fissures. Albinoid fundi, optic atrophy, strabismus and nystagmus have been reported [755]. The coarse facies may be confused with that of mild mucopolysaccharidoses. When faced with such a clinical situation, investigations for sialic acid storage disorder may be included in the laboratory investigation. Presence of clear cornea in this situation also helps to differentiate the two disorders.

Diagnosis

Patients show increased urinary excretion of free sialic acid (20 times higher in ISSD than the 15–30-fold increase in Salla patients), and electron microscopic demonstration of excessive accumulation of free sialic acid in lysosomes within several types of tissues and cultured fibroblasts. Peripheral blood and bone marrow lymphocytes, monocytes, and neutrophils show vacuolation. Prenatal diagnosis is possible on the basis

of free sialic acid estimation in amniotic fluid and free/total sialic acid ratio in amniocytes. DNA testing is confirmatory.

Management

Only supportive measures can be offered. No specific treatment is available.

Sialuria

Definition

Sialuria occurs a result of an increased synthesis of sialic acids in the cytoplasm secondary to a lack of feedback inhibition of the rate-limiting enzyme epimerase. Only urinary levels of free sialic acid are elevated.

History

Montreuil et al. and Fontaine et al. reported massive excretion of free sialic acid in 1968 [756]. Kamerling et al. implicated defective feedback inhibition of one of the enzymes involved in sialic acid synthesis in the genesis of silaiuria [757].

Epidemiology

Sialuria has been reported in only seven persons. The prevalence of silaiuria may be underestimated and is probably higher than that estimated from the existing reports

Systemic Manifestations

Sialuria is the mildest disorder of sialic acid metabolism. It is most characterized by hepatosplenomegaly with transient prolonged neonatal jaundice in the presence of normal liver function tests. Patients also have varying degrees of developmental delay, mild hypotonia, mild failure to thrive with relative macrocephaly, and macroglossia. Hypopigmentation is not seen.

Ocular Manifestations

The only reported oculofacial manifestation of sialuria is the coarse facies (synophrys, epicanthal folds, hypertelorism, periorbital fullness) which may be confused with that of a mild mucopolysaccharidosis syndrome especially those with no corneal clouding or mental retardation (MPS II).

Diagnosis

Levels of free sialic acid in serum are normal whereas urinary levels far exceed those seen in other forms of sialic acid disorders. Liver biopsy is normal to light microscopy but reveals characteristic mitochondrial morphologic abnormalities including abnormal cristae not seen the other sialic acid disorders. The only evidence of lysomal storage abnormality is seen in the Kupfer cells of the liver. There is an absence of the cellular vacuoles seen in the other forms of sialic acid abnormalities. There is no biochemical evidence for lysosomal storage abnormalities.

Management

Patients with sialuria need symptomatic and supportive management, including treatment of anemia, jaundice, and convulsions. Affected individuals benefit from early developmental intervention and appropriate educational programs.

Section Thirteen: Disorder of Sulfur Metabolism

Trichothiodystrophy

Definition

Trichothiodystrophy is a rare autosomal recessive disorder that is characterized by sulfur-deficient brittle hair in addition to clinically heterogeneous systemic manifestations. The name reflects the brittle, sulfur deficient hair seen in all patients with this diagnosis (from Greek, tricho-meaning hair; thio-, sulfur, -dys-, faulty; -trophy, nourishment). The disorder may or may not be associated with photosensitivity. It is also genetically heterogeneous, and a number of patients with this disorder were demonstrated to have defects in a DNA repair genes.

History

In 2 brothers and a sister, with first-cousin parents of Chinese extraction, Tay described a ‘new’ autosomal recessive disorder characterized by nonbullous ichthyosiform erythroderma, growth and mental retardation, somewhat progeria-like appearance, and hair abnormalities [758]. In 1979, Price coined the term “trichothiodystrophy” to include refer to these neurocutaneous manifestations.

Epidemiology

Trichothiodystrophy has been estimated to occur in 1.2 per million live births in a western European population [759].

Systemic Manifestations

Trichothiodystrophy presents clinically as brittle, sulphur-deficient hair with heterogeneous clinical manifestations. When hair is viewed under polarizing light microscopy, it shows an alternating light and dark pattern called “tiger-tail banding” [760, 761]. Disease severity can range from abnormal hair alone to multi-system involvement including severe mental and physical impairment, short stature, decreased fertility, and serious infections, as well as signs of premature aging, and extreme sensitivity to sunlight [762, 763]. Hypomyelination of cerebral white matter maybe seen on MRI of the brain. Patients with trichothiodystrophy do not typically have increased risk of cancer like seen in the similar disorder, xeroderma pigmentosum [763].

Ophthalmic Manifestations

The most common visual abnormality overall was refractive error severe enough to require corrective lenses. Deterioration typically is of progressive nature. Corneal opacities and/or cataract is also a common complication seen in patients with trichothiodystrophy. Nystagmus and strabismus may also been seen in some patients. Adult patients may also show signs of macular degeneration [764].

Diagnosis

In patients with trichothiodystrophy, polarization microscopy of the hair reveals a tiger-tail pattern that corresponds to the diagnostic low sulfur protein content [765, 766]. UV-induced DNA repair analysis may show abnormalities depending on the underlying genetic background. In the photosensitive group of patients, the majority of cases (95 % of patients) are due to mutations within the XPD (*ERCC2*) gene. The remaining cases are caused by mutations within the XPB gene.

Management

Management of patients with trichothiodystrophy is largely supportive. Dermatological assessment and follow up is required for the skin lesions. Families are generally advised to avoid sun exposure, and to use emollients for the dry skin lesions [765].

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Ocular Manifestations of Musculoskeletal Disorders

14

Michael Clarke, Gar-Yun Wong, and Jeffry Hogg

Marfan Syndrome

Definition

Marfan syndrome (MFS) is a multisystem disorder characterised by tall stature, aortic root dilation with increased risk of aneurysm and dissection, and ectopia lentis. MFS is an example of human pleiotropy, in that there is a constellation of causally related manifestations which are thought to be due to a single abnormality. The severity of the condition varies, from mildly affected forms to severely affected neonates who die in infancy.

MFS is caused by a mutation in the *FBN1* gene from which the extracellular glycoprotein fibrillin-1 is derived. MFS is inherited in an autosomal dominant fashion with 25% of cases due to new spontaneous mutations [1]. Fibrillin-1 plays a role in incorporating elastin into connective tissues, and also binds to complexes containing TGF-β molecules [2]. It is thought that it is through the dysfunction of these two roles that the *FBN1* mutation brings about the clinical features of MFS [3]. Recent literature regarding the effects of upregulated TGF-β in MFS provides a more complete explanation for the clinical manifestations of MFS [4]. TGF-β is a paracrine regulator of multiple processes, which is sequestered from circulation by binding to fibrillin-1 [2, 4]. The dysfunctional fibrillin-1 of MFS patients leads to higher plasma levels of TGF-β which has downstream effects on matrix metalloproteinases (MMPs) and bone morphogenic protein-2 (BMP2) activity [4]. These pathways are likely explanations for the decreased aortic elasticity and subsequent aneurysm formation as well as the abnormal skeletogenesis observed in MFS [5, 6]. A MFS-like syndrome, Marfan type II, results from a mutation of the gene encoding TGF-β binding receptor 2 [7].

The Ghent nosology is the accepted means by which Marfan syndrome is diagnosed, and was most recently revised in 2010 to account for increasingly sophisticated molecular diagnostic methods, the age dependent nature of certain manifestations, and emerging differential diagnoses [8]. In the absence of a family history of MFS, aortic root dilatation with either FBN1 mutation, ectopia lentis or a systemic symptom score >6 (Table 14.1) establishes a diagnosis of MFS1 [8]. With an established family history, one of aortic root dilatation, ectopia lentis or a systemic symptom score >6 establishes the diagnosis [8].

In the absence of genetic testing, it has been suggested that the 1996 revision of the Ghent nosology offers greater clinical diagnostic sensitivity and there is still some debate as to which revision should be preferred [9–11]. Despite the high penetrance of FBN1, recent work in patients referred with suspected MFS1 found that around 10% of patients with a positive genotype failed to be diagnosed by either Ghent nosology [10]. Due to the development of clinical manifestations over time, follow up in this positive genotype group of patients is appropriate [12].

The revised Ghent nosology provides for the exclusion of a diagnosis of MFS1 in the light of genetic mutations consistent with other syndromes [8]. There is an increasing list of mutations which affect TGF-β and fibrillin-1 homeostasis, and consequently produce a constellation of symptoms which is very similar to those observed in MFS1 [4]. These include Loeys-Dietz syndrome, autosomal dominant Weill-Marchesani syndrome and ectopia lentis syndrome [8].

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Table 14.1 Systemic features of Marfan syndrome and their associated diagnostic weighting according to the 2010 revised Ghent nosology [8]

System	Feature
Cardiovascular	Aortic root dilation
	Greater propensity to aneurysm rupture
	Mitral and tricuspid valve prolapse
	Aortic and pulmonary valve insufficiency
	Congestive heart failure
	Dysrhythmia
	Calcification of mitral annulus
Musculoskeletal	Dolichostenomelia
	Arachnodactyly
	Hindfoot and Forefoot abnormalities
	Craniofacial abnormalities
	Ligament/tendon laxity
	Osteopenia
	Spine and chest deformities
	Hypotonia
	Osteoarthritis
	Limb length discrepancy
	Muscle wasting
Respiratory	Spontaneous pneumothorax
	Restrictive lung disease
	Bullae
Central Nervous System	Dural ectasia
	Neurodevelopmental abnormalities
Integument	Inguinal hernias
	Stria atrophica

Table 14.2 Non-ocular systemic manifestations of Marfan syndrome

Systemic feature	Score
Wrist and thumb sign (wrist or thumb sign)	3(1)
Pectus carinatum deformity (pectus excavatum or chest deformity)	2(1)
Hindfoot deformity (plan pes planus)	2(1)
Pneumothorax	2
Dural ectasia	2
Protrusio acetabuli	2
Reduced upper/lower segment ratio and increased arm length/height ration in the absence of severe scoliosis	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
>2 of the following facial features; dolichocephaly, enophthalmos, down-slanting palpebral fissure, malar hypoplasia and retrognathia	1
Skin striae	1
Myopia >3 dioptres	1
Mitral valve prolapse	1

History

MFS was first described in 1875 by Williams at the 11th annual meeting of the American Ophthalmological Society [13], but was more fully realised by a report of a 5 year old girl in 1896 by the French physician Antoine Bernard Jean Marfan [14]. Retrospective review of this particular case indicate that the young girl likely had a mutation of the *FBN2* gene consistent with Beals' congenital contractural arachnodactyly syndrome, but Marfan's continued reports of similar conditions established his eponym [15].

Epidemiology

MFS1 affects approximately 1 in 4000 people with no obvious propensity for gender or race [1, 16]. This figure may be an underestimate, as mild phenotypes are likely to go undiagnosed. Around 80 % of MFS1 patients have cardiovascular abnormalities which are responsible for the majority of disease specific mortality, with 10 % suffering aortic dissection [3, 16]. However, developments in treatment have greatly improved prognosis and, with modern management, life expectancy is only marginally decreased in MFS1 [17, 18].

Systemic Manifestations

Individuals with MFS1 can have abnormalities of the cardiovascular, respiratory, musculoskeletal and central nervous systems (Table 14.2). It is beyond the scope of this chapter to detail all systemic manifestations, but some attention should be afforded to the key features.

Aortic root dilatation is almost a requirement for diagnosis of MFS1 [8]. Ninety-six percent of patients fulfilling the revised Ghent nosology have an aortic diameter meeting the diagnostic cut off for pathological aortic root dilatation, measured at the level of the sinuses of Valsalva by echocardiography [19]. The diagnostic cut off is drawn at two standard deviations above the mean, which is described as a Z-score [20, 21]. A Z-score >2 means that the patient is in the upper 2.3 % for aortic root diameter in patients of their age, gender and body surface area. There is evidence to suggest that the development of aneurysms, and subsequent dissection, observed in MFS1 is derived from the high availability of TGF-β [6, 22]. TGF-β upregulates MMPs and elastase, which are responsible for the breakdown of elastic fibres which is postulated to lead to a weakening of the aorta [4]. Work in a mouse model of abdominal aortic aneurysms, outside of the context of MFS1, demonstrates a protective role for TGF-β

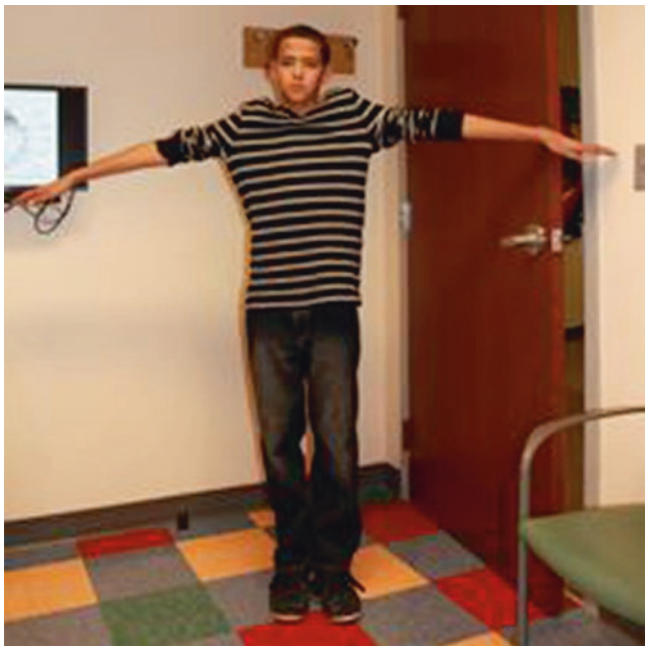

Fig. 14.1 Increased wing span in Marfan syndrome

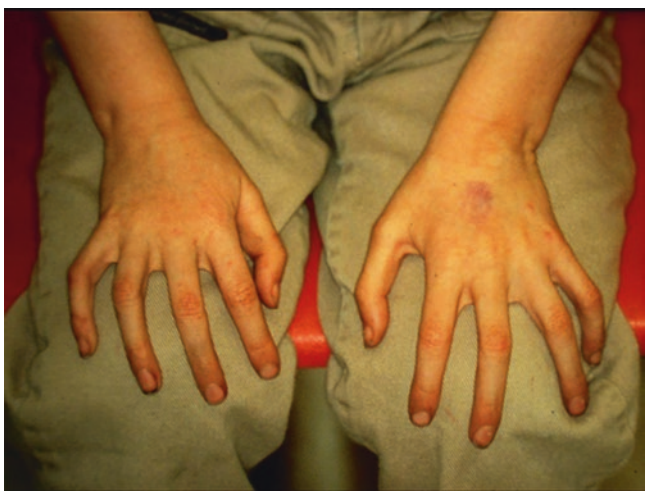

Fig. 14.2 Marfan syndrome arachnodactyly

against the progression of aneurysms and so the pathophysiological details of this pathway remain unclear [23].

The musculoskeletal manifestations of MFS1 are multiple and varied, and are often the most overt suggestion of the diagnosis. The most readily identifiable aspect of MFS1 is the excessive growth of long bones (Fig. 14.1) (dolichostenomelia) and arachnodactyly (Fig. 14.2). With reports of up to 96% of MFS1 patients complaining of pain in at least one part of the body, these manifestations are an important element of the disease [24]. Scoliosis is one of the key features as it is present in 62% of MFS1 cases (though only requiring intervention in 12%) and adult back pain is three times as common with MFS1 than in the general population [24]. The scoliosis observed in MFS1 is particularly challenging as it progresses quicker, responds less well to bracing, and has higher risk surgical solutions than other forms of scoliosis, due to greater risks of bleeding and fixation failure [24]. The pathophysiology of these facets of MFS1 are far from clear, but the effects of TGF-β on the activity of BMPs is likely to play a role [5].

Ophthalmic Manifestations

Fibrillin is located in many structures within the eye leading to a great breadth of ocular pathology associated with MFS1 [25, 26]. Fluctuating blurring of vision, headaches and diplopia are among the most common symptoms. On examination tremulousness of the lens and iris (phacodonesis and iridodonesis) may be noted, as well as visible zonules or lens equator in the pupillary aperture in cases of lens dislocation. A full mydriasis for examination may also be difficult to achieve due to hypoplasia or absence of the pupillary dilator muscle [27]. Glaucoma and retinal detachment are also associated.

Lens

Lens dislocation, or ectopia lentis (EL), is almost always bilateral in MFS1 though it may be subtle and asymmetrical. The lens may even remain central if the zonular laxity is symmetric or 360° with the only manifestation being increasing myopia and a clinically apparent increase in the anterior-posterior lens thickness with or without phakodenesis. This causes the lens to be smaller but true microspherophakia rarely occurs with MFS1 [28] although it is a feature of autosomal dominant Weill-Marchesani syndrome which is also associated with *FBN1* mutations. The pathophysiology is thought to be related to the aberrant fibrillin of the lens zonules and ciliary processes [26, 28]. EL is the most common ocular pathology in MFS1, with reported prevalence ranging from 45 to 87% of eyes. The most recent of these studies describes the majority of EL in the vertical or horizontal direction (classically superotemporal) whilst the remaining 40% demonstrated backwards movement [29–31]. Contrary to some teaching, it is important to recognize that the lens may also deviate inferiorly. EL occurs most commonly before 10 years of age [32]. The presence of EL was also shown to correlate with a longer axial length, poorer visual acuity and higher intraocular pressure (IOP), though EL has been associated with lower IOP elsewhere [29, 33]. Cataract is expected earlier and has a higher prevalence amongst MFS1 patients than in the normal population, perhaps due to lens dislocation [31]. Lens notching may occur in the area of greatest zonular laxity, but true ocular coloboma involving the posterior pole or iris, although rare, has been reported in MFS1 and may be linked to increased levels of TGFβ [34, 35]. Complete dislocation of the lens into the anterior chamber is uncommon in Marfan syndrome. Over time, dislocation into the posterior segment may occur.

Refractive Error

A subluxed lens causes myopia and astigmatism until the point where the visual axis becomes aphakic [29]. Patients with MFS1 also have axial myopia. Amblyopia may also occur as a result of EL [36]. Corneal curvature is reduced in MFS1 which can partially compensate for the increased axial length [37, 38]. Consequently, although myopia is the second most common ocular manifestation of MFS1 and >3 diopters of myopia features in the Ghent criteria, it is only found to have a prevalence of approximately 30 % in the MFS1 compared to 11 % in the general population [29, 37, 39]. Corneal astigmatism is also greater in MFS1, and those with EL have greater levels of astigmatism which has been suggested to be due to the presence of dysfunctional connective tissue in the zonules and cornea [38, 40].

Cornea

As well as displaying a lesser curvature the cornea is thinner both centrally and locally in MFS1 [41]. There is conflicting evidence as to whether either of these differences are associated with the presence of EL [38, 41]. Despite occasional case reports no association between MFS1 and keratoconus has been fully established [42].

Retina

Due to greater liquefaction of the vitreous, forces transmitted to the vitreous from a dislocated lens, and a larger globe, MFS1 eyes have a propensity to retinal breaks. Giant retinal tears have been reported to be 600 times more common in MFS1 than in the general population [28]. Retinal detachment has been reported to have prevalence between 5 and 25.6 % in MFS1 with the risk increased by EL, young age, high axial length and lens extraction surgery [28]. Although retinal reattachment in MFS1 used to have a high rate of redetachment, modern techniques have given the procedure comparable outcomes to when it is performed in the general population [28]. Bilateral detachment is also common, perhaps raising consideration of prophylactic surgery in the fellow eye.

Other

Strabismus is reported at a prevalence ranging from 7 to 45 % of MFS1, most commonly as an exotropia, compared with 3–4 % of the general population [28, 30, 31, 43]. This is likely due to extraocular muscle pulley instability brought about by aberrant microfibrillin.

Glaucoma is also more common in MFS1, most often primary open angle, though angle closure or pupillary occlusion by an anteriorly dislocated lens, and pigment dispersion may occur with mid peripheral iris transillumination [28, 44, 45].

Diagnosis

Due to the variability in the onset of features, and nature of presentation, MFS1 is often challenging to diagnose, and there is substantial intra- and inter-familial phenotype variability. Fortunately, molecular genetic diagnosis has become readily available. *FBN1* is located at 15q21.1. The variety of mutations in this very large gene have made mutations relatively difficult to identify [15]. Mutations of the *FBN1* gene are also part of various mutation constellations in other connective tissue diseases [4, 8]. Prenatal diagnosis and pre-implantation genetic diagnosis are both possible when the parental mutation is known, although there is controversy over its appropriateness and the relevant legislation varies between countries [46, 47]. A handful of antenatal ultrasound diagnoses have been described in Neonatal Marfan Syndrome, a syndrome similar to, but more severe than, classical MFS1, but this is not a sensitive test [32, 48]. Diagnosis is important to identify the need for regular follow-up to ensure timely intervention, and also for genetic counselling and offering investigation to first degree family. Although isolated EL has been described due to *FBN1* mutation, these patients should be screened periodically for the later onset of aortic root dilation [49].

Management

Although management should be through a multidisciplinary approach, in approximately 50 % of cases, the diagnosis of MFS1 is made by an ophthalmologist and so appropriate referral is often their responsibility [28]. Once diagnosed, patients require at least annual ophthalmic review with particular caution to be exercised in young children who are at risk of developing amblyopia. Whether patients should be advised to avoid strenuous exercise and impact sports in the presence of EL remains controversial. Lens dislocation into the anterior chamber is an emergency, as it can cause an acute rise in intraocular pressure. Treatment is by attempted repositioning with maximal pupillary dilatation and posturing, followed by lensectomy to prevent recurrence. The most common intervention necessary is refractive correction, on account of the frequent myopia and astigmatism observed. Refractive corneal surgery is not advised due to the corneal abnormalities often seen. Lensectomy is commonly indicated because of EL where the equator or near-equator of the lens bisects the pupil, anterior lens displacement causes secondary glaucoma, posterior displacement into the vitreous, and cataract formation. The latter usually does not occur until 30–60 years old [28]. Acceptable visual outcomes have been described with all techniques of lens surgery but there is little consensus as to which methodology is superior, and

outcomes of both aphakic and pseudophakic procedures seem similar [50–54].

Management also requires input from the specialties of genetics, orthopedics and cardiology [55]. The orthopedic input is required for the surgical stabilization of scoliosis and to treat pectus deformity, which can be on cosmetic grounds but also to relieve restrictive lung disease [55]. Cardiovascular management involves regular echocardiographic screening, on an annual basis, which is crucial due to the unpredictable rate of aneurysm progression. Pediatric cases and those who have a high rate of aortic expansion should be imaged twice annually [3]. Medical management has previously focused on long term beta-blocker or calcium channel blocker therapy to lower blood pressure and subsequent risk of cardiac complications. There is evidence to suggest the value of angiotensin converting enzyme inhibitors and angiotensin receptor blockers, though a randomized controlled trial comparing atenolol and losartan found no significant difference in the rate of aortic dilation over 3 years [56–58]. Any benefit derived from losartan is thought to be due to its inhibition of TGF-β signalling. During potential episodes of bacteremia, antibiotic prophylaxis is recommended in MFS1 patients with documented valve regurgitation, to minimise the risk of endocarditis. This is not required for intraocular surgery. Surgical intervention for cardiac disease may be needed.

Ehlers Danlos Syndrome

Definition

Ehlers Danlos syndrome (EDS) is an inherited heterogeneous group of connective tissue disorders which is characterised by the presence of joint hypermobility, skin extensibility and tissue fragility. There are six types which have been defined by their signs and symptoms. Each type is distinct and does not alter when inherited (Table 14.3) [59].

History

Ehlers Danlos syndrome was named by Fredrick Parkes Weber an English physician in 1936 [61]. The name commemorated the work of Danish dermatologist Edvard Ehlers (1863–1937) and French dermatologist Henri-Alexandre Danlos (1844–1912).

Epidemiology

The combined prevalence of all types of Ehlers Danlos syndrome is estimated to be 1 in 5000 [59]. Initially this was thought to be higher however it has become apparent that the disorder is more common than initially hypothesised. Elher Danlos III or hypermobility type is the most prevalent form of the disease. It is important to consider that hypermobility is thought to be present in around 10–30 % of the population, most commonly in young Asian and African females [62]. The classic type is the next most common and the other forms of Ehlers Danlos syndrome are extremely rare. EDS affects both males and females and there does not appear to be an ethnic predisposition.

Systemic Manifestation

Ehlers Danlos syndrome affects the body systemically in multiple ways:

Joint Hypermobility (Common)

This is a feature of all EDS, most notably classic, however it is less obvious in the vascular types. Hypermobility can be assessed on examination utilising the Beighton 9 point score (Table 14.4) or indirectly via the 5 question questionnaire [63, 64]. It is important to also examine joints not included in the Beighton score for further evidence of hypermobility.

Skin

EDS patients typically have extendable skin which is smooth or silky to touch (Fig. 14.3). It is delicate and in some cases described as semi-transparent when vasculature and tendons are visible [65]. Minor trauma can result in splitting of the dermis which most commonly occurs on pressure points such as elbows. Wound healing is often delayed as it involves the laying down of collagen to induce scar (Fig. 14.3) [66]. Scar tissue may also vary over time with stretching and widening frequently occurring due to the lack of collagen. Patient with EDS may also bruise easily.

Pain and Subluxation

EDS patients commonly describe multiple joint aches including the spine. These pains can be induced by light exercise and typically patients do not display the signs of an inflammatory arthropathy with a lack of erythema and visible joint swelling. Even though patients may be in pain the joints commonly move well and retain their hyperflexibility. It is also thought that EDS patients may have a resistance to local anaesthetics in around a two thirds of cases [67].

In children with EDS motor delay can be apparent and children may have delayed walking [68]. Children may not crawl and bottom shuffling maybe seen as a substitute. Once walking has commenced the child's motor delay typically resolves however chronic pain and tiredness can ensue and children may demand to be carried.

Table 14.3 Description of the subtypes of Ehlers Danlos Syndrome taken from the British Medical Journal's 'Best Practice' [60]

Type	Clinical signs		Inheritance	Genetic mutation
	Major criteria	Minor criteria		
Classic—Type I/II	– Skin hyperextensibility	– Easy bruising	Autosomal Dominant	*COL5A1*
	– Widened atrophic scarring	– Smooth and velvety skin		*COL5A2*
	– Joint hypermobility	– Molluscoid pseudotumours		
		– Subcutaneous spheroids		
		– Muscular hypotonia		
		– Complications of joint hypermobility		
		– Surgical complication		
		– Positive family history		
Hypermobility—Type III	– General joint hypermobility	– Recurring joint dislocations	Autosomal Dominant	*TNX—B*
	– Mild skin involvement	– Chronic joint pain		
		– Positive family history		
Vascular—Type IV	– Excessive bruising	– Acrogeria	Autosomal Dominant	*COL3A1*
	– Thin translucent skin	– Early onset varicose veins		
	– Arterial, intestinal and uterine	– Hypermobility of small joints		
	– Fragility which are prone to rupture	– Tendon and muscle rupture		
	– Characteristic facial appearance	– Carotid cavernous fistula		
		– Pneumothorax		
		– Positive family history—inparticular sudden death		
Kyphoscoliotic—Type VI	– Severe muscular hypotonia at birth	– Tissue fragility, atrophic scars	Autosomal Recessive	*LH1—PLOD1*
	– Generalised joint laxity	– Easy bruising		
	– Kyphoscoliosis at birth	– Arterial rupture		
	– Sclera weakness and globe rupture	– Marfans features		
		– Microcornea		
		– Osteopenia		
Arthrochalasia—Type VIIA	– Severe generalised joint hypermobility	– Skin hyper extensibility	Autosomal Dominant	*COL1A1*
Type VIIB	– Recurrent subluxations	– Tissue fragility—Atrophic scars		*COL1A2*
	– Congenital hip dislocations	– Easy bruising		
		– Muscular hypotonia		
		– Kyphoscoliosis		
		– Osteopenia		
Dermatosparaxis	– Skin fragility	– Soft doughy skin texture	Autosomal Recessive	*ADAMTS-2*
Type VIIC	– Sagging redundant skin	– Premature rupture of membranes		
	– Excessive bruising	– Large hernia		

Table 14.4 The Beighton criteria for joint hypermobility [64]

Joint Findings	Negative	Unilateral	Bilateral
Passive dorsiflexion of the fifth finger >90°	0	1	2
Passive flexion of the thumbs to the forearm	0	1	2
Hyperextension of the elbows beyond 10°	0	1	2
Hyperextension of the knee beyond 10°	0	1	2
Forward flexion of the trunk with knees fully extended and Palms resting on the floor	0	1	1

Scores are given for the features listed and a total score of greater than or equal to five defines hypermobility

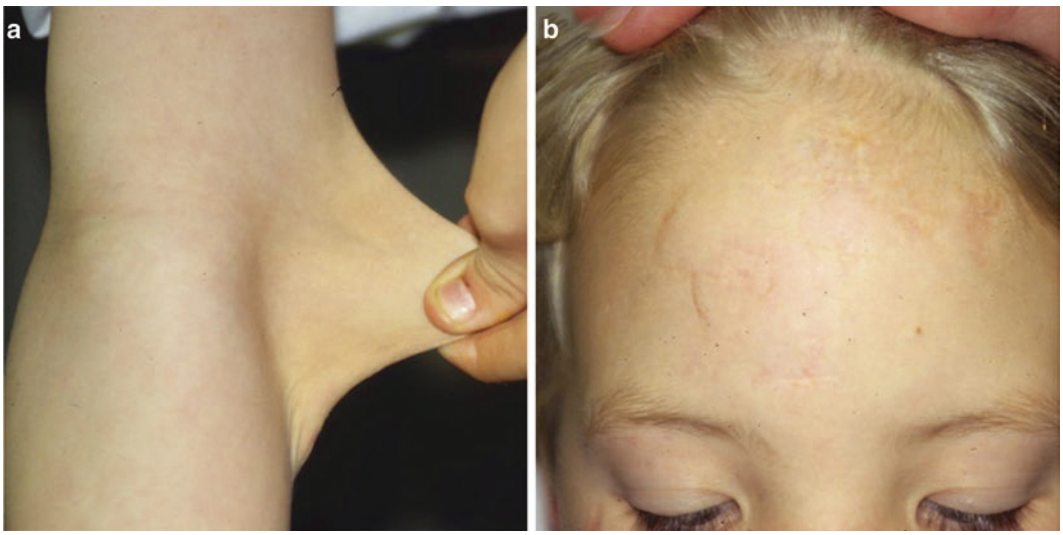

Fig. 14.3 (**a, b**) EDS showing skin laxity/skin scars

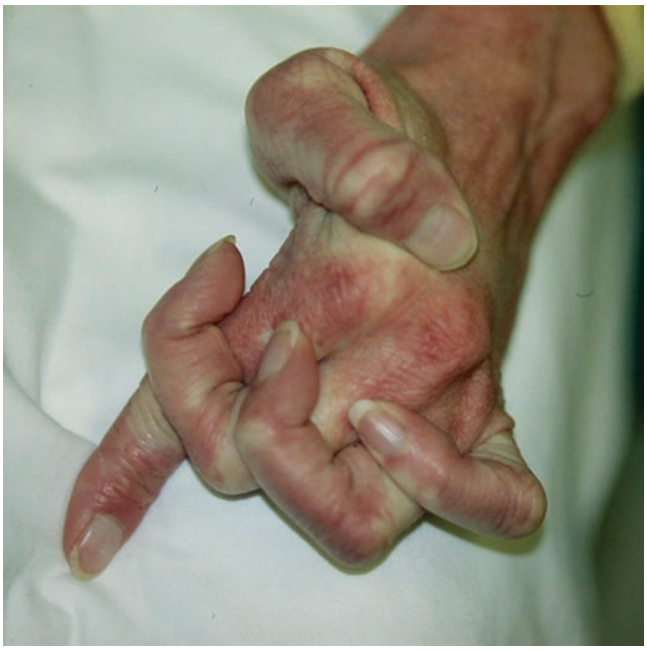

Fig. 14.4 Extreme joint hypermobility in EDS

Subluxation and dislocation is also more common in EDS patients. This is due to laxity in ligaments and unstable joints which can result in repeated subluxations (Fig. 14.4) [69].

Cardiovascular

EDS patients are at increased risk of bleeding diathesis and dissecting aneurysms due to the collagen deficiency [70]. They are also predisposed to rupture and bleeding from larger blood vessels as well as mitral valve prolapse [71].

Ophthalmic Manifestations

EDS can affect the supporting connective tissues around the eye resulting in drooping of the lid [72]. Typically this does not extend into true ptosis but maybe an early subtle sign. Patients have also been described as having an anti-mongoloid slant [73]. In this condition the nasal corners of the palpebral fissure are higher than the temporal corners, the opposite of the typical mongoloid slant.

EDS patients can also be described as having a blue sclera. This is due to thinning or transparency of the scleral collagen which exposes the uvea. Their thin sclera also puts patients at significant risk of globe rupture from mild trauma.

Multiple case reports have also described a link between microcornea and EDS [74, 75]. The cornea may also become keratoconic and cases of keratoglobus have also been described [76].

EDS is a disorder of collagen which can therefore result in ectopia lentis, myopia and an increased risk of retinal detachment [77].

Diagnosis

It is import to establish if a patient has risk factors which include a family history of hypermobility or EDS and predisposing genetic mutations.

Classic EDS

This is inherited in an autosomal dominant fashion with mutations commonly found on the *COL5A1* and *COL5A2* collagen genes [68]. These mutations are positive in around 90 % of patients with a clinical diagnosis of classic EDS.

The altered genes encode for collagen type V and mutation can result in a deficiency of this collagen. Disordered collagen fibres can result in ineffective connective tissue partially in the skin and joints.

Hypermobility EDS

This condition results in joints which move further than the expected range for age and sex. The diagnosis of hypermobility EDS is made when a patient has further systemic associations such as gastrointestinal, skin or autonomic issues. It is most commonly autosomal dominant inheritance however the genetic mutation has not been discovered. It is hypothesised that a genetic mutation results in less effective connective tissue.

Vascular EDS

This is considered a more serious form of EDS due to the risk of vessel rupture. It has autosomal dominant inheritance due to a mutation in the *COL3A1* gene [78]. This encodes for collagen III and the alteration of the gene results in disordered collagen and ineffective connective tissue. Patients with this condition may exhibit a characteristic facial appearance which includes large eyes, small chin, and lobeless ears. Their skin is commonly translucent and thin with visible veins on the chest and abdomen.

Kyphoscoliosis EDS

This is a rare condition which is autosomal recessive and caused by a mutation in the *PLOD1* gene [79]. This results in deficiency of the enzyme lysylhydroxylase and progressive scoliosis. Features also include thin conjunctiva, blue sclera and keratoconus.

Arthrochalasia EDS

This is a rare autosomal dominant condition which effects type I collagen. It occurs due to a mutation in either *COL1A1* or *COL1A2* resulting in abnormally weak collagen and loose joints which may recurrently subluxate [80].

Dermatosparaxis EDS

This is a rare autosomal recessive condition due to a mutation in the *ADAMTS2* gene. It results in a deficiency of collagen and is characterised by fragile, saggy redundant skin [81]. A positive combination of medical history, genetic testing and the Villefrance criteria are highly specific for the diagnosis of EDS.

Management

There is unfortunately no specific treatment for EDS. Symptoms should be managed and treatment provided to reduce the risk of known complications. As the condition is inheritable, genetic counselling should be offered to help prepare and inform families for the future.

Celiprolol, a beta 1 adreniceptor antagonist and a beta 2 adrenoceptor agonist, has been used in an attempt to reduce the risk of arterial dissections in vascular EDS [82]. It is hypothesised that these medications can reduce cardiac stress and hence lower complications. If complications do occur then surgical intervention may well be necessary.

EDS patients are known to have fragile skin with atypical scarring properties. Patients should therefore be encouraged to minimise the risk of trauma to themselves and this may well include wearing protective clothing. It is important to consider the fragility and scarring nature of EDS skin during surgery. Sutures should be placed under minimal tension and it maybe worth considering further deep sutures, or late removal of skin sutures to ensure the wound has completely healed.

Children with delayed motor skills and associated hypotonia may well benefit from physiotherapy. As patients grow older physiotherapy has also been shown to be beneficial [83]. This could be in the form of aquatic therapy to promote muscle development or manual therapies to aid mobilisation through a safe range of motion. Physiotherapist and occupational therapist play an important role in teaching patients how to use and preserve their joints.

Multiple publications have stressed the benefit of ascorbic acid in EDS type IV and VI [69, 84]. It is thought that the ascorbic acid can improve wound healing and reduce bruising in those even without a vitamin C deficiency. The dosage ranges from 1 to 4 g/day of ascorbic acid (vitamin C).

Regarding EDS patients' eyes it is important to ensure that patients are refracted due to their known myopic predisposition. Myopic patients typically have a longer than average axial length increasing the risk of retinal detachment. It is therefore advisable that EDS patients have a fundal review every year especially if they are symptomatic with flashes and floaters, to rule out retinal detachment. Parents of children with EDS should be warned about the increased risk of globe rupture and the risk associated with contact sports especially if the sclera is blue.

Osteogenesis Imperfecta

Definition

OI is a condition which is often referred to as brittle bone disease. It is an inherited disorder of connective tissue characterised by bones that break easily.

History

OI has been known my multiple names over the years. In 1835 Jean Lobstein described the disease and called it

osteopsathyrosis idiopathica [85]. In 1849 Vrolik expanded upon this describing the congenital form of the disease and naming it osteogenesis imperfect [86]. In 1906 Looser concluded through histological analysis that both Lobstein and Vrolik had described the same condition with different severity [87]. Currently OI is differentiated into four types and this was proposed by Sillence in 1979 [88].

Epidemiology

Studies have shown that the incidence of osteogenesis imperfecta is approximately 1 in 20,000 [89]. It must be recognised that the condition is under diagnosed and prevalence may therefore be higher. Frequency is typically similar amongst ethnic groups except for the Shona and Ndebele tribes in Zimbabwe where an increased rate has been observed [90]. The condition appears to affect males and females equally.

Systemic Manifestations

OI was initially classified by Sillence in 1979. He based his types on familial history, clinical presentation as well as radiological findings. His classification was later modified by Glorieux and Rauch who utilised advancements in genetics to add further details and types to OI as a diagnosis [91].

Type I

This is the most common form of OI which has autosomal dominant inheritance and accounts for around 50 % of all of cases [92]. It typically presents at preschool age with mild bone fragility resulting in fractures and minimal limb deformities. There is great variety amongst presentations and some children may only have minimal limb deformities with few fractures whereas others may illicit multiple long bone fractures with chronic pain. The systemic effects occur due to collagen which is of sufficient quality but not quantity. This is due to a lack of *COL1A1* allele resulting in loose joints, poor muscle tone, frequent fractures and blue sclera [93].

Type I can be further subdivided into type IA or type IB based on absence or presence of dentiogenesis imperfecta which is opalescent teeth which are absent in type IA but present in IB. After growth is complete the incidence of fractures significantly reduces. Type I OI typically does not significantly affect height and children are commonly within the normal range for their age.

There is a known association with hearing loss and patients typically become symptomatic as young adults [94]. The diagnosis of OI type I can be a significant burden for patients. To an observer patients may appear to have normal bone structure however the patient may struggle with the psychological burden and stress associated with accommodating their increased bone fragility. Parents of children with OI type I are encouraged to carry documentation of the diagnosis to ensure that fractures are not mistaken for non-accidental injuries.

Type II

This is known as the most severe form of OI [95]. The condition is often lethal in the perinatal period and is due to an autosomal dominant mutation in *COL1A1* and *COL1A2* effecting type 1 collagen. Patients born with the condition have very short limbs with small chests, soft skulls and their legs may be in a frog position. These children commonly develop respiratory failure due to poorly developed lungs and intracerebral haemorrhage leading to a life expectancy of under 1.

Type II can be further subsided into A, B and C by the radiological appearance of the long bones and ribs. Patients with IIA have broad ribs associated with multiple fractures and under modelling of the femur. In type IIB patients present with normal or thin ribs with fractures and some under modelling of the femur. In type IIC patients there is variable thickness of the ribs with malformed scapulae and slender twisted long bones [96].

Parents with the type II genetic mutation should be offered genetic counselling with the severity of the condition being clearly explained.

Type III

OI type III is severe in those children who survive the neonatal period. The condition is again due to mutation in the *COL1A1* or *COL1A2* genes resulting in defective collagen type 1. There is associated bone fragility and the number of fractures present in children can vary widely. Children at birth may have shortened bowed limbs with a small chest and soft calvarium. They frequently suffer respiratory problems with difficulties swallowing [97].

As the child develops there may be multiple long bone fractures with increasing bowing and further deformity. Adults are typically short in stature, under 102 cm which is partly due to scoliosis and vertebral compression fractures. Patient may have a triangular face shape due to overdevelopment of the head and underdevelopment of the facial bone. Dentinogenesis imperfecta is common and patients' sclera is often blue or grey.

Families should be offered genetic counselling and guidance regarding the monitoring of scoliosis and respiratory function.

Type IV

This form of OI can range between type I and type III in severity. It is again typically autosomal dominant and due to a mutation in the *COL1A1* and *COL1A2* genes. Bone fragility is again common with most fractures occurring before puberty. Patients are often shorter than average distinguishing them from type 1 and scoliosis and barrel chest are commonly associated. They

may have a distinctive triangular face and hearing loss however their sclera is often white or normal in colour [98].

Long bone fracture as well as vertebral compression and ligament laxity may also be present. Type IV like type I can be further subsided into 'A' and 'B'. 'A' represents the absence of the dentinogenesis imperfecta and 'B' the presence.

Advancements in microscopic studies have allowed for a more detailed review of type IV bone. This has resulted in two further types of OI being added to the Sillence classification. They have been labelled type V and VI and are clinically similar to type IV however there are distinctive patterns to their bone structure [99]. Therefore types V and VI can only be diagnosed through radiographic and bone studies and they do not involve deficits in type 1 collagen.

Type V

Type V has the same clinical features as type IV OI and has autosomal dominant inheritance. It is distinguished by its 'mesh' like bone appearance on histology. Patients may have large hypertrophic calluses due to fractures of long bones and calcification of the interosseous membrane at the forearm resulting in restriction of rotation and subsequent dislocation.

As with all OI patients should be offered genetic counselling and women can be screened for hypertrophic callus of the iliac bone.

Type VI

This is an extremely rare form of OI and the inheritance mode is yet to be identified [100]. It results in moderate to severe brittle bones and clinically is similar to type IV except there is an increased fracture rate. It can be distinguished from type IV by its characteristic build-up of osteoid caused by a mineralization defect, identifiable in biopsied bone. Patients' sclera are generally white and dentinogenesis imperfecta is typically absent.

Type VII

Type VII is recessively inherited and has been localised to chromosome 3p22–24.1 and not the collagen type 1 gene [101]. The mutation occurs in the *CRTAP* gene which codes for a protein called cartilage associated protein which has a role in bone development. Partial function of *CRTAP* typically results in moderate symptoms however absence was lethal amongst published cases. Patients suffer with fractures from birth with lower limb deformities, proximal limb shortening (rhizomelia) and coxa vara is common.

Type VIII

This type of OI is due to a mutation in the *LEPRE1* gene resulting in a deficiency of *P3H1* [102]. Type VIII patients are similar in appearance to types II or III however their sclera is white. They also are severely growth restricted with reduced skeletal mineralisation.

Ophthalmic Manifestations

OI is a condition which effects collagen. Type 1 collagen is an important structural component of the sclera [103]. OI patients tend to have a thin sclera which results in a blue discolouration due to visualisation of the choroid. The reduced thickness also increases OI patients' risk of traumatic and spontaneous scleral rupture [104].

Type I OI patients have the most apparent blue sclera. Type III patients also have blue sclera however it commonly fades over time. Type IV patients often have a grey coloured sclera. Type VI, VII and VIII typically have a white sclera.

There have also been published cases showing an association between OI and reduced central corneal thickness with subsequent reduced ocular rigidity [105]. The reduction in central corneal thickness increases the risk of cornea perforation in OI patients. Both corneal and sclera perforations require repair and cyanoacrylate glue can be utilised however a patch graft is thought to provide a more reliable repair [106].

OI patients also develop progressive myopia which can result in staphyloma formation [107]. With this they are also at increased risk of retinal detachment and case reports have also highlighted an increased risk of glaucoma [108].

In children and young adults it is important to consider that patients are at increased risk of vitreous haemorrhage and fracture which may complicate cases of non-accidental injury. Another condition which may present in early adulthood is keratoconus as the cornea relies up collagen to maintain its shape [109].

Diagnosis

OI is primarily diagnosed on its clinical presentation. As the condition is rare it is important to involve a clinician who is familiar with the various presentations. It is often an inheritable condition and it is therefore important to examine family members.

Classic clinical features include frequent fractures, reduced growth, blue sclera, dentinogeneis imperfecta and progressive hearing loss.

Patients should be investigated with imaging looking specifically for Wormian bones which are extra bone which occur within a suture in the cranium [110]. Laboratory tests include genetic testing for mutations and DNA sequencing for *COL1A1* and *COL1A2*. This allows the identification of the collagen type 1 gene mutation responsible for the majority of OI. These genetic tests have sensitivity of around 90% in patients with OI. In individuals where the genetic tests are negative for both *COL1A1* and *COL1A2*, yet the clinical signs are present for OI, further investigations should be completed. These include genetic tests of other collagen genes such as *CRTAP* and *P3H1* which are responsible for the rarer types of OI. Skin biopsies may also be useful in identifying collagen to analyse.

Management

OI is an inheritable genetic condition which has no cure. Management is therefore multi-disciplinary and focuses upon improving the patients' symptoms. Surgical correction has been described for joint deformities and frequent fractures must clearly be managed appropriately [111]. Physiotherapy plays an important role in maintaining joint mobility and orthotics can be used to help stabilise lax joints. Some patients with poor mobility will benefit from mobility aids and occupational therapists input.

Over the years our genetic understanding of OI has developed resulting in management focusing on the molecular causes of the condition. Evidence now shows that improving bone mass and strength can reduce the associated risk of fracture in OI patients. Bisphosphonates which are typically used to treat osteoporosis by slowing the loss of bone have been found to be beneficial by reducing the amount of vertebral compressions along with some long bone fractures [112].

It is also important to consider that patients may need treatment of conditions related to their OI. These include hearing aid for reduced vision, dental work and in some cases oxygen administration for associated respiratory problems.

Ocular Treatments

OI patients are at increased risk of myopia and therefore patient should be refracted every year and any errors corrected. It is important to consider the known association with keratoconus during optician visits. If there is progressive irregular astigmatism then the patient should be referred to a corneal specialist for consideration of collagen cross linking.

Patients may also require scleral or cornea repairs due to their increased risk of perforation.

When completing any ocular surgery on OI patients it is important to consider that their abnormal collagen results in less forgiving tissue. Scleral perforation during strabismus surgery has been published and scleral incisions created by ports utilised during vitreoretinal surgery, due to patients increased risk of retinal detachment, may need to be sutured [113].

Ensure that OI patients also have an ocular pressure check due to the known associated risk of glaucoma. Patients with evidence of glaucoma can be treated as appropriate with medications and surgeries.

Type II Collagenopathies

Definition

Aberrations of the *COL2A1* gene, located on the long arm of chromosome 12, cause a spectrum of bone dysplasias with a range of phenotypes and severities frequently exhibiting ocular manifestations [114]. These diseases have often been considered in a spectrum of severity ranging from perinatally lethal conditions such as achondrogenesis, to those causing congenital dwarfism such as spondyloepiphyseal dysplasia congenita (SEDC) to Stickler syndrome type I (STD-1) [115]. Other non-lethal phenotypes include Kniest dysplasia (KND) and spondyloepimetaphyseal dysplasia Strudwick type (SEMD-ST) [115, 116]. In recent years the literature has moved towards considering these pathologies as a spectrum of disease with variable phenotypes, which is much more consistent with their genetic origins [115, 117]. Type 2 collagenopathies are autosomal dominant, though mutations are frequently *de novo*, and are often characterised by bone abnormalities, vitreoretinal pathology and early onset deafness [115, 117].

Type 2 collagen is a molecule composed of 3 α1(II) chains [118]. *COL2A1* codes for procollagen α1(II) [119]. There are 2 alternative splicing isoforms depending on the inclusion or exclusion of exon 2 of the *COL2A1* gene during transcription [115, 120]. The longer procollagen α1(II) isoform, known as the IIA isoform, is only found in the vitreous [118]. Therefore mutations in exon 2 will only have ocular manifestations.

Each of these helical polypeptides has glycine in every third amino acid position which is a key contributing factor to collagen's stability and structure [115]. Though *COL2A1* mutations are firmly established as the cause of this group of diseases, the process by which the clinical phenotype is predicted by the exact mutation observed is unclear [117, 121–123]. No mutational hotspots within *COL2A1* have been described and there is great heterogeneity amongst the reported mutations [121]. A recent study found that the majority of patients with SEDC or SEMD-ST had a missense mutation causing a glycine substitution in the helical domain [117]. There were however a small number of splicing mutations as well as C-terminal mutations which question the fidelity of this genotype-phenotype relationship [117]. Exon skipping splice mutations and loss of function mutations have been associated with KND and STD-1 respectively, though exceptions to these relationships have also been described [117, 121, 124, 125].

History

The German pediatrician Wilhelm Kniest first reported his eponymous bone dysplasia in 1952 in a 3½ year old girl [126]. Stickler syndrome was characterised by the German born American pediatrician Gunnar Stickler [127]. Spondyloepiphyseal dysplasia congenital was first proposed as a separate diagnosis from Morquio syndrome and Spondyloepiphysial Dysplasia Tarda by German pediatricians Jürgen Spranger and Hans Wiedemann in 1966 with a report of 6 neonatal cases [128]. SMED-ST was first reported by Murdoch and Walker and the name of the patient described was later attributed to the condition, though it has also been

known as dappled metaphysis syndrome after its distinctive radiologic appearance [129, 130].

Epidemiology

There is no comprehensive epidemiological data on type 2 collagenopathies but Stickler syndrome is thought to be the most common at 1 in 7500 [131]. The prevalence of SEDC is substantially less at 3.4 per million [132]. KND and SMED-ST prevalence are unreported, but they are known to be rare.

Systemic Manifestations

Type II collagen accounts for 90 % of the collagens found in adult hyaline cartilage, and its dysfunction consequently has extensive musculoskeletal effects [120]. The physiological development of cartilage is dependent on both the extracellular matrix and the ability of chondrocytes to organize themselves within it. In a histopathological report of KND, the microscopic structure of the articular cartilage was found to be disorganised with cystic areas giving a "Swiss cheese" appearance [133]. Similar cartilaginous disorganisation with growth plate abnormalities was reported in a mouse model, and electron microscopy from both studies revealed a congested endoplasmic reticulum, which has been suggested as a cause for chondrocyte apoptosis [122, 123, 133]. A transgenic mouse model confirmed these findings but also demonstrated a *COL2A1* mutation-dependent shortening and disorganization of chondrocyte sensory cilia and disorganization of the collagen II in the extra cellular matrix [134]. These findings suggest that a mutation of *COL2A1* leads to dysfunction of both the protein framework in which chondrocytes organise themselves and also the intracellular means by which they navigate that framework.

Whilst there is considerable overlap between the systemic features of the type 2 collagenopathies discussed here we consider them separately (Table 14.5).

Table 14.5 Non-ocular systemic manifestations of non-lethal Type 2 colleganopathies with ocular manifestations [115, 135]

System	SEDC/SEMD-ST/KND	STD-1
Skeletal	Short-trunked dwarfism	Normal stature
	Early onset osteoarthritis	Early onset osteoarthritis
	Delayed endochondral ossification of appendicular skeleton	
Respiratory	Neonatal respiratory distress	
Orofacial	Cleft palate	Micrognathia (Pierre-Robin sequence)
	Flat mid-face	Flat mid-face
		Bifid uvula (Fig. 14.5)
		Cleft palate (Fig. 14.5)
CNS	Paralysis from atlanto-axial instability	Hearing loss
	Infantile hypotonia	
	Hearing loss	

Stickler Syndrome

Stickler syndrome is distinct from the other type 2 collagenopathies, in that it does not result in short stature. Although STD-1 is derived from abnormalities of *COL2A1* and is the most common variant of Stickler syndrome, there are other forms of the disease due to mutations of the genes which encode type 9 or 11 collagen (Table 14.6). These subgroups express similar systemic features to a variable extent with the exception of the 'ocular only' type, where mutations occur in exon 2 of *COL2A1* which is only expressed in the vitreous [118, 136].

Deformity of both hard and soft palate can be observed in all forms of Stickler syndrome, though notably cleft lip is not a feature (Fig. 14.5) [137]. Pierre Robin sequence with micrognathia is common. Although not always present, auditory defects are common and can be sensorineural or conductive in nature [138]. Conductive loss is thought to be due to the presence of defective type II collagen in the articular interfaces of the middle ear bones and the tympanic

Table 14.6 Distinguishing features and genetic aetiology of the known types of Stickler's disease as summarised by Snead et al. (2011) [137]

Type	Affected gene	Distinguishing features
Type 1	*COL2A1*	Membranous congenital vitreous anomaly, congenital megalophthalmia, deafness, arthropathy, cleft palate
Type 2	*COL11A1*	Beaded congenital vitreous anomaly, congenital megalophthalmia, deafness, arthropathy, cleft palate
Type 3	*COL11A2*	Normal vitreous and ocular phenotype, deafness, arthropathy, cleft palate.
Type 4	*COL9A1*	Recessive inheritance, sensorineural deafness, myopia, vitreoretinopathy, epiphyseal dysplasia
	COL9A2	
Ocular only	*COL2A1* exon 2	Membranous congenital vitreous anomaly (usually), congenital exorbitism. No systemic features
Other	unknown	Hypoplastic vitreous, deafness, arthropathy, cleft palate

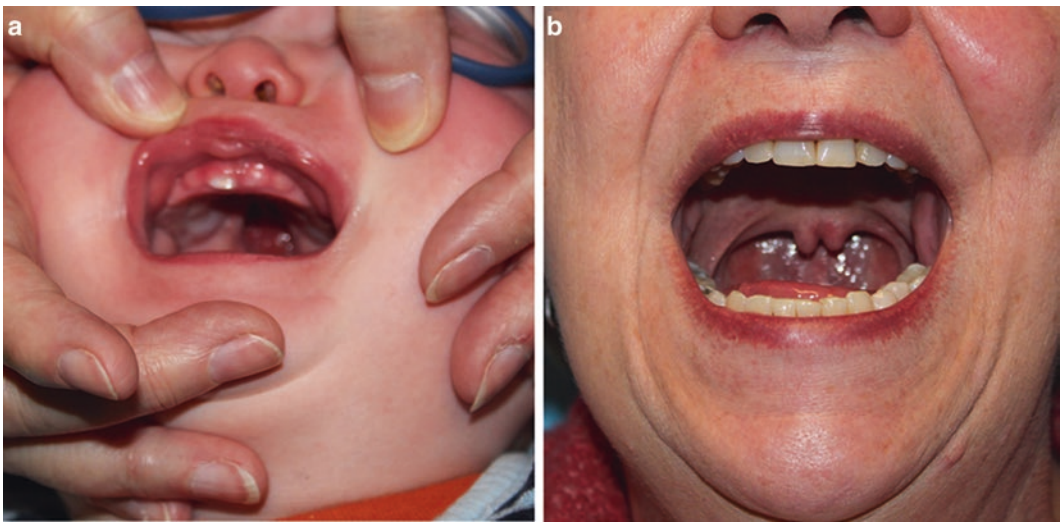

Fig. 14.5 (**a, b**) Stickler bifid uvula/U shaped cleft palate/facies

membrane [138, 139]. Expression of *COL11A1* and *COL11A2* has been described in the developing cochlea and so aberrations of these genes are thought to lead to sensorineural hearing deficits [137]. Recurrent otitis media, more common with the altered facial anatomy which can be observed in Stickler syndrome, characterized by midfacial hypoplasia and the appearance of exorbitism, may also play a role in conductive hearing loss [140]. A range of non-specific musculoskeletal symptoms have also been described and affect more than 80 % of patients, including hypermobility and chronic back and joint pain [141].

Spondoepiphyseal Dysplasia Congenita

SEDC presents at birth, or following antenatal screening, with short stature with or without pectus deformity, cleft palate, lumbar lordosis, talipes equinovarus, short neck and hip flexion contracture [132, 142]. Through infancy and early childhood, abnormal gait due to coxa vara and kyphoscoliosis may become apparent. The appearance of these features and their severity helps divide SEDC into mild and severe phenotypes, though such a distinction can only be made around 4 years old [143]. SEDC is also characterised by its radiological features. Axially, a flattening of the vertebral bodies known as platyspondydly is common, along with atlanto-axial instability due to odontoid hypoplasia [132]. The latter of these features can cause spinal cord compression leading to lasting neurological disability or even sudden death and so is important to identify [144]. During intubation it is important to avoid hyperextension. In the appendicular skeleton delayed epiphyseal ossification is the hallmark of SEDC although abnormalities of the metaphyses are also seen [132]. These peri-articular bone abnormalities lead to precocious osteoarthritis. Audiological deficits, as described in Stickler syndrome, are also common [117].

Kniest Dysplasia and Spondyloepimetaphyseal Dysplasia Strudwick Type

These two disorders both exhibit a great degree of overlap with SEDC. In addition to the features shared with SEDC, there are two additional radiological signs which are considered highly diagnostic of KND. Firstly, the long tubular bone metaphyses exhibit exaggerated flaring which creates the impression of a 'dumbbell' femur and humerus. Secondly, clefts seen in the coronal plane can be observed in the vertebral bodies [125]. As for SEMD-ST a flocculated appearance of the metaphyses which also exhibit neighbouring regions of osteosclerosis and osteopenia, giving a radiographic 'dappled' appearance, are distinguishing features [145].

Ophthalmic Manifestations

COL2A1 is expressed throughout the ocular tissues during development and so the broad anatomical extent of ocular manifestations of the type 2 collagenopathies is to be expected [114, 120]. Due to its greater relative frequency, the ophthalmic manifestations of STD-1 are the best characterised in the literature, although most of the ocular signs are reported in the other type 2 collagenopathies, and mechanistically it seems likely they have a very similar constellation of signs and symptoms [117, 121, 146]. It has been suggested that the most severe ophthalmic manifestations are seen in individuals with a splicing mutation of *COL2A1* [117].

Vitreoretinal

Type 2 collagen accounts for 70 % of the total protein content of the vitreous and mutations in the *COL2A1* lead it to appear optically empty [146–148]. Vitreous abnormality is

one of the key clinical signs suggestive of type 2 collagenopathies, but it also is the key to the differentiation of the aforementioned variants of Stickler disease, and directs genetic investigations to secure the diagnosis [137]. Although not always consistently observed, the nature of the congenitally abnormal vitreous has been suggested to allow for distinction between the two most common variants; STD-1 and STD-2. In STD-1 membranous anomaly of the virteous, also described in other type 2 collagenopathies, represents the visualisation of a retrolental detached posterior hyaloid membrane on slit lamp examination, whilst a beaded vitreous anomaly is more characteristic of STD-2 [137, 146]. Optically empty vitreous spaces may be observed in both STD-1 and STD-2. These anomalies infer a predilection for retinal detachment, with prevalence as high as 70 % and 50 % reported amongst STD-1 and STD-2 respectively, and similar rates have been reported in other type 2 collagenopathies [149–151]. It should also be noted that Stickler syndrome is the most common cause of heritable retinal detachment in childhood [146]. This retinal detachment is often the result of a circumferential separation of the hyaloid membrane near the pars plana. The retina also commonly exhibits thinning, posterior retinal tears, traditional circumferential lattice and perivascular pigmented radial lattice degeneration [146].

Refraction

A moderate or severe congenital myopia was recently reported in 45 % of patients in a report of a large type 2 collagenopathy cohort: for approximately one quarter the myopia was found to be progressive [117]. Myopia has also been suggested to be particularly severe in KND [120]. However, work plotting the association between *COL2A1* and high myopia has failed to demonstrate a relationship in Chinese populations suggesting this relationship may be dependent on other factors [114, 152].

Lens

Cataracts have been reported in 24 % of a Stickler syndrome cohort and 16 % in a type 2 collagenopathy cohort mainly consisting of SEDC patients [117, 141]. They are typically described as cortical wedge, fleck or quadrantic lamellar cataracts [146, 153]. They are often visually insignificant. Ectopia lentis is also rarely reported [154].

Glaucoma

Glaucoma has been shown to increase in prevalence with age in Stickler syndrome, with 35 % of patients aged 50–59 reporting glaucoma [141]. Yet congenital and infantile glaucoma are a manifestation of KND [155]. The majority of glaucoma in Stickler syndrome has been noted in the presence of retinal detachment however, so whether the mechanism of raised intraocular pressure relates to the collagen 2 dysfunction or the anatomical alterations from retinal detachment is unclear. The glaucoma of KND is a primary goniodysgenesis.

Diagnosis

Genetic testing is of value to confirm the clinical diagnosis of a type 2 collagenopathy and also may have prognostic value given the developing association between genotype and phenotype [117]. For example, those with splicing errors are thought to be at greater risk of retinal detachment and hearing loss [117]. Differentiation between bone dysplasias is still largely ascertained on clinical and radiological grounds. In cases of suspected type 2 collagenopathy a complete skeletal survey should be performed [156]. The presence of platyspondyly with abnormal epiphyses in the extremities is consistent with SEDC and KND, whilst the addition of metaphyseal involvement is consistent with SEMD [156]. Antenatal radiological diagnosis of skeletal dysplasias is also possible but DNA testing may be more reliable [157].

Management

Regular multidisciplinary review is the basis for management of these diseases. Ophthalmological survey is key for diagnosis but also for ongoing screening of retinal detachment or risk factors such as peripheral lattice, breaks or tears. Adequate refractive correction must also be ensured. Ocular examination is recommended at birth and annually thereafter until adulthood with an additional early check-up at 6 months of age [117]. Should retinal findings or glaucoma be seen, more frequent follow-up is indicated. Neonatal audiology screening is recommended with regular follow-up until speech development and hearing aids should be considered if indicated. To monitor neurological risk in type 2 collagenopathies other than STD-1, flexion/extension cervical spine films should be performed at age 3 as well as before any anaesthesia requiring procedure throughout life [117]. Some ophthalmologists advise patients to avoid contact sports to minimise retinal detachment risk although this practice is not universal.

Prophylactic 360° retinal laser or cryotherapy just posterior to the ora serrata has been suggested to be effective in preventing anterior retinal detachment in STD-1 [149, 158]. Surgical interventions for atlanto-axial instability may also be appropriate; the most common approach in SEDC is decompression and subsequent fusion around the craniovertebral juncture [159].

Sclerosteosis

Definition

Sclerosteosis is a rare autosomal recessive bone sclerosing disorder characterised by tall stature, increased bone density and entrapment of cranial nerves caused by excessive bone growth [160]. It is caused by a mutation of the *SOST* gene located on 17q, which is responsible for the protein *sclerostin*, largely produced by osteocytes [161]. A phenotypically similar disorder, known as sclerosteosis 2, has also been reported as a result of heterozygous and homozygous mutation on 11p in the gene which codes for low density lipoprotein-related protein 4 (LRP4), a *sclerostin* interaction partner [162]. The mutation observed in sclerosteosis leads to an undetectable plasma *sclereostin* level [161]. The physiological role of *sclerostin* is to reduce deposition of bone by osteoblasts and osteoclasts [161].

Van Buchem disease is another autosomal recessive disease caused by *SOST* dysfunction but presents with a milder phenotype than sclerosteosis. It is caused by a deletion on the *SOST* gene which affects a regulator domain leading to low levels of *sclerostin* rather than its absence. Key phenotypic differentiating features are the absence of gigantism, syndactyly or nail dysplasias likely because the *SOST* mutation of Van Buchem disease does not impact embryonic *SOST* expression [163, 164].

History

Sclerosteosis was described in 1929 by Hirsch [165]. The most comprehensive reports in the limited literature have been from South Africa [160, 166].

Epidemiology

Sclereostosis is an exceedingly rare condition with less than 100 cases reported [167]. It has mostly been recorded amongst South African white Afrikaners of Dutch heritage, though it is reported globally [168]. Amongst this population of descendants of farmers who left the Dutch East India Company, 1 in 100 individuals is thought to carry the determining gene [169].

Systemic Manifestations

The most striking features of sclerosteosis are those of distorted facies from excessive bone deposition and gigantism (Table 14.7). Bone density far in excess of the mean by 4–14 standard deviations [169]. Fractures therefore do not occur [160]. Symptoms derived from increased bone density are largely confined to the skeletal and nervous systems, and whilst symptoms develop through to young adulthood they tend to stabilise from the third decade onwards [160].

Table 14.7 Non-ocular systemic manifestations of sclerosteosis

System	Feature
Skeletal	Syndactyly—usually of 2nd and 3rd fingers
	Tall stature
	Radial deviation of terminal phalanges
	Highly resistant to fractures
	Distorted facies
Cutaneous	Nail dysplasias
Central Nervous System	Facial nerve palsy
	Hearing loss
	Olfactory dysfunction
	Intracranial hypertension

The most serious complication of the disorder is sudden death resulting from brainstem compression at the foramen magnum due to intracranial hypertension [170]. Impingement of cranial nerves also leads to substantial morbidity through sensory dysfunction and there is clinical evidence of a role for SOST in vascular calcification although cardiovascular features are absent from the sclereostosis literature [171–173].

Ophthalmic Manifestations

Literature detailing the ocular manifestations of sclerosteosis are sparse, but given the bone overgrowth and consequent impingement of foramina the following reported features are mechanistically intuitive. In the largest reported cohort of 45 patients, epiphora was reported in 28 % due to occlusion of the physiological lacrimal drainage system [160]. Proptosis and divergent strabismus was described in a quarter of cases due to excessive bone deposition within the orbit [160]. Papilledema is an observed consequence of raised intracranial pressure in 70 % of cases and whilst there was no reported visual loss in this largest series, it has been described in a case report [174].

Diagnosis

The sclerosteosis phenotype is dependent on biallelic findings of 6 loss of function mutations of the *SOST* gene [161]. Family history is key to diagnosis with syndactyly offering an early clinical diagnostic feature and distorted facies becoming evident by the age of 10 years old [170]. Carriers of the condition are phenotypically normal, with normal levels of *sclerostin*, though tend to have bone density on the upper limit of normal [169].

Management

Management options are limited and based around symptom control. Cranial decompression can be indicated as a treatment for intracranial hypertension. Although there is no specific genetic therapy in development for sclerosteosis, the pathophysiology is being explored as a treatment for osteoporosis. The first *sclerostin* targeting monoclonal antibody was romosozumab which has demonstrated an ability to increase bone density in phase 1 and 2 clinical trials [171, 175]. Its fracture preventing effects in osteoporosis are being explored in a phase III clinical trial [30].

Osteopetrosis

Definition

Osteopetrosis, also known as marble bone disease, is a genetic condition which is characterized by increased bone mass due to osteoclast dysfunction and a tendency to sustain fractures (Fig. 14.6). It is genetically heterogenous with six distinct types described in the 2007 revision of the nosology of genetic skeletal disorders (Table 14.8) [176]. Inheritance patterns and mutation loci vary with the autosomal recessive (ARO) types tending to be most severe with potential for neonatal mortality and the autosomal dominant (ADO) and X-linked (XLO) types sometimes presenting incidentally in adulthood [177]. These conditions all arise from dysfunction of osteoclasts which are responsible for the catabolic aspect of bone remodelling and fundamental to mineral homeostasis and skeletal stability [178]. Osteoclasts are derived from precursor cells of hematopoietic lineage which merge to form the mature cells which are multinucleated [178]. Osteoclasts demonstrate polarity: a portion of their membrane is 'ruffled' and forms an osteolytic interface with the bone tissue. Transporters in this region of the membrane move hydrochloric acid, responsible for hydroxyapatite dissolution, and cathepsin, responsible for collagen matrix breakdown, out of the cell [178]. Most of the genes in which mutation results in osteopetrosis are involved in acidification machinery, for example carbonic anhydrase, protein pumps and chloride channels, which facilitate resorption of inorganic bone material [179].

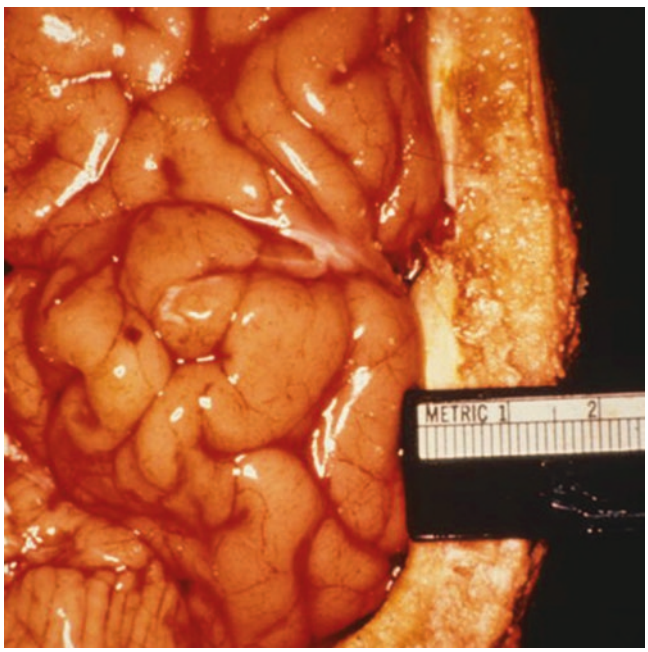

Fig. 14.6 Sclerosis of the skull in osteopetrosis

The disease formerly known as ADO type I, which features mild osteosclerosis, has been found to be caused by an osteoblast defect due to a mutation in the *LRP5* gene and is therefore no longer considered part of the osteopetrosis family of diseases [180]. This leaves ADO type II which is also known as Albers-Schönberg disease.

History

Heinrich Ernst Albers-Schönberg is credited with the first description of osteopetrosis in 1904 which is thought to have been an autosomal dominant case [181].

Epidemiology

Collectively osteopetroses are rare conditions though ARO is substantially less common than ADO. The incidence of ARO is 1 in 250,000, although a report from Costa Rica reports an

Table 14.8 Subtypes of osteopetrosis as per the 2006 nosology and classification of genetic skeletal disorders [176]

Osteopetrosis type	Inheritance pattern	Gene affected
Severe neonatal or infantile form	AR	*TCIRG1, CLCN7, OSTM1*
Intermediate form	AR	*CLCN7*
With renal tubular acidosis	AR	*CA1*
Late onset form type II, also known as Albers-Schönberg disease	AD	*CLCN7*
With ectodermal dysplasia and immune defect	XL	*IKBKG*
With infantile neuraxonal dysplasia	?AR	unknown

eightfold greater frequency [182]. Meanwhile, ADO has an incidence of 5 in 100,000 births [183]. ARO is the most common osteopetrosis in childhood with diagnoses most commonly made in the first year of life. This form of the disease has a high mortality with only 30 % surviving until 6 years of age [184]. In adults suffering from osteopetrosis life expectancy is normal [185].

Systemic Manifestations

The systemic features of osteopetrosis are primarily a consequence of the increased thickness of bone tissue (Fig. 14.6). Narrowing of foramina through which cranial nerves run can lead to palsies and sensory impairment. For example, hearing loss affects approximately 80 % of patients with ARO [186]. Encroachment of the medullary space interferes with hematopoiesis in the bone marrow and can lead to pancytopenia or hepatosplenomegaly.

In some of the rarer variants of osteopetrosis extraskeletal manifestations are due to the dysfunction of other processes in which certain aspects of osteoclast molecular machinery are involved. Osteopetrosis with renal acidosis results from a mutation in *CAII* which codes for carbonic anhydrase II. Although this protein is fundamental to the production of intracellular protons in osteoclasts it also plays an important role in renal function [187]. Osteopetrosis associated with immune deficiency can also be due to mutations in genes involved in the differentiation of the hematopoietic system as osteoclasts and many white blood cells have a common stem cell precursor [188]. The neurodegenerative aspects seen in neuropathic ARO are thought to come from the dysfunction of the protein CLCN-7 which is responsible for the transport of chloride ions out of osteoclasts and also the acidification of lysosomes in neuronal cells [189, 190].

Although there is a great deal of overlap in systemic features between the subtypes of osteopetroses the timing, severity and constellation of symptoms help to point to a likely diagnosis. Table 14.9 describes the combined systemic features from all subtypes which can be observed in osteopetrosis.

Table 14.9 Non-ocular systemic manifestations of Osteopetroses

System	Feature
Skeletal	Frontal bossing
	Macrocephaly
	Predilection to fractures
	Predilection to osteomyelitis
	Arthritis
	Short stature
	Dental abnormalities
Haematological	Pancytopaenia
	Hypersplenism from extramedullary hematopoiesis
	Myeloid metaplasia
Renal	Renal tubular acidosis
Neurological	Hydrocephalus
	Facial palsy
	Deafness
	Seizures
	Delayed myelinisation
	Cortical and subcortical atrophy
	Mental retardation
Endocrine	Hyperparathyroidism secondary to hypocalcaemia
	Pituitary hypoplasia

Ophthalmic Manifestations

Visual compromise is the most common neurological complication of osteopetrosis. Other manifestations include strabismus, proptosis and limitation of eye movements [190]. Whilst most of these features are simple mechanical consequences of the increased volume of bone material bordering the orbit, the cause of visual loss is less clear despite its frequency. One of the earliest indicators of damage is a change to visual evoked potential latency [191]. Abnormalities of flash electroretinograms are also present less commonly and may help to diagnose visual dysfunction in osteopetrosis [191]. Twenty-three and 42 % of pediatric patients with ARO undergoing hematopoietic stem cell transplant (HSCT) in one study had severe or mild visual impairment respectively [192]. The most common causes of visual loss are direct compression of the optic nerve through optic canal stenosis, increased backflow pressure causing optic nerve edema and primary neuropathy, which unfortunately has no treatment at present. Increased backflow pressure could be due to venous occlusion within the optic canal or in the jugular foramen or by intracranial hypertension from foramen magnum impingement [193]. Identification of these situations can be achieved through measurement of the optic nerve sheath diameter using ultrasound as well as identification of papilledema [194]. Primary neuropathy associated with osteopetrosis has been demonstrated at post-mortem in a patient with a normal fundus examination prior to death and so may be more common than clinically apparent [195]. Lysosomal storage disease is a facet of neuronopathic ARO which is due to *ClCN7* or *OSTM1* genes which leads to retinal dysfunction [189, 196].

Diagnosis

Osteopetrosis is usually diagnosed through radiographic imaging. Typical radiological findings as described by Stark et al. are [177]:

- Diffuse sclerosis of the skull, spine, pelvis and appendicular bones.

- Bone modelling defects at the metaphyses of long bones.
- 'Bone-in-bone' appearance, most marked in the vertebrae and phalanges
- Focal sclerosis of the skull base, pelvis and vertebral end plates.

Identification of the osteopetrosis subtype can be achieved by the constellation of systemic features manifest or genetic testing [176]. Raised concentrations of creatine kinase BB isoenzyme and tartrate resistant acid phosphatase may also be indicative of ADO [197, 198]. Bone biopsy can be used to subdivide ARO into osteoclast poor and osteoclast rich subtypes although this is rarely performed. This subdivision identifies if the pathogenic mutation has resulted in poorly functioning osteoclasts, known as osteoclast rich ARO, or an error in osteoclastogenesis, inferring osteoclast poor ARO.

Management

Medical management for osteopetrosis includes treatment of hypocalcemia with calcium and vitamin D supplementation and also interferon gamma therapy, although impact is minimal with a reduction in severe infections and a slight improvement in bone resorption [199]. It is thought that interferon gamma improves resorption of the organic bone component through the up regulation of superoxide production. This may explain its failure to demonstrate impact in many cases as most osteopetroses are caused by inadequate inorganic bone resorption [200]. Bone marrow failure can also be treated with red blood cell and platelet transfusions.

The main surgical intervention for ARO is HSCT although this is not of benefit for all subtypes. This is not curative, as one study reports a 5 year overall survival of 46 % though this was only 24 % when considering HLA-haplotype mismatch HSCT [192]. Reports of HSCT from HLA-identical siblings describe 5-year overall survival rates of 73–79 % [192, 201]. Another key variable in outcome is age at HSCT with younger recipients demonstrating better preservation of vision [192]. Although visual function can decline despite HSCT there are reports of optic canal stenosis being reversed by the procedure [202]. When optic canal stenosis is known to be the cause of visual impairment deroofing of the orbit has also been shown to improve vision [203]. For visual compromise due to backflow pressure causing papilledema acetazolamide and optic nerve sheath fenestration have been shown to improve vision [194, 204].

As with sclerostesosis occlusion of the nasolacrimal foramen is a known ophthalmic complication of osteopetrosis. Dacrocystorhinoplasty can provide a solution but the surgeon must anticipate the challenges of working with ultradense bone [205].

Fibrous Dysplasia

Definition

Fibrous dysplasia (FD) is a condition which is characterised by scar-like fibrous tissue replacing normal bone [206]. This can result in pain, swelling of bones and subsequent disfigurement due to the fibroblastic expansion. Patients are prone to fractures due to their weakened bone. The condition most commonly affects a single bone (monostotic) such as the cranium or long bones of the arm or leg. Monostotic FD patients typically present in early adolescence [207]. If the condition affects multiple bones (polyostotic) there is an association with McCune-Albright syndrome (MAS) which can result in cutaneous pigmentation and endocrine dysfunction. Polyostotic FD patients become symptomatic before 10 years old with malignant transformation rarely occurring.

FD is thought to occur when primitive bone fails to remodel into mature lamella bone [208]. This lack of maturation results in immature trabeculae within dysplastic fibrous tissue as well as an immature, poorly mineralised matrix. Patients' bones are therefore fragile as a result of the lack of stress alignment and reduced mineralisation.

History

FD was initially described in 1891 by Von Recklinghausen, but the term Fibrous Dysplasia was first used by Litchtenstein in 1938 [209]. In 1937 McCune, Bruch and Albright described a condition of osteodystrophia fibrosa disseminata[210]. Patients had associated endocrinopathies, cutaneous hyperpigmentation, and precocious puberty in females. This condition was labelled as MAS.

Epidemiology

FD is thought to make up approximately 5 % of benign bone lesions and 1 % of primary bone tumours [208]. The true incidence is challenging to monitor especially in the monostotic form as many patients are asymptomatic and are commonly only diagnosed after radiographic investigation which may be unrelated. Onset is most commonly in late childhood or early adolescence with studies reporting an average age of 22 years [208]. The polyostotic form is known to present in patient younger than 10 years old. Monostotic FD is thought to be the most common form occurring four times more frequently than polyostotic [211]. It is however difficult to confirm this as many studies have not fully evaluated the extent of patient disease. The prevalence of monostotic and polyostotic FD between genders is thought to be equal however MAS is known to have a marked female predominance.

FD can affect any bone however the most common sights are as follows in order of frequency

- Femur
- Tibia
- Skull and facial bones
- Pelvis
- Ribs
- Upper extremities
- Lumbar spine
- Clavicle
- Cervical spine

FD is typically unilateral however it can occur bilaterally. The most commonly involved bones in polyostotic FD are the craniofacial bones, ribs and the femur, with the associated skin pigmentation changes on the same side [212]. Craniofacial involvement is far more frequent in polyostotic FD in comparison to monostotic. When only the cranial facial bones are involved the condition has been termed craniofacial fibrous dysplasia.

Systemic Manifestations

FD signs and symptoms vary depending on the location of the involved bone and the type. If the disorder involves the facial bones, then patients often have visible deformities. Twenty percent of patients will display craniofacial involvement and most orbital lesions tend to be monostotic, with multiple skulls bones involved. Patients with orbital involvement may present to an ophthalmologist with visual symptoms, facial deformity or globe displacement. Patients with FD may also present with fractures, deformity of other bones, nasal congestion, hearing impairment, pain and paraesthesia [213]. FD lesions typically enlarge in proportion to skeletal growth which can result in significant early deformity in patients with polyostotic disease in comparison to monostotic. Polyostotic lesions may increase in size even after skeletal maturation increasing the risk of pathological fracture [214].

Patients with the triad of polyostotic FD, unilateral café au lait spots and endocrine abnormalities, often resulting in precocious puberty, must be investigated for MAS. Skeletal lesions in MAS tend to be larger and have an increased rate of complications. Café au lait spots are most commonly found on the trunk, or the proximal limbs and extremities. The spots tend to be bigger than those seen in neurofibromatosis type 1 and have sharper and straighter edges. Endocrine abnormalities are due to an increase in production of hormones which are produced by glands regulated by G proteins [215]. The glands are over stimulated resulting in autonomous production of multiple hormones including estrogens, growth hormone, cortisol and thyroid hormones. Patients may present with Cushing syndrome, hyperthyroidism, precocious puberty, premature menarche and excessive growth. Female patients are also prone to the formation of ovarian cysts [216].

The most frequent initial symptom in FD is pain of the involved area which can be associated with fractures or weakness. High stress areas are most commonly affected, such as the femoral neck. Females may experience fluctuating levels of pain with their menstrual cycle. Pregnancy can also result in an increase in the level of pain.

Approximately 70 % of patients with leg involvement have a discrepancy in leg length caused by structural insufficiency and subsequent bowing [208]. The risk is increased in patients with diffuse polyostotic lesions especially in large long bones. In polyostotic disease the classic deformity is labelled as a "shepherd's crook" due to curvature of the femoral neck and proximal shaft resulting in coxa vara deformity [217]. Patient with FD also have an increased rate of scoliosis which is reported in approximately 40 % of polyostotic patients [218].

FD has also been linked to an increased incidence of sarcoma which occurs within the abnormal bone [208]. Benign intramuscular myxoma has been reported with polyostotic patients [219].

Ophthalmic Manifestations

The most common neurological complication of FD involving the skull is visual impairment [206]. Patients may also present to an ophthalmologist with facial asymmetry and axial or non-axial displacement of the globe. Both monocular and binocular visual impairment can occur [220]. A case of acute monocular blindness due to optic canal narrowing has been described [221]. This was managed with surgical orbital decompression and steroids which restored vision. A case of optic nerve compressive due to a sphenoidal mucocele associated with FD was also described. Katz et al. described multiple cases of FD associated visual loss. These included visual symptoms due to compression of the optic nerve because of an ethmoidal mucocele, hemorrhage into a dysplastic bone and an aneurysmal bone cyst [206]. Aneurysmal bone cysts are composed of multiple vascular channels which lack endothelium separated by fibrous stroma containing giant cells, macrophages and histocytes.

Studies have shown that intervention, either surgical with orbital decompression or medically with intravenous steroids can help preserve sight in patients with FD associated visual impairment [221]. These studies also highlight that resection of FD bone carries a risk of iatrogenic visual loss, especially when the optic canal is involved. Patients with orbital involvement require serial CT imaging and assessment of optic nerve function to monitor for optic canal disease. There has been no direct study into whether prophylactic orbital decompression offers a more favourable

visual outcome. MRI scans may also be beneficial when considering soft tissue pathology and lesions such as a mucocele or anyeursmal bone cyst. The majority of patients with dysplasia involving the orbit will have monostotic FD which can cross suture lines and involves multiple cranial bones (still classified as monostotic as the skull is regarded as a single entity). FD of the orbital bones is regarded as a disease of childhood however it is important to consider that bony changes may continue to occur in adulthood and therefore the diagnosis should not be excluded based on a patient's age.

Zhao et al. studied the importance of OCT when examining the optic nerve head in patients with Fibrous Dysplasia [222]. They found that optic canal stenosis resulted in a rising pressure at the level of the lamina cribrosa which was thought to result in ganglion cell dysfunction and a reduction in blood circulation which could induce visual impairment. After surgical decompression the study found that lamina cribrosa pressure reduced, resulting in improved visual function. There is a lack of further evidence surrounding OCT but as a readily available imagining modality, it may well be beneficial to monitor fibrous dysplasia patients with optic nerve head OCTs before and after management.

Diagnosis

Clinical examination should be supported with appropriate diagnostic tests. These may include initial plain X-rays of the affected area. The characteristic findings include a mottled appearance with sclerosis and a homogenous loss of the normal trabecular pattern resulting in what is often described as a "ground glass" appearance [223]. CT scans can have a variable appearance based on the ratio of bone to fibrous tissue within the lesion. As the disease process progresses, further dysplasia occurs and a heterogeneous Pagetoid pattern of radiolucent and radiopaque areas are visible. Feller et al. describes FD as having smooth cortical margins and no soft tissue involvement [224].

For a more definitive diagnosis bone biopsies can be acquired but is usually not needed. Gross examination typically reveal firm gritty pink or white material. Histologically, FD bone has dense fibrous stroma which may contain aneurysmal bone cysts and myxomatous areas. It also has a low cellularity and the stroma is surrounded by irregular shaped bony trabeculae [208]. FD bone can be distinguished from malignant conditions by the fact that no osteoblastic rimming of the trabeculae is seen.

Although isolated FD is not heritable, MAS is due to somatic mosaicism for mutations in the *GNAS1* gene which encodes for the alpha subunit of the stimulatory G protein coupled receptor [225]. All cells that derive from the mutated cells have dysplastic features. It has been postulated that more severe forms of FD occur with an earlier mutational event resulting in an increased amount or a wider spread of mutant cells [226]. This genetic mutation can be identified by taking a patient's blood sample and utilising amplification techniques such as polymerase chain reaction.

During active growth of FD lesions, blood results may show a raised alkaline phosphatase [227]. Urine analysis may also reveal raised levels of hydroxyproline, although it is important to remember that both tests may be raised in periods of normal growth and other conditions with high bone turn over.

Management

There is no cure for FD and it is a chronic disorder. The condition is often progressive, but lesions can stabilize with time. FD lesions which are asymptomatic tend not to progress and should simply be monitored.

Throughout the years FD non-surgical management has included the use of steroids, calcitonin and external beam radiation [228]. These treatments were found to be ineffective and increased the risk of malignancy. Only bisphosphonates have been proven to be beneficial in FD. They work by inhibiting osteoclasts and therefore reducing bone loss [229]. This is thought to be beneficial in FD as expansion of a lesion is thought to be driven by osteoclastic reabsorption. The other theory is that there is a high turnover rate of bone and limiting osteoclastic function would therefore slow this process down reducing the progression of FD. Studies have shown that high dose intravenous bisphosphonates can result in reduced pain and decreased markers of bone metabolism [214]. The most commonly used treatment has been intravenous pamidronate. Other oral and intravenous bisphosphonates have also been shown to be effective. A treatment regime utilised by Plotkins et al. was 1–1.5 mg/kg/day on three consecutive days given every 4 months [230]. This study was beneficial in showing that children who were treated did not suffer from reduced growth however the radiological appearance of their FD did not improve. When using bisphosphonates it is important to utilise the minimum dose necessary to relieve pain, as there have been reported cases of associated osteonecrosis.

If fractures occur surgical management may be necessary, but there is no evidence for prophylactic surgery to prevent a fracture. Symptoms such as increased pain or deformity may indicate a risk of fracture. Surgical procedures depend on the bones involved however intramedullary rods have been shown to protect from fracture [231]. FD patients also suffer with scoliosis [232]. Braces and fixation surgery may be needed. Shepherd's crook deformity of the proximal femur often requires surgery to restore the mechanical axis. Medial displacement valgus osteotomy has been recommended [233].

It is important to consider the presence of endocrine dysfunction before surgical intervention. Hyperparathyroidism

especially can result in fragile bones due to the increased osteoclast activity.

Patients with FD are at risk of malignancy at a rate of approximately 0.5–1 %, which is further increased in polyostotic patients with MAS [234]. Transformation is thought to occur more often in FD lesions involving the craniofacial bones and femur. The most frequently occurring malignancy is osteosarcoma followed by fibrous sarcoma, chondrosarcoma and malignant fibrous histiocytoma [235]. The average time from diagnosis to malignancy is thought to be around 13.5 years. Signs of malignant transformation include rapid growth in lesion size or increase in pain, necrosis of the lesion or bleeding and raised alkaline phosphate levels [236].

Jeune Syndrome

Definition

Also known as Jeune asphyxiating thoracic dystrophy (JATD) and thoracic-pelvic-phalangeal dystrophy, this condition is one of a subset of the skeletal ciliopathies (Table 14.10), and is characterised by shortened limbs and a reduced thoracic capacity [237–239]. The reduction in thoracic volume, derived from shortened ribs and a bell-shaped chest, commonly lead to asphyxiation and perinatal mortality. It is an autosomal recessive condition with heterogeneous genetic origins, the most common being mutation of *DYNC2H1,* though mutation of genes responsible for the transport of molecules along cilia; known as intra-flagellar transport (IFT), can also be causative [240]. Which of these IFT genes is affected relates to the observed phenotype: for example, mutations of *IFT140* are associated with a predominance of retinal manifestations [241, 242]. The extra skeletal manifestations of JATD include pathology of the kidney, liver and eye [243, 244].

History

The syndrome was first described in 1955 in twins with narrow thoraces by the French pediatrician, Mathis Jeune [245]. Along with other seemingly unrelated syndromes, JATD was subsequently attributed to the relatively newly discovered family of diseases termed ciliopathies, which are characterised by dysfunction of the primary cilia [246].

Table 14.10 Skeletal ciliopathies with clinical features and known causative mutations [238, 244]

Skeletal ciliopathy	Clinical features	Known causative genes
Jeune asphyxiating thoracic dystrophy	Postaxial polydactyly, short limbs, short and slender ribs, small ilia, irregular acetabulum and cystic kidney	*IFT80, IFT140, IFT172, CSPP1, CEP120, DYNC2H1, TTC21B, WDR19, WDR60, WDR34,*
Ellis-Van Creveld syndrome	Polydactyly, short ribs, dysplastic fingernails/teeth and cardiac defects	*EVC1, EVC2*
Wyers acrofacial dystosis	Post-axial polydactyly, anomalies of the lower jaw dentition and oral vestibule, prominent ear antihelices, hypoplastic and dysplastic nails, and mild shortness of stature with short limbs	*EVC2*
Sensenbrenner syndrome	Sagittal craniosynostosis, short limbs, narrow thorax, brachydactyly, protuberant abdomen, and facial and ectodermal anomalies	*WDR19, IFT122, WDR35, IFT43*
Short Rib-Polydactyly (SRP) type I or Saldino-Noonan Syndrome	Lethal	Unknown
	Shortened flipper-like limbs, metaphyseal dysplasia of long bones, post-axial polydactyly, defective ossification of calvaria, vertebrae, pelvis and hand and foot bones post-axial polydactyly and defective, pelvis, and bones of the hands and feet	
SRP type II or Makewski syndrome	Lethal	*DYNC2H1, NEK1*
	Short and narrow thorax, with horizontally oriented ribs, short tubular bones with smooth ends, pre- and post-axial polysyndactyly, tibial agenesis, or ovoid tibiae shorter than fibulae, cleft lip and/or palate, malformed epiglottis and larynx, renal cysts, and genital, cardiac and intestinal abnormalities	
SRP type III or Verma-Naumoff syndrome	Lethal	*IFT80, DYNC2H1*
	Extreme narrowness of the thorax, severely shortened tubular bones with round metaphyseal ends and lateral spikes (Fig. 14.3), cleft lip/palate and multiple anomalies of major organs including heart, intestine, genitalia, kidney, liver, and pancreas	
SRP type IV or Beemer-Langer syndrome	Lethal	Unknown
	Short and narrow thorax with horizontally oriented ribs and small iliac bones, short tubular bones with smooth metaphyseal margins, bowed radii and ulna, tibiae relatively well tubulated and longer than fibulae, and rarely post-axial polydactyly	
SRP type V	Acromesomelic hypomineralization, campomelia, polysyndactyly, laterality defects and cystic kidneys	*WDR35*

Epidemiology

This condition affects 1 in 100,000–130,000 live births [237]. It is often fatal in the perinatal period with mortality reported between 40 and 80 % [241, 247].

Systemic Manifestations

The systemic nature of ciliopathies such as JATD is derived from the near universal presence of primary cilia, which are non-motile, in cells membranes [246]. These primary cilia, also known as sensory cilia, also exhibit great evolutionary preservation having developed from early multicellular organisms [246]. As these cilia are separated from the cytoplasm of the cell's body the molecules required to facilitate their various signalling functions are brought into and out of the cilia by IFT, a process which depends in part on genes found to be mutated in JATD [246]. Knockout of genes involved in IFT in mouse models has impaired signalling in the hedgehog pathway which in turn impairs the development of bone and cartilage tissue presumably leading to the skeletal phenotypes we observe in humans [248–250]. The observed renal pathology is of unknown etiology but there is work to suggest it also has its origins in dysfunctional hedgehog signalling [251].

The reported extra-ocular manifestations of JATD are listed below (Table 14.11) but particular attention should be paid to the respiratory and renal features which are almost exclusively responsible for mortality under 2 years of age and between the ages of 3 and 10 years old respectively [237].

Table 14.11 Non-ocular systemic manifestations of JATD

System	Feature
Skeletal	Short, horizontal ribs
	Bell-shaped chest
	Polydactyly
	Brachydactyly/Micromelia
	Acetabular bone spurs
	Cone-shaped epiphyses
	Atlanto-axial instability
Respiratory	Restrictive lung disease
	Subglotic stenosis
	Pneumonia susceptibility
Renal	Progressive cystic nephropathy
	Hypertension
	Renal failure
Gastro-intestinal	Neonatal jaundice
	Polycystic liver disease
	Hepatic cirrhosis
	Pancreatic cysts
Central Nervous System	Spinal cord stenosis
	Corpus callosum agenesis
	Hydrocephalus

Table 14.12 Clinical and diagnostic criteria for JATD employed by Keppler et al. [237]

Clinical findings	Narrow chest
	Variable short stature
	Limb shortening
	Brachydactyly
	Polydactyly
Radiological findings	Short ribs with bulbous anterior ends
	Clavicles with horizontal/handlebar configuration
	'Trident' pelvis
	Shortening of extra axial bones
	Cone shaped epiphyses
	Normal vertebrae

Ophthalmic Manifestations

Ocular manifestations are only reported in approximately 15 % of JATD cases in the bulk of the literature but more recent studies which have involved systematic eye surveys have reported involvement in up to 50 % of patients 5 years or older [237, 247]. This suggests that the retinal pathology associated with this syndrome is a key consideration for patients who survive the early respiratory mortality.

When considering the retinal dystrophy often observed in JATD mechanistically it is crucial to appreciate that the outer segment of a photoreceptor is a modified cilium [252, 253]. As such it is likely that the aberrant IFT proteins observed in JATD are detrimental to the function of the photoreceptors. In a zebrafish model loss of function of *ift80*, one of the homologous genes implicated in JATD, leads to opsin mislocalisation [254]. However, a similar experiment in mice produced normal retinas, although the work suggested retinal dystrophy developed over time [249].

At present there are not available treatment options for the decline in retinal function. Screening for photoreceptor dysfunction with electroretinogram every 2 years is suggested [247].

Diagnosis

Diagnosis of JATD is made upon the basis of clinical, DNA and radiological findings (Table 14.12). Due to the overlap with other skeletal ciliopathies, other diagnoses such as short rib polydactyly syndromes 1–4 or Ellis-van Creveld syndrome should be considered in the presence of congenital heart defects, oral facial defects and ectodermal, dental or nail defects [237]. Antenatal ultrasound diagnosis of JATD has also been described [255, 256].

Management

Management should include consideration from hepatology, orthopedic, respiratory, renal, genetics, psychology and ophthalmology specialists. Regular screening with physical examination, blood tests for renal and liver function, anthropometric measurements, blood pressure, spirometry, abdominal ultrasound and electroretinogram are recommended [247, 257]. The main goal of surgical intervention is to increase the thoracic circumference, either through augmenting the ribs or sternum. This can either be done with bone grafts or with a variety of implants which are either fixed or dynamic, allowing the distance between sternal or rib margins to be increased over time. Improvement in lung function tests and on thorax CT scan show improvement with these techniques in the short term and long term data is awaited [258].

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Ocular Manifestations of Neurologic Diseases

15

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Introduction

The intersection between pediatric neurologic disease and the eye is vast, with nearly all neurologic diseases having an eye manifestation of some kind. Most involve the optic nerve, but many involve eye movements, and others involve other parts of the eye, such as the retina and even the lens. While we know we have not been comprehensive, we attempted to highlight pediatric neurologic diseases that are either common, have common or unique ophthalmic manifestations, or have management concerns involving the eye. We attempted to omit diseases covered elsewhere in this book.

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Epilepsy

Definition

The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy define an epileptic seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition [1].

History

The oldest known description of an epileptic seizure comes from around 2000 B.C. in Mesopotamia [2]. Subsequently, many cultures' texts have described epileptic seizures, and most attributed the seizures to possession of evil spirits or otherwise as "a spiritual condition" of some kind. In the fifth century B.C., Hippocrates published a paper called "The Sacred Disease" in which he rejects the idea that seizures were caused by spirits and rather, by an underlying medical condition [2]. He called the disorder the "great disease" instead, and this gave rise to the term, "grand mal" which was used in the past to describe a convulsive seizure. His ideas however, were not widely accepted until several centuries later.

In the mid-1800s, bromide, the first effective anti-seizure medication, was introduced. However, phenobarbital and phenytoin were the first modern anti-epileptic drugs (AEDs), developed in 1912 and 1938, respectively. Carbamazepine was approved for use in the UK in 1965 and in the US since 1974 [3]. Since then, several other AEDs have been introduced.

Epidemiology

The Centers for Disease Control (CDC) analyzed data from the 2010 National Health Interview Survey (NHIS) to estimate epilepsy prevalence among adults and found that approximately 1.8 % adults had been told they had epilepsy [4]. In a population based study in Olmsted County,

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Minnesota, the incidence of new onset epilepsy in children was reported as 44.5 per 100,000 per year [5]. In another study using data from the 2007 National Survey of Children's health, in which households of 91,640 children under the age of 18 were surveyed, the prevalence of ever having a childhood epilepsy diagnosis was found to be 1.03 % [6]

Systemic Manifestations

Generalized seizures involve altered states of consciousness, and there are six main types: tonic-clonic, tonic, clonic, myoclonic, atonic, and absence. Simple focal (partial) seizures do not, by definition, involve altered states of consciousness, however, complex partial seizures do.

Tonic-clonic seizures are convulsive seizures that were formerly known as the classic "grand mal" seizures. Typically they present with involuntary muscle contraction (tonic phase), followed by involuntary shaking of the extremities (clonic phase). It is not uncommon during convulsive seizures for a patient to defecate, urinate, or bite their tongue or otherwise cause injury to themselves unwittingly. After the clonic phase, a post-ictal state of confusion is often present (typically 10–30 min, but variable) before the patient's mental state returns to baseline. Tonic seizures only involve a tonic phase, and clonic seizures only involve a clonic phase. Atonic seizures involve sudden loss of (usually all) muscle tone. Absence seizures are the most subtle, and involve staring with or without eye blinking.

Ophthalmic Manifestations

As in absence seizures, sometimes eye blinking is the only eye manifestation of seizure activity. However, during epileptic activity from a focal seizure, the eyes classically deviate to one side and a horizontal jerk nystagmus is often present. If the seizure manifests from the supplementary motor area, a versive head turn could occur. Other various abnormal eye movements have been described as well [7–9]. The abnormal eye movements stop when the seizure activity resolves.

Diagnosis

The diagnosis can be made clinically. An electroencephalogram (EEG) is also done to better obtain important diagnostic information. Neuroimaging is also often a part of the work up, to rule out structural or metabolic abnormalities.

Management

The mainstays of treatment are antiepileptic drugs (AEDs), but these are reserved for patients who have had more than one unprovoked, non-febrile seizure. The choice of anticonvulsant is based on seizure type, epilepsy syndrome, other medications used, other health problems, and the person's age and lifestyle. Other treatments are attempted with varying degrees of success when AEDs fail to control the epileptic events, and these include epilepsy surgery, the ketogenic diet, and vagal nerve stimulator placement.

These medications can have various visual and oculomotor consequences. The eye is highly susceptible to drugs that penetrate the central nervous system due to its rich blood supply and relatively smaller mass. Tissues with high metabolic rates, such as the retina and the optic nerve, are particularly vulnerable [10]. Neurologists and ophthalmologists must be aware of potential ocular toxicity of these drugs, and appropriately monitor for potential adverse events (see Table 15.1).

Disturbances of all functional classes of eye movements—saccades, smooth pursuit, vestibulo-ocular reflex, fixation, vergence and gaze-holding mechanisms—occur with many AEDs and other drugs that act on the central nervous system [10]. The mechanism of the oculomotor disturbances may be due to a pharmacologically induced transient dysfunction of the vestibulo-cerebellar flocculus loop [11].

The most common ocular movement disorder seen with phenytoin or carbamazepine is gaze-evoked nystagmus [12–15], and rarely others are seen such as downbeat nystagmus [16–18], periodic alternating nystagmus [19], pendular nystagmus [20], opsoclonus, or partial or total gaze palsy [21, 22].

Table 15.1 Antiepileptic medications with common ophthalmic side effects and their treatments

Medication	Ophthalmic side effects	Management
Phenytoin	Oculomotor dysfunction (nystagmus, opsoclonus, gaze palsy)	Reduce dose
Carbamazepine	Oculomotor dysfunction	Reduce dose
Steroids: Adrenocorticotropic hormone (ACTH) and decadron	A. Cataracts	A. May require surgical extraction
	B. Elevated intraocular pressure/steroid response glaucoma	B. Topical IOP lowering medications, systemic IOP lowering medications, cessation of steroids, may require IOP lowering surgery
Topiramate	Rare ciliochoroidal effusion: angle closure glaucoma or myopic shift	Stop topiramate, topical IOP lowering medications (NO carbonic anhydrase inhibitors), cycloplegia, IV hyperosmotic medications, IV steroids, NO peripheral iridotomy or miotics
Vigabatrin	Visual field loss >30 %	Monitor vision every 3 months, periodic visual field or ERG, consider stopping if ERG or visual acuity reduced

Other AEDs are not exempt from causing oculomotor dysfunction. Lamotrigine has been described as causing oculogyric crises with toxic doses [23], downbeat nystagmus [24], and other forms of nystagmus in various case reports in the literature. Topiramate has also been described to cause diplopia, nystagmus, and visual field defects only very rarely; its most well-known complications are that of acute closed angle glaucoma and myopic shift, both of which are secondary to ciliochoroidal effusion syndrome [25, 26].

The oculomotor side effects of AEDs occur more often at toxic doses, but can also be seen at therapeutic doses. There have been some studies on specific genetic polymorphisms that increase the plasma concentration of some of these drugs, increasing the risk of toxicity at otherwise therapeutic doses (such as CYP2C9 and CYP2C19 for phenytoin) [27].

In addition to those described in the table a newer AED, Ezogabine (Potiga), which is a potassium channel enhancer that was approved in 2010 for the treatment of partial-onset seizures, has been associated with the development of retinal pigment changes. The clinical significance and duration of these findings has yet to be determined [28, 29].

Infantile Spasms

Definition

Infantile spasms [30] are types of early childhood seizures characterized by clusters of flexor or extensor epileptic spasms, along with characteristic EEG changes, and progressive neurological development deterioration [31, 32].

History

The first description of epileptic encephalopathy dates back to Dr. William James West who, in 1857, described the syndrome [32], initially in his own son. The term 'West Syndrome' has been used to indicate infantile spasms, hypsarrhythmia, and cognitive impairment.

Epidemiology

The incidence is 0.25–0.4:1000 live births [31]. When not idiopathic/cryptogenic (which is approximately 25% of cases,) the causes are often similar to the causes of cortical visual impairment, and include hypoxic ischemic encephalopathy, cortical immaturity, congenital abnormalities of the brain or occipital cortex, or neurometabolic and genetic diseases such as Aicardi's and tuberous sclerosis [33]. When one of these causes is identified, the disease is termed "symptomatic" as opposed to idiopathic or cryptogenic [34].

Systemic Manifestations

The first symptoms of infantile spasms are usually manifest during the first year of life, age 6–9 months, paralleling a critical period required for proper maturity of visual pathway, including both retina and the visual cortex [35]. The child develops infantile spasms and then progressive deterioration of cognition, and disruption of cortical bioelectrical activity. With this disruption of cortical activity comes cortical impairment and associated vision loss.

Ophthalmic Manifestations

A maturation defect of fixation shift skills is generally observed in infants with infantile spasms, often paralleling a cognitive deterioration, several weeks before the onset of spasms [36]. This decrease in visual attention is separate from the cortical vision loss described in the systemic manifestations section, which these patients can also experience [33].

Diagnosis

Clinically, one suspects infantile spasms by parental history or observation of the event. Hypsarrhythmia is seen between seizures, and is characterized by a high voltage (>300 μV), disorganized electrocerebral background with multifocal spikes [37]. The spasms also have a characteristic EEG appearance.

Workup for a metabolic or genetic cause is indicated in cases that do not have other identifiable abnormalities on imaging. A large number of inborn errors of metabolism have been identified in the setting of infantile spasms. These include, but are not limited to, biotinidase deficiency, pyridoxine deficiency, mitochondrial disorders, Menkes Disease, congenital disorder of glycosylation type III, phenylketonuria, peroxisomal disorders, and lysosomal disorders [37]. Defects in a variety of genes have likewise been reported.

Management

As with other seizure disorders, AEDs are the mainstays of treatment. See the special section on Vigabatrin below, as ACTH or vigabatrin are first line for infantile spasms. The ketogenic diet has also been used.

Vigabatrin-Related Visual Field Loss

Definition

Vigabatrin is a gamma-aminobutyric acid (GABA) analog that inhibits GABA transaminase. It has been approved for use in the US as an antiepileptic drug (AED) since 2009 [38], and is typically used as adjunctive therapy for adult patients with refractory complex partial seizures, or as monotherapy for infants with infantile spasms, especially in those patients with tuberous sclerosis [39]. Unfortunately, an irreversible, bilateral constriction of the visual fields from retinal toxicity can occur with vigabatrin use.

History

This adverse reaction to the drug was first reported in 1997, and since then many other studies have illustrated similar visual field loss with reproducibility [40].

Epidemiology

Visual field loss has been found in approximately one half of adults and one third of children treated with vigabatrin [39].

Systemic Manifestations

Vigabatrin can cause fatigue. There have been some associated MRI changes of unknown significance, as well.

Ophthalmic Manifestations

The onset of visual field loss tends to occur in the first few years after starting vigabatrin [39]. Initially believed to remain stable in early studies, the deficits seem to slowly progress with continued vigabatrin exposure, as demonstrated in a 10-year follow-up study [41]. The deficits are typically not self-recognized early on because they relatively spare the macula, but there is electrophysiological evidence of decreased macular function. Visual field loss is probably correlated with cumulative dose, but individual variation is not uncommon [42].

The mechanism for the retinal toxicity associated with vigabatrin-induced visual field loss is uncertain. However, there is some evidence that vigabatrin induces a taurine deficiency in retinal photoreceptors that leads to phototoxicity [43]. These patients also can show associated thinning of the retinal nerve fiber layer (RNFL) [44–46]. The risk to the developing retina from vigabatrin exposure *in utero* is unknown [10].

Diagnosis

The Food and Drug Administration has recommended eye examinations and visual field tests every 3 months because automated static perimetry is the most sensitive test for the detection of early visual field changes. In children who require vigabatrin, however, this can be quite difficult, as perimetry requires active cooperation of the patient, and typically successful perimetry requires a developmental age >9 years [47]. Kinetic perimetry may be considered over automated static perimetry, as the latter may produce variable results in patients with epilepsy[47]. Perimetry is excellent for diagnosis and detection of visual field loss in the cooperative, older patient, but they are imprecise and insensitive in younger children and children with neurological impairment. Inconclusive tests are frequent, reproducibility is poor, and many patients are untestable, which is part of the reason that prevalence of visual field loss in children seems to vary considerably from one study to another [48].

A number of alternative objective tests have been proposed to this end, including serial electroretinograms (ERGs), optical coherence tomography (OCT), visual-evoked potentials, and serial fundus examinations [49]. OCTs may demonstrate thinning of the RNFL and are suggested as alternative for young patients who cannot perform perimetry but this test also has practical difficulties in children [42, 46]. ERGs can be very difficult to interpret in these patients and all of these tests may be of minimal value, if any, in the detection of early field changes [50]. As it stands, there is currently no simple, effective method to screen for vigabatrin-associated visual field deficits in many younger or neurologically impaired children.

Management

Regular, age-appropriate vision testing is considered critical, starting with baseline testing and every 3 months during therapy, as well as 3–6 months after discontinuation [42]. Also the ongoing need for treatment with vigabatrin should be periodically reconsidered [47], and the lowest effective dose of the drug should always be used.

Headaches

Migraine (Ophthalmoplegic)

Definition

Ophthalmoplegic migraine, or recurrent painful ophthalmoplegic neuropathy, is characterized by at least 2 attacks of headache and ipsilateral neuropathy, of either the 3rd, 4th, or the 6th cranial nerves, or a combination thereof. It is a diagnosis of exclusion and an orbital or intracranial lesion must be excluded [51].

Epidemiology

In a review of all cases published in the English literature, the median age of those affected is 8 years old. Two-thirds of all cases occurred in females. The third cranial nerve was most often affected, followed by the 6th cranial nerve and then the 4th cranial nerve [52].

History

The term "ophthalmoplegic migraine" was first coined by Charcot in 1890 [53]. Prior to 1890, however, other physicians reported cases that resemble ophthalmic migraines [54].

Systemic Manifestations

The headache can occur up to 2 weeks prior to cranial nerve paresis. The pain associated is not as much a migraine as a painful neuropathy. The majority of patients present with peri or retro-orbital pain. Some can also present with photophobia, nausea, or vomiting.

Ophthalmic Manifestations

In addition to the strabismus and potential diplopia associated with the various possible cranial nerve palsies, other eye findings can include mydriasis and ptosis.

Diagnosis

On MRI imaging with gadolinium, there is often nerve enhancement or thickening [55]. One review of ophthalmoplegic migraine cases published in the literature found that vascular imaging was obtained in half of the reported cases and vascular abnormalities of unclear significance were noted in only 3 patients [52], which was a small minority.

Management

Anti-inflammatory and other typical migraine medications can be used. Treatment with corticosteroids is beneficial in some patients.

Concussion

Definition

Concussion is a result of head trauma that causes transient disruption of brain function through concussive forces leading to neurologic symptoms [56].

Epidemiology

Estimates show that nearly 150,000 children and adolescents are seen in emergency departments for concussion each year [57].

History

Many physicians in history have written about and described what is now known as concussion. The corpus Hippocraticum, dating back to the fourth and fifth century, BC, contains references to cerebral concussions, which were translated as *commotio cerebri*—"caused by a blow, the victim loses his speech and cannot see or hear [58]."

Systemic Manifestations

Higher function problems include difficulties with attention, memory, and concentration. One study showed that headache, fatigue, and dizziness were most common at initial presentation and sleep disturbance, frustration, and forgetfulness developed after the initial injury.

Ophthalmic Manifestations

Ocular symptoms may include diplopia, blurred vision, transient loss of vision and visual processing problems. One may see abnormalities in saccade generation, pursuit, convergence, and accommodation [56]. All of these can cause difficulty with reading. Ocular symptoms resolved faster than the other symptoms listed, which can last anywhere from 2 weeks to more than 3 months [59]. More permanent injuries would include 4th nerve palsy or traumatic optic neuritis.

Diagnosis

The diagnosis of a concussion is based on the history of recently having an injury to the head or neck with any resultant neurologic symptoms. Sideline assessment tools such as the Post-Concussion Symptom Scale (PCSS) and Graded Symptom Checklist (GSC) can be useful for trainers and coaches at sporting events. These tests are not used to rule out concussion, however. The child should be taken out of the game and if there are any persistent symptoms, medical care should be sought immediately to check for any abnormal neurologic signs. CT should not be used to diagnose concussion but should be used to evaluate hemorrhage or fractures if there is clinical suspicion [60]. If there are focal neurologic signs, imaging with an MRI should be done emergently, along with consultation with Neurology.

Management

Treatment is symptomatic for the patient's specific manifestations, which can include headaches, visual disturbances, nausea, sleep difficulties, and mood lability. Though most symptoms improve with time, repeated concussions can cause more severe symptoms that take longer to resolve. The effects are often cumulative, with frontal and temporal lobe damage as shown on histopathology [56]. Athletes should not return to play until they have been cleared by their physician. A step-wise approach with monitoring for any recurrence of symptoms is best.

Elevated Intracranial Pressure (Including Idiopathic)

Definition

Papilledema is the swelling of the optic disc as a consequence of increased intracranial pressure. Initially, there is interstitial edema in the optic nerve. This is followed by axoplasmic stasis and neuronal dysfunction that lead to vision loss [61].

Idiopathic intracranial hypertension can occur in children and adults and is defined as elevated intracranial pressure that is not explained by another cause.

History

Sir John Herbert Parsons, a British Ophthalmologist, first coined the term "papilledema" in 1908 to refer to optic disc swelling associated with increased intracranial pressure [62].

Heinrich Quincke reported the first recorded cases of intracranial hypertension of unknown cause in what he described as "meningitis serosa" in 1893 [63]. The term "pseudotumor cerebri" was coined in 1904 by Max Nonne [64].

Epidemiology

Idiopathic intracranial hypertension is most common among obese women between 20 and 40 years of age, but it can occur in all age groups and genders. It is reported to occur in 1 in 100,000 individuals [65]. In the pediatric population, studies have shown that there is no gender predilection prior to puberty, there is less of an association with obesity than in adults, and more frequently, secondary causes exist [66, 67].

Systemic Manifestations

Headache is the most common symptom [68]. Other symptoms can include pulsatile tinnitus, or vomiting. Patients may experience headaches that are worse in the morning, while laying down, after exertion or vagal maneuvers, or those that wake them up from sleep.

Ophthalmic Manifestations

Patients can experience transient visual obscurations, blurred vision, and decreased color vision. Optic atrophy can also occur from severe or long-term papilledema. Cranial nerve 6 may be affected secondary to mass effect from elevated intracranial pressure, causing esotropia and diplopia [69].

Diagnosis

The differential diagnosis of optic nerve head swelling with elevated intracranial pressure includes hydrocephalus from congenital hydrocephalus, brain tumor, meningitis, craniosynostosis, idiopathic intracranial hypertension, and leukemic infiltrate. Key findings on physical exam include a bulging fontanelle in an infant or abnormal head shape suggestive of craniosynostosis. Optic disc swelling that mimics papilledema but is not due to elevated intracranial pressure may be caused by inflammatory, vascular, or autoimmune etiologies, or may be pseudopapilledema, which can be from optic nerve drusen.

On clinical exam, initially vision, color vision, and pupils can be normal, but these will become abnormal if the papilledema is severe or chronic. Acute papilledema will present with obscuration of the optic disc border, elevation of the entire optic nerve, obliteration of the optic nerve cup, with or without retinal hemorrhages. In severe cases, there can be nerve fiber layer edema and infarction, and the swelling can extend into the retina, including the macula, causing circumferential retinal folds (Paton's lines), or hard exudates in the form of a macular star. Often, the retinal vessels are engorged and tortuous.

Chronic papilledema can present with optic nerve pallor, hard exudates, and retinal nerve fiber layer atrophy, and can have decreased vision and visual field changes. A cautionary note is that an atrophic nerve that has been damaged from chronic insult may not appear swollen at all, even in the setting of elevated ICP.

Recommended testing includes neuroimaging with an MRI and MR venogram (MRV). If these studies do not reveal any etiology for the increased ICP, such as a mass or venous sinus thrombosis, the patient should then have a lumbar puncture (LP). This should be done to measure opening pressure with other appropriate CSF tests, including cell count and differential, glucose, protein, and cytology. Other labs, including serum Vitamin A level and thyroid studies can be sent depending on clinical suspicion. Vision, color vision, fundus exam, and visual field testing are necessary to monitor progression of disease.

Management

Management is aimed at treating the underlying cause and to decrease intracranial pressure. Treatments may include therapy or surgery for the underlying tumor, infection, or skull abnormalities, or cessation of medication that causes elevated intracranial pressure (including Vitamin A analogues, tetracycline, and steroids).

In the case of idiopathic intracranial hypertension, the goal of treatment is to reduce intracranial hypertension to

preserve optic nerve function, and manage headaches. Weight loss is recommended if the patient is obese. Acetazolamide can medically reduce elevated intracranial pressure. Other medications that have been tried include furosemide and steroids, although steroids paradoxically can also cause idiopathic intracranial hypertension. Repeated lumbar punctures might be necessary to reduce the intracranial pressure if it recurs. Rarely a ventriculoperitoneal or lumboperitoneal shunt may be needed for long-term treatment of both papilledema and headaches. In severe cases, optic nerve sheath fenestration may be indicated, but it does not treat headaches. Papilledema typically resolves within weeks to months after the underlying cause is treated. Rarely, papilledema may resolve in days.

Central Nervous System Neoplastic & Paraneoplastic Processes

Though most headaches are benign, some can be the result of a malignant intracranial process. Red flags include headaches that wake one from sleep, are associated with persistent vomiting after laying down or sleeping, or are associated with focal neurologic signs, including nystagmus.

Brainstem Tumors

Definition

Brain stem tumors consist of tumors in the medulla oblongata, pons, and midbrain.

History

It is unknown when the first report of childhood brainstem tumors was done.

Epidemiology

Midbrain gliomas comprise approximately 10–20 % of brain tumors in children [70]. The median age at diagnosis is 6–7 years [71], and 80 % of brainstem gliomas occur in the pons and carry a poor prognosis [72].

Systemic Manifestations

Presenting symptoms include those of increased ICP, including headache, vomiting, and altered mental status. Midbrain tumors are suggested by ataxia, long track signs, (spasticity, hyperreflexia), and cranial neuropathies. Additionally, a patient with a midbrain tumor may present with facial paresis, absent cough reflex, or depressed gag reflex. Swallowing or feeding abnormalities often indicate medullary involvement

Ophthalmic Manifestations

Pontine gliomas commonly present with 6th and 7th nerve palsies, often together. Strabismus and diplopia from involvement of intracranial portions of the nerves ensue. Pontine tumors have characteristic horizontal eye movement abnormalities such as internuclear ophthalmoplegia or one-and-a-half syndrome, in cases when the paramedian pontine reticular formation is involved. Late stage pontine gliomas may cause elevated intracranial pressure and papilledema. Seesaw nystagmus is a sign of tumor in the diencephalon [73].

Diagnosis

On diagnostic MRI, diffuse pontine gliomas have the characteristic appearance of irregularly-shaped lesions with partial contrast enhancement and surrounding edema. Low-grade brain stem gliomas are discrete, exophytic, and often have cyst formation [74].

Management

Because these tumors are located near vital parts of the brain, surgical excision is not typically an option. Treatment consists of local irradiation with or without chemotherapy. Over 90 % of patients who have diffuse intrinsic lesions transiently respond, but ultimately succumb to disease progression [75].

Pineal Tumors

Definition

Pineal tumors are derived from cells located in and around the pineal gland. Pineal tumors can be divided into germ cell tumors and non-germ cell tumors. Most are germ cell tumors and up to half of those are germinomas. Nongerminomas include teratomas, choriocarcinoma, yolk cell tumors, and embryonal carcinoma [76].

Epidemiology

Pineal tumors make up 3–11 % of brain tumors in children, have a male preponderance, and present at an average age of 13 years. The most common type of pineal tumor in children is the germ cell tumor [76].

History

The term Parinaud's syndrome was named after Henri Parinaud, a French ophthalmologist. In a paper in 1886, he described patients who had limitation in upgaze, no convergence, and no pupillary reaction to light [77]. This triad is still used today to define dorsal midbrain, or Parinaud's, syndrome.

Systemic Manifestations

The most common presentations of pineal tumors include hydrocephalus due to compression of the Sylvian aqueduct and dorsal midbrain syndrome due to compression of the dorsal mesencephalon.

Ophthalmic Manifestations

Dorsal midbrain syndrome is characterized by pupillary light-near dissociation, impaired upgaze, and convergence-retraction nystagmus. In light near dissociation, pupils do not constrict in reaction to light, but do constrict when the patient accommodates to look at a near target.

Diagnosis

MRI with contrast will show well-defined and homogenously enhancing germinomas and variable enhancement for non-germinomas. Definitive diagnosis is made by tumor biopsy and histopathological analysis [76].

Management

Tumor treatment depends on histology. Some tumors can be resected, where others, such as pure germinomas, are sensitive to radiation and chemotherapy. Nongerminoma germ-cell tumors have poor prognosis [78].

Posterior Fossa Tumors

Definition

The posterior fossa is a small space in the skull, found near the brainstem and cerebellum. Medulloblastomas are by far the most common posterior fossa tumors.

History

In 1925, Cushing and Bailey named a hypothetical, multipotential cell, the 'medulloblast'. The medulloblast was thought to be one of five stem cells populating the primitive neural tube. The term medulloblastoma was then conceived [79].

Epidemiology

Medulloblastomas are usually diagnosed in children younger than 15 years of age. There is a bimodal distribution, with one peak at 3–4 years of age and then one between 8 and 9 years of age [80].

Systemic Manifestations

The tumors can grow and impinge on the roof of the 4th ventricle, causing elevated intracranial pressure and papilledema. Symptoms include headaches associated with vomiting, especially in the morning, vision changes, and gait abnormalities. Infants can develop rapidly increasing head size due to hydrocephalus.

Ophthalmic Manifestations

In addition to papilledema, other ocular sequellae can include nystagmus, 3rd, 4th, 6th, and 7th cranial nerve palsies. Unilateral or bilateral internuclear ophthalmoplegia might also occur. In some children (who are old enough to be able to express themselves and do not suppress an eye) diplopia can result from the strabismus caused by either cranial neuropathies or internuclear ophthalmoplegia.

Diagnosis

On MRI, medulloblastoma has heterogeneous enhancement and location adjacent to and extending into the fourth ventricle. Biopsy and histopathology are used to confirm the diagnosis [81].

Management

The first step is surgical resection, and based on the patient's age and tumor risk factors, radiation or chemotherapy might follow [82].

Optic Nerve Gliomas

To be discussed in neurocutaneous chapter, along with neurofibromatosis.

CNS Leukemia

Definition

Leukemia is the most common childhood malignancy and the most common form is acute lymphoblastic leukemia (ALL) followed by acute myeloid leukemia (AML).

History

Leukemic infiltration of the optic nerve in children was reported increasingly in the latter half of the twentieth century, and is attributed to longer survival rates and poor penetration of standard chemotherapies into the CNS [83].

Epidemiology

In one study, it was found that 44 % of children with acute leukemia who were referred for an ophthalmological evaluation had ophthalmic involvement. All of those with ophthalmic manifestations were found to have bone marrow relapse or CNS involvement. In patients with ALL, 5 out of 17 Ophthalmology referred patients had optic nerve infiltration and 1 had uveal infiltration [84].

Systemic Manifestations

Leukemia is a group of so-called liquid tumors of bone marrow and white blood cells, that result in overproduction of immature white blood cells called blasts. Systemic manifes-

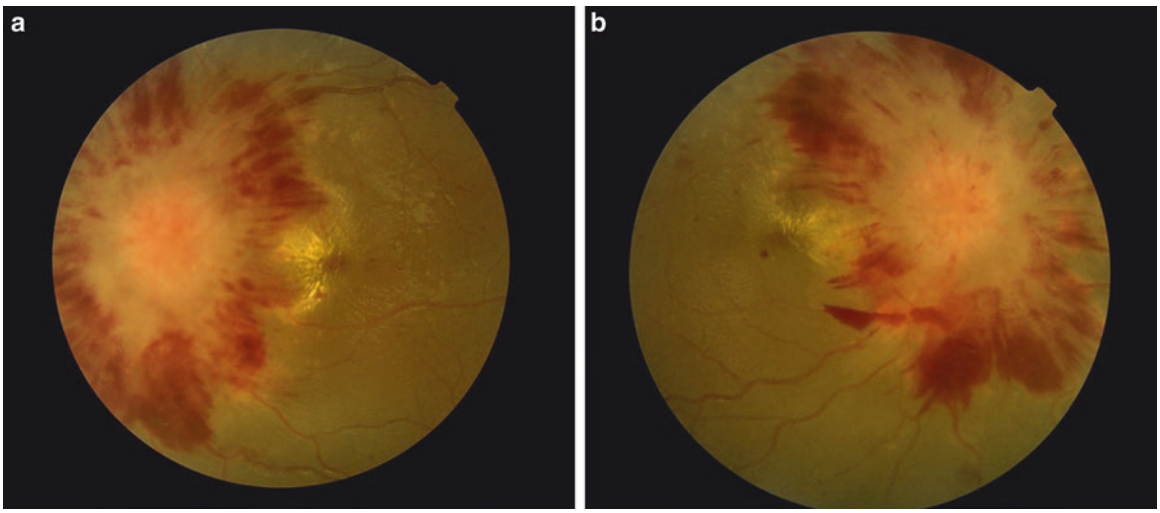

Fig. 15.1 (**a**, **b**) Right and left eye fundus photographs showing leukemic infiltration of the optic nerves. Note the clear media, edematous and elevated nerve heads with obscured margins, extensive peripapillary flame-shaped hemorrhages, obscuration of the vessels at the optic nerve head, and macular star formation in each eye

tations are beyond the scope of this text, but include fatigue, infections, bleeding, and death if untreated.

Ophthalmic Manifestations

Ophthalmic involvement from leukemia usually can precede or coincide with bone marrow involvement. The most common leukemic recurrence sites in the eye include the optic nerve and choroid. Optic nerve infiltration presents as unilateral or bilateral optic nerve swelling, with peripapillary hemorrhages, and some lead to central retinal vein and/or artery occlusion (see Fig. 15.1.) Retinal detachment can occur as a result of choroidal infiltration. Recurrence of leukemia may not only affect the retina and optic nerves, it can also present as a conjunctival mass or hypopyon not responsive to steroids [85, 86]. Though more commonly occurring during relapses, leukemic ophthalmopathy can also occur at the time of initial diagnosis. The most frequent symptoms were blurred vision, photophobia, and eye pain [87]. But asymptomatic patients are not uncommon, especially in younger children.

Diagnosis

The diagnosis of optic nerve involvement of leukemia is a combination of clinical exam and imaging. On exam, findings usually include reduced vision, reduced color vision, APD, and a swollen optic nerve. Often both nerves are involved, although the severity can be asymmetric. The preferred diagnostic modality is MRI orbits with contrast. Optic nerve enlargement with enhancement is a typical sign of leukemic infiltration [88].

Management

Infiltration of the optic nerves by leukemia is an ophthalmic emergency. If not promptly acted upon, drastic and permanent vision loss can occur. Treatment includes emergent radiation with systemic and/or intrathecal chemotherapy.

Paraneoplastic Processes

Neuroblastoma

Definition

Neuroblastoma is a cancer of the neural crest cells that give rise to sympathetic neural ganglia and the adrenal medulla. Opsoclonus-myoclonus syndrome (OMS) is an associated paraneoplastic syndrome of chaotic eye movements, myoclonic jerks, and ataxia.

History

In 1891, German pathologist Felix Marchand first described a sympathetic nervous system tumor [89]. In 1910, James Homer Wright noted the tumors originated from primitive neural cells, and named it neuroblastoma. He also noted circular clumps of cells now termed "Homer-Wright pseudorosettes [90]."

The first report of neuroblastoma and OMS in the same patient was by Cushing and Wolbach in 1927, but the emphasis of this report was different [91, 92]. The association of neuroblastoma and OMS was not recognized until the 1968 report by Soloman and Choturian [93].

Epidemiology

Neuroblastoma is the most common extracranial tumor of childhood. The incidence of neuroblastoma in North America and Europe approaches 10.5 per million children between 0 and 14 years of age [94, 95]. It is the most commonly diagnosed cancer in infancy with most patients diagnosed before 4 years of age. Familial neuroblastoma is rare and the inherence pattern is autosomal dominant with incomplete penetrance. Neuroblastoma can occur in other neural crest disorders, such as Hirschprung disease and congenital central

hypoventilation syndrome [96]. OMS is usually diagnosed between 1 and 3 years of age. It occurs in 2–3 % of patients with neuroblastoma [97].

Systemic Manifestations

Symptoms of neuroblastoma may differ based on tumor location and extent. They most commonly arise in the adrenal glands and may cause hypertension, abdominal pain, and constipation due to the abdominal mass. In infants, they more commonly arise in the cervical sympathetic chain and may lead to Horner's syndrome (ipsilateral ptosis, miosis, anhydrosis). Paraneoplastic symptoms can also include diarrhea caused by vasoactive intestinal peptide and opsoclonus myoclonus ataxia syndrome [98, 99].

Opsoclonus-myoclonus syndrome is a paraneoplastic syndrome, that in children, is associated with neuroblastoma in more than half of the cases [100]. It presents as an acute onset of myoclonic jerks, ataxia, along with the chaotic eye movements of opsoclonus described below.

Neurological symptoms can also include difficulty or refusal to walk, sleep disturbance, irritability, or speech abnormalities.

Ophthalmic Manifestations

When Horner's syndrome is noted, the ptosis is usually 1–2 mm. In addition to upper eyelid ptosis, patients may present with reverse ptosis, (in which the lower lid is higher and covers more of the cornea than normal,) heterochromia iridis, conjunctival congestion, and transient hypotony.

Opsoclonus is defined as conjugate (ie, both eyes moving in the same direction,) fast, multidirectional eye movements.

Diagnosis

All patients with OMS should undergo an evaluation for neuroblastoma, which includes MRI of the brain and neck, along with MRI or CT of the chest, abdomen, and pelvis. Urine catecholamine metabolite levels, such as vanillylmandelic acid (VMA) and homovanillic acid (HVA) are tested, but normal values do not rule out a neuroblastoma. An iodine-123-meta-iodobenzylguanidine (MIBG scan) is sometimes necessary to find the abnormal tissue. Diagnosis is definitively made by tumor tissue biopsy.

Most cases of congenital Horner syndrome have benign etiologies and many of them are associated with birth trauma. The presence of birth trauma does not exclude the possibility of neuroblastoma. All children with acquired Horner syndrome should undergo systemic evaluation, lab testing, and imaging [101].

Management

After assessing tumor genetics and histopathologic features, as well as signs of metastasis, the patient is stratified into a risk group. Treatments such as surgical resection, chemotherapy, radiotherapy, or immunotherapy are based on individual patient's risk category [102].

Children with OMS and neuroblastoma often have favorable prognosis and a high survival rate [103]. The neurologic symptoms can often be treated with steroids, ACTH, or IVIG. However, many of them may have long-term deficits in speech, coordination, eye movements, or development [104].

Cerebral Malformations

Septo-Optic Dysplasia

Definition

Optic nerve hypoplasia is a congenital, non-progressive cerebral malformation that can involve optic nerves, midline brain structures, and cerebral hemispheres. Along with low vision or blindness, it can have associated Endocrine, Neurologic, and Developmental abnormalities [105, 106]. The definition of septo-optic dysplasia is the combination of optic nerve hypoplasia and absence of septum pellucidum, but other findings can be present as well [107].

History

The first description of a hypoplastic optic nerve was written in 1884 by Magnus [106]. In 1915, Schwarz is credited with describing hemi-hypoplastic nerves. In 1941, Reeves reported on a 4 month-old child with absence of septum pellucidum and blindness that was thought to be secondary to congenital aplasia of the optic nerves [108]. After Georges de Morsier's 1956 report on a series of autopsy brains with absent septum pellucidum, one of which had a hypoplastic optic nerve, the terms "septo-optic dysplasia" and "De Morsier syndrome" came into use [109]. The septum pellucidum need not be absent in order to have the constellation of other findings, and there is now some push for abandonment of the two terms linking optic nerve hypoplasia and absent septum pellucidum [108]. In 1970, Hoyt et al. described the association between optic nerve hypoplasia and hormone insufficiency [110].

Epidemiology

Although optic nerve hypoplasia is rare, it is a leading cause of congenital blindness, and is the most common congenital anomaly of the optic disc [111]. There is limited information on the incidence and prevalence of optic nerve hypoplasia, but studies suggest that the disease may be on the rise [105, 108]. A population-based study done in Minnesota found the annual incidence of optic nerve hypoplasia to be 1 in 2287 live births over the study period from 1984 to 2008. They also found an increase in the prevalence per 100,000 people under age 19 in their population when they compared the first 5 years of their study to the last 5 years (from 2.4 to 3.05) [105]. A study in Sweden found that the prevalence

quadrupled to 7.1 per 100,000 between the years of 1980 and 1999, and a 2006 study from England found the prevalence to be 10.9 per 100,000 [108].

The explanation for the apparent increase in prevalence is not clear, as causative factors are largely unknown. It has been postulated that it can be explained by increased recognition among clinicians [112]. Young maternal age and first born children are reported to be associated with optic nerve hypoplasia, but data on potentially causative prenatal exposures is un-convincing. Similarly, data on genetics in this condition is limited, but there are rare reports of clusters in families, and reports of associated *PAX6* mutations [113].

Systemic Manifestations

Reported systemic manifestations are variable and depend on which areas of the brain and body have associated defects. They can include global developmental delay, cortical malformations, focal deficits, or epilepsy secondary to the associated malformations, pituitary hormone deficiency, dysmorphic features (facial midline, skull, musculoskeletal system), sensorineural hearing loss, anosmia, cardiac anomalies, and esophageal anomalies [109].

Of special concern for a patient with a new diagnosis of optic nerve hypoplasia is the potential associated pituitary hormone deficiency, which may not yet have been recognized. It can range from a single hormone deficiency to panhypopituitarism with associated absence of stress response elevation in cortisol. This can result in adrenal crisis, hypoglycemia, and death in times of stress if not appropriately managed [107]. This should be kept in mind when these patients undergo anesthesia, or other stressful events.

Ophthalmic Manifestations

As with the many possible associated systemic findings, optic nerve hypoplasia itself is highly variable in its severity. Optic nerve findings can range from a unilateral, mildly small nerve, to complete bilateral optic nerve agenesis. Vision can range from near normal to no light perception. There can also be associated microphthalmia, which can range to anophthalmia in the most severe cases [109].

Nystagmus is often present, and is considered secondary to the low vision resulting from the hypoplastic nerves. This can result in an anomalous head position, which patients may adopt for improved vision they can have when gazing in the direction of their nystagmus null point. Strabismus is also seen, as is superimposed amblyopia [105].

Diagnosis

The diagnosis of optic nerve hypoplasia is a clinical one made by ophthalmoscopy, and a small optic nerve head is the unifying characteristic. This can be difficult to visualize in these children, as nystagmus is often present and there can be a so-called double ring sign mimicking a normal optic nerve. Vascular anomalies including tortuosity or straightening, anomalous branching, and vessels that are large-appearing compared to the size of the nerve can be helpful clues. A thin peripapillary retinal nerve fiber layer can also be found. When feasible, fundus photography can be helpful in confirming the clinical diagnosis of optic nerve hypoplasia [106].

In uncertain cases, MRI can be helpful in confirming the presence of hypoplastic optic nerves. It is also prudent to consider MRI to evaluate for ectopic posterior pituitary with absence of the typical bright spot, as this is highly correlated with endocrine anomalies [114]. Keep in mind that endocrine anomalies have occurred in absence of MRI findings, however [105].

In newborns, or when there have been any potential endocrine issues, such as recurrent hypoglycemia, jaundice, and temperature instability, referral for endocrine work-up for possible panhypopituitarism should be considered. Basic laboratory testing is done, and growth should be monitored.

Management

Management of systemic complications is highly variable, but may require a multidisciplinary approach, including the pediatrician, ophthalmologist, endocrinologist, neurologist, and others, depending on case-specific manifestations. hormone replacement is often necessary. If the patient requires stress-dose steroids prior to surgery, this is usually determined by the pediatrician or pediatric endocrinologist.

Management of ophthalmic manifestations may include optical correction, even for small refractive errors, and low vision services. Amblyopia treatment should be undertaken, keeping in mind that the final visual outcome may be limited by the reduced amount of optic nerve tissue present in these patients. Some children may benefit from strabismus surgery, and occasionally, extraocular muscle surgery for severe anomalous head position for nystagmus null-point [105].

Aicardi Syndrome

Definition

Aicardi syndrome is a neurodevelopmental disorder with complete or partial agenesis of the corpus callosum, chorioretinal lacunae, and infantile spasms [115].

History

Jean Aicardi first described the syndrome in 1969 as a triad of agenesis of corpus callosum, ocular anomalies, and spasms in flexion [115–117].

Epidemiology

So called X-linked dominant, or hemizygous male-lethal, the syndrome is only seen in females or XXY males [118]. It is therefore, always considered to be a novel mutation, which has been localized to Xp22 [115, 116].

Although the incidence is unknown, there are about 200 cases in the literature, and Jean Aicardi states that he personally knows of around 450 cases worldwide [117]. The NIH estimates the current prevalence at about 4000 individuals worldwide, and incidence to be between 1/93,000 in the Netherlands and 1/105,000 newborns in the US [119]

Systemic Manifestations

Typical brain anomalies include some degree of agenesis of the corpus callosum, polymicrogyria, periventricular and subcortical heterotopia, intracranial cysts, cerebellar anomalies, and large cisterna magna [120]. Epilepsy is often difficult to treat and can be intractable [115].

Also seen are developmental delay, costovertebral anomalies, cleft lip and palate, and anomalous facies. The facial features described are sparse lateral eyebrows, upslanting palpebral fissures, upturned nasal tip, decreased angle of nasal bridge, deep philtrum, prominent premaxilla, and large ears. The developmental delay is usually severe, with most affected girls having little or no language function [121].

Ophthalmic Manifestations

Chorioretinal lacunae are considered pathognomonic, and appear as hypopigmented lobules, which can have retinal vessels crossing their margins. Their size can range from ~1/10 disc diameter to several disc diameters. They usually are multiple and bilateral, and clustered around the optic nerve. They are stable in size in shape over time, but can become more pigmented with time [117].

Optic disc colobomas are present in about half of cases, and are often associated with dilation of the retrobulbar optic nerve. A morning glory like anomaly can also be present, as can microphthalmia.

Diagnosis

Neuroimaging, a neurologic evaluation with EEG, and a dilated fundus exam are required to find the corpus callosum abnormalities, infantile spasms, and chorioretinal lacunae in the classic triad [117]. The criteria have been revised over time to include at least two of the classic features above, plus other supporting criteria, but the triad is pathognomonic.

Management

For infantile spasms, ACTH or Vigabatrin are typically first line. If these fail, the ketogenic diet is also an option. If the patient has other seizure types, there are a variety of antiepileptic drugs that can be utilized.

Traditional therapies should be started as soon as possible for developmental delays.

An orthopedic evaluation and possibly monitoring is recommended for any vertebral anomalies, including scoliosis.

The most common cause of death is from pulmonary infections, so these should be treated aggressively.

As with any primary anatomic eye problem that may have superimposed amblyopia, amblyopia treatment should be undertaken to maximize vision. This includes spectacle correction and patching, when appropriate.

Neuromuscular Disorders

Guillain-Barre Syndrome (Miller Fisher Variant)

Of the acute neuromuscular disorders known to affect children, Guillain-Barré (specifically the Miller-Fisher variant) has been known to have ocular manifestations.

Definition

Guillain-Barré syndrome (GBS) is an inflammatory demyelinating polyneuropathy characterized by acute, typically bilateral limb weakness and loss of deep tendon reflexes. It is an autoimmune disorder and presents after an infectious illness, most commonly Campylobacter jejuni, a gram-negative bacterium that causes enteritis. Less commonly, other bacteria and viruses have been implicated such as cytomegalovirus, (in up to 10% of cases [122, 123]), also *Haemophilus influenza*, *Mycoplasma pneumoniae*, Epstein–Barr virus and varicella zoster virus [124].

GBS is often used as an umbrella term describing a heterogeneous group of subtypes, including the Miller-Fisher Syndrome variant (MFS). Patients with classic GBS develop a bilateral ascending flaccid paresis in two or four extremities, with variable involvement of bulbar, cervical, facial, and upper limbs, with or without paresthesias. The MFS variant of GBS is specifically characterized by the triad of ophthalmoplegia, ataxia, and areflexia.

There is overlap between the subtypes and variants. Bickerstaff's brainstem encephalitis, defined by the presence of either altered consciousness or hyperreflexia in addition to progressive ophthalmoplegia and ataxia, is often on the differential for acute onset of ophthalmoplegia [125].

Epidemiology

About two thirds of GBS cases are preceded by either diarrhea or upper respiratory infection, but less than 1 in 1000 individuals who have a C. jejuni infection go on to develop GBS [126]. Because only a minority of infected individuals develop the disease, genetic factors may potentially confer susceptibility [126]. GBS is therefore considered to be a complex multifactorial disorder with both genetic and environmental factors.

The MFS variant is more common among patients in eastern Asia, accounting for approximately 20–25 % of cases of GBS [127], compared to the United States where reportedly about 5 % of GBS cases are MFS [128].

History

The syndrome was named after the French physicians Guillain, Barré, and Strohl, who first described it in 1916, although a variant had been described by Landry as early as 1859. This is the reason it has also been called Landry's paralysis. In 1932, the triad of ataxia, areflexia, and ophthalmoplegia was first described as a variant of the Guillain-Barre syndrome by J. Collier. However it was not until 1956 that Charles Miller Fisher reported three patients with ataxia, areflexia, and ophthalmoplegia as a separate entity, and thus the Miller Fisher variant was named after him [129].

Systemic Manifestations

The patient will often have a history of a recent gastrointestinal or upper respiratory illness, predating the onset of symptoms as short as 3 days or as long as 6 weeks, with a median time interval of 10 days [124]. The patient may complain of numbness, paresthesias, dysesthesias, and/or weakness of extremities that progressively worsens over several days, and may also complain of facial weakness or diplopia depending on the subtype. Classically the limb weakness begins more distally and progresses proximally, termed an "ascending paralysis."

In the majority of patients, the GBS continues to progress for up to 1–2 weeks after the onset of symptoms. Approximately two thirds of patients have such severe distal limb involvement that they are unable to walk at the peak point in the illness, while 25 % progress to have involvement of the respiratory muscles causing respiratory insufficiency, sometimes requiring intubation [122]. Patients with the MFS variant typically have a more benign course, with 5 % progressing on to develop respiratory insufficiency [130]. The symptoms then resolve at variable rates, making prognostication difficult.

Ophthalmic Manifestations

The MFS variant (ophthalmoplegia, ataxia, and areflexia) is the subtype to most likely present with ocular manifestations. The classic ophthalmoplegia is a symmetric paresis of upgaze and progressive impairment of horizontal gaze, with variable involvement of downgaze [131]. Ptosis is typically very mild or not present at all and pupillary dysfunction is variable [131]. There are often asymmetries between the eyes, and a variety of other ocular problems can be found including abduction, adduction, or third nerve palsies, abnormal pursuit, Optokinetic reflex (OKR), vestibulo-ocular reflex (VOR), and VOR-cancellation [125, 132]. Rare reports have also documented nystagmus of various kinds (gaze-evoked, dissociated abducting, convergence-retraction, rebound, and upbeat lid nystagmus) [131].

Diagnosis

Several diagnostic criteria for GBS have been proposed, including the recent Brighton Criteria (formed by the Brighton Collaboration, sponsored by the World Health Organization), which proposes various clinical findings, each with a related level of diagnostic certainty. The more findings that are present the higher the likelihood of the GBS diagnosis, helping to account for the syndrome's heterogeneity and subtypes. It includes the following findings: bilateral and flaccid weakness of limbs, decreased or absent deep tendon reflexes in weak limbs, monophasic course and time between onset-nadir 12 h to 28 days, CSF cell count <50/u, CSF protein concentration > normal value, nerve conduction study findings consistent with one of the subtypes of GBS, and absence of alternative diagnosis for weakness.

A lumbar puncture is typically performed to rule out infectious or malignant causes, and also can support the diagnosis by demonstrating albumin-cytologic disassociation in the cerebrospinal fluid. Of note, however, only 50 % will show this classic albumin-cytologic dissociation during the first week of illness, and only 75 % by the third week of illness. Therefore the absence of albumin-cytologic dissociation does not rule out the diagnosis of GBS. Nerve conduction studies may show prolonged distal latencies, conduction slowing, conduction block, absent F waves, and temporal dispersion of compound action potential in demyelinating cases. They can be helpful to confirm a diagnosis but they are not necessary for diagnosis.

Management

Management is largely supportive. Intravenous immunoglobulin (IVIg) or plasmapheresis can be used in the acute phase. Steroids do not affect the course of the disease [130].

Other Considerations

Other neurological conditions, which commonly mimic GBS variants include: brainstem stroke, myasthenia gravis, botulism (described more often as descending paralysis), lyme disease, tick paralysis, and bacterial, carcinomatous, or lymphomatous meningitis [133].

Myasthenia Gravis

Myasthenia gravis is a neuromuscular disorder that frequently has ocular manifestations.

Definition

Myasthenia Gravis (MG) is an autoimmune mediated disorder of the neuromuscular junction that results in weakness and fatigue of skeletal muscles. Autoantibodies directed against the Acetylcholine receptor (AChR) or Muscle-Specific Kinase (MUSK) block the transmission of nerve impulses to muscles and prevent the appropriate muscle contraction from occurring.

Epidemiology

MG occurs in all ethnic groups and both genders, and while it may occur at any age from infancy to late adulthood, the onset in childhood is less common and accounts for only 10–15 % of cases [76]. When the classic disease does present in children, it is called juvenile myasthenia gravis (JMG), and the manifestations are the same as those in adults. In post-pubertal children, JMG is more prevalent in females, but in pre-pubertal children the incidence is the same between girls and boys [76].

JMG should not be confused with neonatal myasthenia gravis or congenital myasthenic syndrome.

In transient neonatal myasthenia gravis, a fetus may acquire immune proteins (antibodies) via placental transfer from a mother affected with myasthenia gravis. Between 10 and 25 % of babies born to mothers with MG may have this temporary form of the condition. Generally, the child's symptoms resolve within weeks to months after birth [134]. Treatment is still important in these cases, as the neonate may be very ill during this period.

Congenital myasthenic syndrome is a similar but different disease of the neuromuscular junction that is genetic rather than autoimmune in origin. It is rare, and rather than being autoimmune in nature, it is caused by genetic mutations that produce abnormal proteins leading to defective acetylcholine, acetylcholinesterase, or the acetylcholine receptor [134].

History

MG was first recognized as a distinct clinical entity in 1672 by Oxford physician Thomas Willis. His report, which was in Latin, went largely unnoticed, and subsequently the first modern description was made in 1877 by Samuel Wilks, a London physician [135].

Systemic Manifestations

The degree of muscle weakness involved varies greatly, ranging from a form limited to eye muscles (ocular myasthenia), to a severe, generalized form. In this more severe form, a myasthenic crisis can occur when the respiratory muscles weaken to the point that ventilation is inadequate. This is the most serious complication of MG, is life threatening and a medical emergency, requiring assisted ventilation. In individuals whose respiratory muscles are weak, these crises may be triggered by infection, fever, or an adverse reaction to medication [134].

In about 15 % of patients with MG there may be a tumor of the thymus gland, called a thymoma. Thymoma-related MG has a peak onset around 50 years of age and tends to be more severe than early-onset non-thymoma MG. A thymoma is a neoplasm derived from thymic epithelial cells, which are capable of expressing epitopes that are cross-reactive with skeletal muscle proteins, such as acetylcholine receptor (AChR), titin, and ryanodine receptor (RyR). When MG occurs together with a thymoma, MG is a paraneoplastic disease caused by the presence of the thymoma. However, even in the absence of a thymoma, the thymus gland is abnormal in about 75 % of patients with MG [136].

Ophthalmic Manifestations

Muscles that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are most frequently affected. The muscle weakness in MG increases during periods of activity and improves after periods of rest. The extraocular muscles and levator muscles are affected early in the course, resulting in double vision and ptosis, respectively. These are commonly the only presenting symptoms of MG. A classic presentation of this disease is asymmetric ptosis that is fatigueable.

The patient may therefore present complaining of a drooping eyelid that is worse at the end of the day. They might also report binocular diplopia that varies in severity throughout the day, again often being worse at the end of the day. Variable muscle weakness, including intermittent difficulty swallowing or chewing, depending on which muscles are affected, can occur.

Diagnosis

When MG is suspected, there are several different tests that can help establish the diagnosis. In the office, a patient's ptosis should be measured before and after having them patient look upwards for 90 s. A levator muscle affected by MG is expected to fatigue with this exercise, and the degree of ptosis should increase. Ptosis should improve after rest, such as

keeping the eyes closed for 20 min in a dark room ("sleep test"). Ptosis is also expected to improve after the external application of ice for 2–5 min, which can also be tested in the office ("ice pack test").

Serologic antibody titers are then helpful in confirming the diagnosis. Approximately 85 % of patients with myasthenia gravis have abnormally elevated levels of anti-acetylcholine receptor (anti-AChR) antibodies. A second antibody—called the anti-Muscle-Specific Kinase (anti-MuSK) antibody—has been found in about 30–40 % of individuals with myasthenia gravis who do not have anti-AChR antibodies [137]. However, neither of these antibodies is present in some individuals with MG, most often in pre-pubertal patients and those with purely ocular myasthenia gravis.

Other tests include the edrophonium test, and electromyography (EMG) studies. The edrophonium test (also called Tensilon test) uses intravenous administration of edrophonium chloride to very briefly relieve weakness in people with MG. The drug blocks the degradation of acetylcholine, temporarily increasing the levels of acetylcholine at the neuromuscular junction and causing increased signal transmission. EMG studies (Repetitive nerve stimulation and Single Fiber EMGs) record characteristic muscle responses when small pulses of electricity stimulate the nerves. Repetitive stimulation of a nerve classically demonstrates gradual decreases of the muscle action potential over time in MG due to impaired nerve-to-muscle transmission. These tests are often used when clinical suspicion is high but serologic tests are negative.

Diagnostic imaging of the chest, using computed tomography (CT) or magnetic resonance imaging (MRI), may be used to identify the presence of a thymoma.

Management

The choice of management is based on age, severity and extent of symptoms, and other existing medical conditions. The mainstay of medical therapy is cholinesterase inhibitors such as pyridostigmine (Mestinon,) which provides symptomatic treatment. This may be all that is needed for patients with mild symptoms.

Oral steroids can be used if the symptoms of myasthenia gravis worsen despite using pyridostigmine. Additional immunomodulatory therapy such as azathioprine, methotrexate, or mycophenolate may also be considered, especially to reduce the use of long-term steroids.

Plasmapheresis and IVIG are good therapeutic choices when a quick response is needed, such as in myasthenic crisis, but the effect is temporary and usually only lasts a few weeks. This is not a suitable long-term therapy.

Thymomas, when present, should be removed surgically. Pre-thymectomy plasmapheresis/IVIG should be considered.

In the absence of thymoma, the thymus gland is still thought to promote harmful antibody production, although the exact mechanism is not fully understood. Thymectomy has been found to improve symptoms even in non-thymoma cases, but does not always work. Also the effect is delayed, with patients showing some improvement typically after 6 months to 1 year following surgery [136]. Thymectomy may be used in children with generalized JMG who are not responding to medical treatments, or those who would be heavily dependent on medication in the long term. This is usually not indicated in cases of pure ocular myasthenia.

Myotonic Dystrophy

Definition

Myotonic dystrophy is a progressive, autosomal dominant myopathy caused by a cytosine-thymine-guanine (CTG) repeat expansion in the dystrophia myotonica-protein kinase (*DMPK*) gene [138–140]. Myotonic dystrophy demonstrates anticipation, the genetic phenomenon whereby the disease severity increases and age of onset decreases in successive generations. Myotonic dystrophy type 1 is the most common muscular dystrophy in adults. Type 1 ranges from an asymptomatic form to a congenital form which can be life-threatening. Myotonic dystrophy type 2 is less common and has a milder phenotype.

History

Hans Steinert first described myotonic dystrophy (previously known as Steinert's disease) in 1909. Steinert described the precise observations and subtle neurologic exam findings seen in this multisystem disorder that he encountered at the medical hospital of Leipzig University [141]. Myotonic dystrophy type 2 was first recognized in 1994 as a milder version of myotonic dystrophy type 1.

Epidemiology

The prevalence of myotonic dystrophy is 3–15 per 100,000 [142]. The breakdown of how many diagnosed are myotonic dystrophy type 1 and type 2 are unknown. Patients with myotonic dystrophy type 1 are clinically divided into five main subtypes based on the age of presentation. The "classical" or adult-onset form can affect any organ. Congenital myotonic dystrophy is characterized by >1000 CTG repeats, onset at birth, infantile hypotonia, respiratory failure, learning disability, and feeding difficulty. Childhood-onset disease is characterized by >800 repeats, onset at ages 1–10

years, psychosocial problems, and low IQ. The classical phenotype has 50–1000 repeats, onset between 10 and 30 years, muscle weakness with respiratory failure, myotonia, cataracts, cardiac arrhythmias, and excessive daytime sleepiness. The mild phenotype has fewer repeats, onset between 20 and 70 years, cataracts, and mild myotonia. The premuation phenotype has no clinical signs [143].

Systemic Manifestations

Both types of myotonic dystrophy are multiorgan disorders with a wide and diverse clinical spectrum. Both are characterized by skeletal muscle weakness and myotonia, cardiac conduction abnormalities, cataracts, cognitive impairment and personality disturbances, and endocrine disturbances such as hypogonadism and glucose intolerance [144, 145].

Regarding the skeletal muscle weakness, the most frequently affected muscles are the facial muscles, levator palpebrae superficialis, temporalis, sternocleidomastoids, distal muscles of the forearm, intrinsic muscles of the hand, and ankle dorsiflexors (causing foot drop). The term "hatchet facies" has been used to describe the dysmorphic facial appearance due to temporalis muscle wasting. Action myotonia can be demonstrated when a patient has difficulty relaxing his or her hand after grasping an object.

Myotonic dystrophy in children can be classified as congenital, infantile, late-infantile, and juvenile. Congenital myotonic dystrophy can be viewed as the most severe form of the clinical spectrum. These patients may have reduced fetal movements, polydramnios, and preterm delivery. At birth, they may have hypotonia, hyporeflexia, and difficulty breathing, swallowing, and feeding resulting in respiratory distress. They may also present with a tent-shaped upper lip, arthrogryposis, and clubfeet. Neonates can also have cardiomyopathy. A less severe form of congenital myotonic dystrophy may present with similar features without respiratory distress [146].

Infantile myotonic dystrophy type 1 presents within the first decade of life, while juvenile myotonic dystrophy type 1 presents between 10 and 20 years of age. The increased number of repeats is usually greater when passed maternally, so children diagnosed with this disease typically have affected mothers. It is, therefore, especially important to examine the mothers in younger patients. Motor delay, delayed milestones, speech delay, difficulties at school, and cognitive impairments are seen in the majority of patients. The onset, severity, and manifestations vary considerably between patients [146].

Ophthalmic Manifestations

Patients often present with ptosis, extraocular muscular weakness, and orbicularis weakness. Facial nerve palsy may also cause orbicularis weakness and meibomian gland dysfunction. The orbicularis weakness in myotonic dystrophy type 1 is much more pronounced than that seen in chronic progressive external ophthalmoplegia and oculopharyngeal muscular dystrophy. All of these signs worsen with time.

Slit lamp exam may reveal the classic Christmas tree, polychromatic cataract. This is characterized by reflective, polychromatic, iridescent crystalline deposits deep in the lens that may progress to a posterior subcapsular cataract or complete cortical opacification. This cataract can cause visual acuity loss, but are rarely symptomatic in childhood. Central macular lesions, pigmentary retinal degeneration, and hypotony may also occur [147]. Recent studies have suggested that myotonic dystrophy may also be associated with Fuchs endothelial corneal dystrophy [148]. Children with myotonic dystrophy type 1 have a variety of visual function pathologies, including hyperopia and astigmatism, that may impact the developing visual system requiring early eye exams and follow-up [149].

Diagnosis

A diagnosis of myotonic dystrophy can be made clinically with the presence of muscle weakness and myotonia in the setting of a positive family history. Diagnosis is usually confirmed through genetic testing. Specific genetic testing showing the expanded CTG repeat in the *DMPK* gene is the gold standard for the diagnosis of myotonic dystrophy type 1. Myotonic dystrophy type 2 is caused by a CCTG tetranucleotide expansion [150]. Electromyography (EMG) may be useful in demonstrating myotonia if this is not found clinically, but might not be reliable in infants. Muscle biopsy may be useful in atypical cases to distinguish myotonic dystrophy type 2 from an inflammatory or metabolic myopathy that cannot be differentiated by clinical presentation alone [151]. Other diagnostic investigations include electrocardiography (ECG), creatine kinase concentration, g-glutamyltransferase level, slit lamp examination, follicule-stimulating hormone levels, and testosterone levels.

Management

The management of myotonic dystrophy requires a multidisciplinary team including neurologists, cardiologists, pulmonologists, endocrinologists, and occupational/physical therapists. Though recent studies in gene therapy have tested targeted molecular treatments in animal models, there is currently no cure for myotonic dystrophy. Each organ system should be addressed directly by the appropriate specialists. Neonates often require intubation and ventilation.

Regarding the ophthalmologic management, slit lamp exams are appropriate at the time of diagnosis and periodically thereafter. In congenital myotonic dystrophy type 1,

cataracts are uncommon before age 10. Cataract surgery is carried out in 13–32 % of patients based on the patient's symptoms and activities of daily living [144, 145].

Special attention should be paid to poor orbicularis tone and compromised Bell's phenomenon. Patients may benefit from elevation of the eyelids via a primary silicone frontalis sling [152]. Lower lid elevation may also be necessary. Warm compresses, oral doxycycline, and oral fish oil may be part of the treatment to address the meibomian gland dysfunction [153].

It is important to note that all patients should undergo cardiac surveillance due to their cardiac rhythm abnormalities. In addition to seeing ophthalmologists for early cataracts and neurologist for muscle weakness, 70 % of mortality in myotonic dystrophy type 1 is caused by cardiorespiratory disorders.

Demyelinating Disorders

Multiple Sclerosis

Definition

Multiple sclerosis (MS) is a chronic, autoimmune inflammatory demyelinating disease with episodes disseminated in space and time. Demyelination occurs in the brain, optic nerves, and spinal cord. Pediatric multiple sclerosis is defined by its onset, which is prior to the age of 18 years.

History

In 1868, Jean-Martin Charcot, a professor at the University of Paris, wrote a complete description of the disease he had seen in a series of patients. After a young woman with a tremor, slurred speech, and abnormal eye movements died, Charcot examined her brain and found "plaques." He eventually described a triad describing the clinical signs of multiple sclerosis: intention tremor, nystagmus, and scanning speech. This triad is not considered to be pathognomonic [154].

Epidemiology

Pediatric MS comprises 5 % of all MS [155, 156]. Less than one percent present before age 10 [157]. Just as with adults, pediatric MS is more common in females than males [158].

Systemic Manifestations

Both pediatric and adult patients can present with optic neuritis, brainstem syndrome, or symptoms of encephalopathy (headache, vomiting, seizures, or altered consciousness). In pediatric patients, optic neuritis is more often bilateral. Patients may also present with hemiparesis, hemisensory symptoms, and bladder or bowel incontinence. Most children have the relapsing-remitting course of multiple sclerosis. Primary progressive multiple sclerosis is much less common in children.

Within the first 2 years of onset, 30 % of children have significant cognitive impairment, 50 % show signs of depression, and 75 % are fatigued. While childhood multiple sclerosis usually has a relapsing-remitting course, the relapse rate is higher than that of adult-onset disease. Childhood-onset multiple sclerosis patients reach permanent disability or have secondary progressive disease 10 years younger than patients with adult-onset multiple sclerosis [155]. Patients with childhood-onset multiple sclerosis take longer to reach states of irreversible disability, but they do so at a younger age [158].

Ophthalmic Manifestations

The primary ophthalmologic manifestation of pediatric MS is optic neuritis. In general, optic neuritis in the pediatric population has a prevalence of 3.2 per 100,000, with a lower incidence in the African-American population [159]. Patients may present with central vision loss and pain with eye movement. Younger patients (below age 12–15 years) are more likely to present with bilateral optic neuritis than older children and adults. Optic neuritis usually presents with a slowly progressive onset of partial or complete vision loss with a rapid decrease in acuity to <20/200, a relative afferent pupillary defect, red desaturation, and visual field defects over several hours to a few days. Pain with eye movements might or might not be present. Optic nerves may appear edematous, however this can be mild or absent especially if the inflammation is retrobulbar, (not present at the optic nerve head.)

Patients may also present with internuclear ophthalmoplegia from a lesion in the medial longitudinal fasciculus. This results in medial rectus palsy in the adducting eye on attempted lateral gaze and nystagmus in abducting eye. Convergence is normal.

Visual field testing, optical coherence tomography, and visual-evoked potentials may be used to characterize the visual changes. Some patients may have subtle color impairment and stereoscopic abnormalities even after normal or near-normal visual recovery.

Diagnosis

The differential for acute central nervous system demyelination in children includes multiple sclerosis, acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, neuromyelitis optica, CNS lymphoma, CNS vasculitis, Hemophagocytic Lymphohistiocytosis (HLH), and other infectious, metabolic, and rheumatologic conditions. Certain clinical features, lab tests, and imaging studies can differentiate multiple sclerosis from other conditions. It is largely a diagnosis of exclusion.

The main tests recommended for diagnosing multiple sclerosis are MRI of the brain and orbits with fat suppression and lumbar puncture with cerebral spinal fluid evaluation. Typical neuroimaging findings include periventricular white-matter plaques of demyelination and demyelination that

occurs in a bilateral asymmetric distribution. Cerebral spinal fluid should be evaluated for infectious causes, IgG index, and oligoclonal bands. In pediatrics, given the infrequency of MS, more comprehensive testing to distinguish MS from the other disorders in the differential should be pursued. Antimyelin oligodendrocyte glycoprotein antibodies may be elevated in patients with recurrent optic neuritis [160].

The International Pediatric Multiple Sclerosis Study Group criteria for diagnosing pediatric multiple sclerosis was published in 2013 and differentiated it from ADEM [161–163]. The McDonald criteria were published to simplify the use of neuroimaging in the diagnosis of multiple sclerosis.

Management

There are no approved guidelines for treating pediatric optic neuritis. Although steroids have not been proven to improve final outcomes in pediatric optic neuritis, patients usually receive 3–5 days of intravenous steroids followed by a slow oral taper over 4–6 weeks for quicker recovery from acute attacks [164]. Faster tapers may result in a quick relapse.

Resistant patients may require an additional course of intravenous steroids, intravenous immunoglobulin, and/or plasmapheresis. Patients should be followed every 3 months [159]. Immunomodulatory agents such as glatiramer acetate and interferon beta are used for long-term treatment, though there have been no randomized controlled trials evaluating these therapies in pediatric MS. In addition to immunomodulatory agents, other agents may be used to care for the specific needs of individual patients such as depression, fatigue, and cognitive impairment.

Neuromyelitis Optica

Definition

Neuromyelitis optica (NMO, also known as Devic disease) is an inflammatory central nervous system disorder characterized by demyelination and axonal damage mainly targeting the optic nerves and spinal cord. The serum NMO-IgG antibody binds to aquaporin-4 (AQP4) resulting in this disease's unique immunologic features.

History

Devic and Gault first described NMO in 1894. They described patients with bilateral optic neuritis and myelitis [165, 166]. Since first described, variation in the features, clinical course, and prognosis has broadened our understanding of NMO.

Epidemiology

The prevalence of NMO ranges from 0.5 to 4 per 100,000 people [167–171]. Women are 10 times more likely than men to be diagnosed with recurrent NMO. The median age of onset is 32–41 years, though cases have been reported in younger and older patients. In one study of pediatric patients presenting with a first episode of optic neuritis, 52 % were associated with an underlying diagnosis (39 % multiple sclerosis, 7 % acute disseminated encephalomyelitis, and 7 % neuromyelitis optica) [171].

Systemic Manifestations

NMO is characterized by acute attacks of bilateral optic neuritis and transverse myelitis. Transverse myelitis can follow optic neuritis. It often causes limb weakness, sensory abnormalities, and bladder dysfunction. The optic neuritis leads to vision loss. Attacks usually occur over days and recover over weeks to months. Other symptoms include intractable vomiting, daytime somnolence, narcolepsy, and neuroendocrine disorders.

The natural history of NMO is a progressive deterioration from recurrent attacks. An older age of onset is associated with a worse prognosis. Mortality rates are most often secondary to neurogenic respiratory failure. The visual prognosis for optic neuritis in patients with neuromyelitis optica is worse than the visual prognosis in patients with multiple sclerosis [172]. In the long term, this disease leads to severe bilateral visual impairment [173].

Brain lesions in NMO patients occur more commonly in the pediatric population (>50 %) compared to the adult population (25 %). When looking at the pediatric population, one series reported that more patients present with optic neuritis (75 %) than with transverse myelitis (30 %). This same series showed that most cases were relapsing (90 %). Of the 20 children in this cohort, 3 were wheelchair dependent and half had visual impairment [174].

Ophthalmic Manifestations

Optic neuritis may present with a range of vision loss and eye pain. The majority of optic neuritis attacks in NMO are bilateral in children. Sequential optic neuritis in rapid succession is also highly suggestive of NMO [175].

Optical coherence tomography (OCT) has shown greater thinning of the retinal nerve fiber layer in patients with NMO compared to patients with multiple sclerosis. NMO patients with a history of optic neuritis may also develop microcystic macular edema of the inner nuclear layer [176, 177]. Further studies are needed to determine if differences in retinal nerve fiber layer thickness can be used as an early diagnostic marker for NMO [178].

Diagnosis

Clinical, imaging, and laboratory data can confirm the diagnosis of NMO. In 2006, Wingerchuck et al. proposed diagnostic criteria for NMO [163]. Patients must have optic neuritis, myelitis, and two of three supportive criteria. Supportive criteria include MRI evidence of a contiguous spinal cord lesion, no MRI evidence of multiple sclerosis,

and serum NMO-IgG antibodies (also known as AQP4 antibodies). Of note, MRI of the brain may show enhancement of the optic nerves in addition to lesions elsewhere in the brain. In addition to these studies, cerebrospinal fluid may show elevated protein levels and pleocytosis. There may or may not be oligoclonal bands in the cerebrospinal fluid studies. NMO antibodies can be found in the CSF or serum, but they can often be negative on initial evaluations. If the clinical suspicion for NMO is high and the initial labs are negative, these should be rechecked during subsequent evaluations.

In the future, OCT may prove to be helpful for diagnosis, and also may be helpful for monitoring disease course.

Management

Acute attacks are treated with intravenous glucocorticoids. Refractory or progressive symptoms are treated with plasmapheresis. Immunosuppression with drugs such as azathioprine, rituximab, and mycophenolate mofetil, is used to prevent recurrent attacks. Increased understanding of the pathogenesis of NMO has led to the development of novel therapies such as targeted non-immunosuppressive AQP4-IgG blocking therapies, cytokine modulators, and complement inhibitors. These novel therapeutic strategies may lead to a more promising prognosis for patients in the future [179]. Treatment of pediatric NMO requires an individualized regimen to optimize the frequency and dosage of therapeutic agents while minimizing overtreatment [180].

Autism Spectrum Disorder

Definition

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by core deficits in two domains: social communication and restricted interests and repetitive behaviors [181]. The skill deficits range along a spectrum and can, at times, be difficult to diagnose. This can be especially difficult if there are other comorbid diagnoses present. This diagnosis is only applicable if there are signs of the syndrome from a very young age, although it may not be apparent to the family or clinician for several years, until the social demands exceed the skill set of the individual.

The DSM 5 [181] defines diagnostic criteria for ASD as the following:

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history
   1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):
   1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
   3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
   4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and ASD frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

History

Autism spectrum disorder was first described in 1943 by Leo Kanner, a psychiatrist from Austria who worked at Johns Hopkins Hospital. His paper, "Autistic Disturbances of

Affective Contact" described several children with similar symptoms, primarily without the drive to be social [182]. In addition to the difficulties with engaging socially, Kanner described other difficulties including insistence on sameness and the symptoms of self-stimulatory behaviors were related to attempts by the child to maintain sameness [182]. In 1944, Hans Asperger, a physician from Vienna, described boys who had normal language development but were also socially impaired [183]. Asperger's report had several overlapping features to Kanner's description including insistence on sameness, unusual sensory responses, and all levels of intelligence.

The *Diagnostic and Statistical Manual of Mental Disorders* has included ASD since the third edition as its own diagnostic category. However, the diagnostic criteria have changed slightly throughout each of the revisions and now encompasses several previous diagnoses including autistic disorder, Asperger syndrome, and Pervasive Developmental Disorder-Not Otherwise Specified. Those who previously were diagnosed with these three diagnoses under the previous DSM IV-TR criteria are now re-categorized to ASD.

Epidemiology

Autism spectrum disorder is the second most common neurodevelopmental disorder in the United States [184]. While initially this disorder was thought to be an interesting clinical conundrum, it is now recognized as a large and growing population of individuals with varying degrees of needs. The most recent data from the Centers for Disease Control specifies the rate of ASD of 1 in 68 children aged 8 years old according to data collected in 2010 [185]. This number is higher than previous data from 2005 which indicated that ASD was only 1 in 88 children. There are 1 in 42 boys diagnosed with ASD which is nearly five times the prevalence of diagnosis for girls at a rate of 1 in 189 girls [185]. These numbers are the prevalence for the United States although these rates are somewhat similar in other countries. South Korea has a prevalence of 2.6 % in children 7–12 years old and other countries have rates between 1 and 2 % as well [186, 187].

Systemic Manifestations

Autism spectrum disorder affects many aspects of an individual's life. The social communication and restricted interests and repetitive behaviors can cause difficulties in the individual's interaction with their environment and others around them. However, other symptoms are not specific to ASD and can be complicated by the central features of autism spectrum disorder.

Compared to the general population, children with ASD are at higher risk for sleep disorders, constipation, seizure disorders, and motor clumsiness.

Sleep disorders are common in the general population. However, children with ASD have high rates of sleep disorders as well. Sleep disorders can be behavioral, or may be caused by medical conditions, including abnormal melatonin regulation [188].

Few studies have included appropriate control groups to determine the prevalence of constipation in children with ASD [188]. However, one study showed a prevalence of abnormal stool patterns including constipation in 70 % of children with ASD, 42 % in children with developmental delay, and only 28 % in typically developing children [189].

Seizures are more common in children with ASD than in the general population (5–30 % prevalence of epilepsy, vs. 2–3 %, respectively) [190]. This is due in part to the increased association of ASD and genetic conditions such as tuberous sclerosis and Rett syndrome [190]. It can be difficult to diagnoses seizures in children with ASD as several features of this disorder may be mistaken for seizures (staring spells and stereotypies) and several features of epilepsy may be mistaken for features of ASD (failing to respond to one's name, or tic-like movements) [190].

Asperger noted in his first paper that children with the syndrome he described had poor motor movements and tended to be clumsy [183]. This same finding of poor motor control was also described by Kanner in his discussion of infantile autism [183]. Motor control and clumsiness has frequently been cited by the literature as a common finding, however, it does not manifest homogenously [191]; gait and balance, motor planning, and/or arm motor functions can all be affected in individuals with ASD [191].

Ophthalmic Manifestations

Ophthalmologic disorders frequently occur in children with ASD. Ophthalmic pathology has been reported in the literature to occur in 27–68 % of children with ASD [192, 193] The most common manifestations include significant refractive error (22–29 %), strabismus (8.6–60 %) and amblyopia (10–11 %) [192, 194–196] As the prevalence of strabismus, amblyopia, and significant refractive error are higher among patients with ASD than the general population, regular ophthalmologic evaluation is of particular importance.

In addition to these relatively common ocular abnormalities, rarely seen ocular manifestations of vitamin A deficiency including xerophthalmia and rod-predominant retinopathy have been reported in the setting of autism and food faddism [197–200]. Providers should be cognizant of the possibility of this otherwise infrequent presentation within this population due to behavioral risk factors.

A large body of literature describes abnormal sensory processing in ASDs and many accounts describe both hyper and hyposensitivity to sensory stimuli [201]. Extensive research has been devoted to ascertaining possible visual differences in ASD and typical control populations. Although patients with ASD were initially thought to have superior visual acuity [202], more recent studies have found no difference in binocular visual acuity between adults with and without ASD

[203, 204]. Oculomotor dysfunction including abnormal saccades has also been suggested but not confirmed and may be related to shorter fixation duration identified in individuals with ASD [205, 206]. Motion perception has also been an area of great interest within ASD with early studies arguing for impaired motion processing [207] while later studies have been more equivocal [208]. There is significant evidence that individuals with ASD have different visual attention to human faces including reduced attention to the central face (particularly the eyes) with prolonged fixation to the mouth [209, 210] as well as lower face-recognition performance [211]. Finally recent studies looking at pupil changes in response to visual stimuli have demonstrated differences in baseline pupil size, transient pupillary light reflex and pupillary responses to faces in populations with ASD as compared to controls [212–215]. These differences in pupillary responses have been suggested as an index of emotional reactivity [216]. The significance of these findings is not yet clear but may help to shed light on altered sensory processing and neurodevelopmental differences in ASD.

Diagnosis

As described above, the DSM-5 delineates criteria for ASD. It should be noted that previous diagnoses of pervasive developmental disorder and Asperger syndrome now fall under ASD and periodic reevaluation is not required to maintain the diagnosis of ASD [217].

Both history and observations must be present to qualify for a diagnosis of ASD. As described in the diagnostic criteria, symptoms must be present from an early age. However, sometimes the symptoms are not noticeable until later when social demands outstrip the child's ability to cope [217]. The Autism Diagnostic Interview—Revised (ADI-R) is an interview based on the diagnostic criteria for ASD and may be used to obtain relevant history to support or rule out a diagnosis [218]. This tool can be used to collect data about a child's early history and current history based on the criteria for autism spectrum disorder. However, this tool may take at least 1.5 h to complete [218] and can be quite bulky. A semi-structured interview that covers the diagnostic criteria may be used to diagnose ASD in lieu of the use of the ADI-R.

In addition to history, behavioral observation is required to make a diagnosis of ASD. This can be completed by using the Autism Diagnostic Observation Schedule—2nd edition (ADOS-2). The ADOS is a semi-structured tool that standardizes behavioral observations that distinguish autism spectrum disorder from other developmental disabilities and typical children [219]. There are now four different modules that are based on age and language level of the child, adolescent or adult [220]. There are several activities that pull or press for social communication skills, restricted interests, repetitive behaviors, play, and other behaviors including anxiety and ADHD [219, 220]. These observed behaviors are scored, and an algorithm helps determine likelihood of the diagnosis of autism spectrum disorder [220]. Therefore, the use of the ADOS-2 for behavioral observations and ADI-R or other autism symptom interview each aid in the diagnosis of ASD.

Management

The management of children with ASD is based on gaining behavioral and developmental skills and symptom management. ASD is chronic, and management of symptoms and core deficits is key. The primary goals for management include maximizing skills for independence, treating symptoms, and family support [188]. The individual child's strengths and skill deficits will determine the needed supports. Examples of therapies and supports required for children and adults with ASD include behavior therapy using principles of Applied Behavioral Analysis, speech-language therapy, social skills training, occupational therapy, physical therapy, educational intervention, management of comorbid conditions and systemic symptoms, and psychopharmacology [188]. Early identification and intervention has been shown to be instrumental in maximizing skills [188]. While there is no "cure" for ASD and most children will carry this diagnosis and core deficits throughout their lifetime, symptoms can be managed and coping skills can be learned, and some children may no longer meet criteria for autism spectrum disorder after supports have been in place.

Management of ophthalmic manifestations including correction of significant refractive error, treatment of amblyopia, and strabismus surgery when indicated should be pursued in children with ASD as in other populations. Difficulties with social interactions, verbal and non-verbal communication as well processing sensory stimuli may make cooperation with eye examinations more difficult in individuals with ASD. However, a small study demonstrated good testability within an examination protocol on vision and eye tests [221]. Regular eye examinations should be performed due to the increased risk of ophthalmologic disorders in ASD.

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Phakomatoses-Neurocutaneous Syndromes

16

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Introduction

The phakomatoses represent a heterogeneous group of neurocutaneous syndromes collectively arranged on the basis of congenital origin, presence of hamartomas in multiple organ systems including skin and central nervous system and primarily dominant heredity [1]. Van der Hoeve described the ocular findings associated with neurofibromatosis and tuberous sclerosis [2]. He coined the term phakomatoses (phakos, "mother spot", Greek) to collectively describe the recognized neurocutaneous syndromes of the time, neurofibromatosis, tuberous sclerosis and cerebroretinal angiomatosis [3]. Encephalotrigeminal angiomatosis was later added to the traditional classification [3]. Several other less common conditions sometimes classified as phakomatoses are ataxia-telangiectasia, incontinentia pigmenti, racemose angioma and hemangiectatic hypertrophy or angioosteohypertrophy syndrome. These conditions with their eponyms are noted in Table 16.1 [4–9]. Each phakomatosis is recognized as a distinct clinical disorder and most have specific genetic markers. Rarely, patients can exhibit more than one neurocutaneous syndrome [10–20], perhaps purely as a chance association or possibly because of an ill-defined inter-relationship between the various phakomatoses.

Hamartomas are tumors composed of cells normally present in the involved tissue. For example, the vascular tumors associated with encephalotrigeminal angiomatosis arise from blood vessels normally found at the involved site. Similarly, the glial retinal tumors seen in neurofibromatosis and tuberous sclerosis arrive from astrocytes normally present in the retina. In contrast to hamartomas, choristomas are composed of cells not normally present at the involved site. Limbal and orbital dermoids are the most common choristomas seen by ophthalmologists.

Ocular involvement occurs frequently in the phakomatoses. Recognition of characteristic eye lesions in the context of related skin and systemic abnormalities may be crucial to making the diagnosis of a specific neurocutaneous syndrome [5]. Also, ocular involvement in these conditions may at times lead to blindness, especially without early diagnosis and treatment. The purpose of this chapter is to review the ophthalmologic and systemic findings characteristic of these neurocutaneous syndromes, commonly termed phakomatoses.

Neurofibromatosis

The neurofibromatosis are a diverse group of genetic conditions consisting of three subgroups: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and schwannomatosis. Schwannomatosis, originally reported as neurofibromatosis type 3 is a rare form of neurofibromatosis characterized by multiple cutaneous neurilemmomas and schwannomas but without characteristic ocular lesions, acoustic tumors or other signs of NF1 or NF2, and therefore will not be further discussed in this chapter [3, 21, 22].

NF1 and NF2 patients have characteristic melanocytic and neuroglial cell lesions derived from neural crest mesenchyme tissue [23]. These lesions are characterized as hamartomas but may be indistinguishable histologically from low-grade neoplasms. NF1 and NF2 have significant genetic, clinical and management considerations which will be addressed in this chapter.

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Table 16.1 The Phakomatoses

Name	Eponym
Neurofibromatosis	von Recklinghausen disease
Tuberous sclerosis	Boumeville disease
Cerebroretinal angiomatosis	von Hippel–Lindau disease
Encephalotrigeminal angiomatosis	Sturge–Weber syndrome
Less accepted	
Ataxia telangiectasia	Louis–Bar syndrome
Racemose angiomatosis	Wyburn–Mason syndrome Bonnet–Dechaume–Blanc syndrome
Angioosteohypertrophy or Hypertrophic haemangiectasia	Klippel–Trenaunay–Weber syndrome
Incontinentia pigmenti	Bloch–Sulzberger syndrome

Neurofibromatosis Type I

Definition

Specific diagnostic criteria were established for Neurofibromatosis Type I at the National Institute of Health consensus conference in 1988 (Table 16.2). The individual associated physical features can be determined by a combination of clinical inspection and specific tests (see Diagnostics below). Initial examination can reveal café au lait macules, skinfold and axillary/inguinal freckling as well as Lisch nodules, which are pathognomonic for NF1 [31].

Because family history is a diagnostic criterion, the majority of familial cases are clinically identified by 1 year of age. Almost all de novo cases are clinically apparent by 8 years of age [32].

NF1 is caused by a mutation in the NF1 gene located (17 q11.2). Neurofibromin interacts with Ras leading to increased downstream activation of mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) signaling. These pathways are related to the increased tumorgenesis and glial proliferation seen in affected individuals. Current testing identifies ~95 % of the mutation, with the majority (>90 %) of these resulting from sequence variants. An additional 4–5 % are detectable via deletion/duplication analysis, and <1 % via cytogenic analysis of larger scale rearrangements.

History

Dr. Robert William Smith first described this disease in 1849 in his "A Treatise on the Pathology, Diagnosis and Treatment of Neuroma" [24]. This work received little attention in the medical community which resulted in *multiple neurofibromatosis* becoming synonymous with the brilliant German pathologist von Recklinghausen who described the main features of this nosological entity in his classical paper of 1882 [25].

Table 16.2 Diagnostic criteria for neurofibromatosis type I

Two or more of these features are necessary to meet the diagnostic criteria
• Six or more café au lait macules (>0.5 cm in children or >1.5 cm in adults)
• Two or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
• Axillary or groin freckling
• Optic pathway glioma
• Two or more Lisch nodules (iris hamartomas seen on slit lamp examination)
• Bony dysplasia (sphenoid wing dysplasia, bowing of long bone ± pseudarthrosis)
• First degree relative with NF1

NIH consensus development conference 1988

Epidemiology

The incidence of NF1 is estimated to be approximately 1 in 2500–3500 births [26, 27]. As such, it is the most common single-gene disorder affecting the nervous system. There is no sex or race predilection. The disease is inherited through an autosomal dominant inheritance with almost 100 % penetrance [28] and variable expressivity. Approximately 50 % of cases are sporadic, likely from new mutations [29].

A diagnosis can still be established without molecular confirmation (Table 16.2) [30]. Half of all cases result from a de novo mutation, while the other half are familial.

Systemic Manifestations

Cutaneous involvement in NF1 may result from **melanocytic** or **neuroglial** cell involvement or a combination of both neural crest mesenchyme sources. The principal cutaneous lesions are cafe-au-lait spots and neurofibromas of both the diffuse and plexiform type. Cafe-au-lait spots are flat, uniformly hyperpigmented lesions, with sharply demarcated borders of varying size and shape. They are usually present on the trunk, but may occur anywhere on the body. Cafe-au-lait spots are often the earliest clinical sign to present (Fig. 16.1). Histopathologically, the cafe-au-lait spots reveal hyperpigmentation resulting from an increase in the total amount of melanin, scattered, abnormally large melanin granules, and an increased concentration of melanocytes which are metabolically more active [33]. Whereas normal individuals may have 1–3 café au lait spots, the majority of NF1 patients will have 6 or more café au lait spots. The number of cafe-au-lait spots increases through childhood and puberty, followed by a period of relative stability which in turn is replaced by a decrease in pigmentation [26]. Clusters of small cafe-au-lait spots and/or freckling in the axillae or groin regions is highly supportive of the diagnosis, this has been termed "Crowe's sign" (Fig. 16.2) [34].

Fig. 16.1 Multiple café' au lait macules

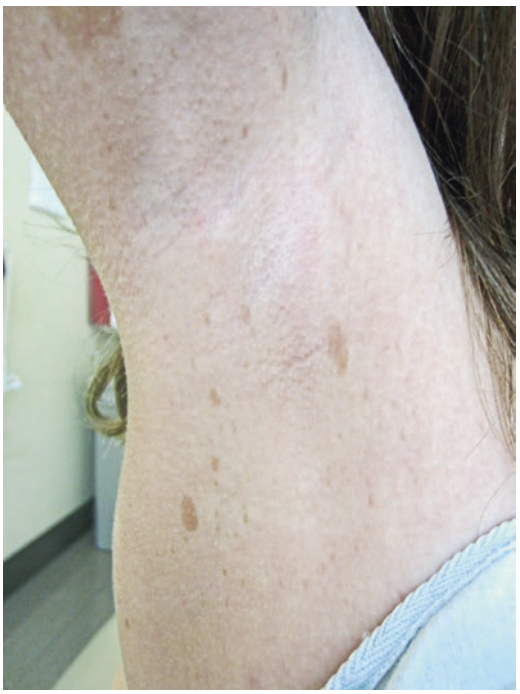

Fig. 16.2 Axillary freckling, Crowe's sign

The most common neuroglial NF1 lesions are the neurofibromas and optic pathway gliomas. Neurofibromas rarely occur as an isolated solitary non-NF1 lesion. They are

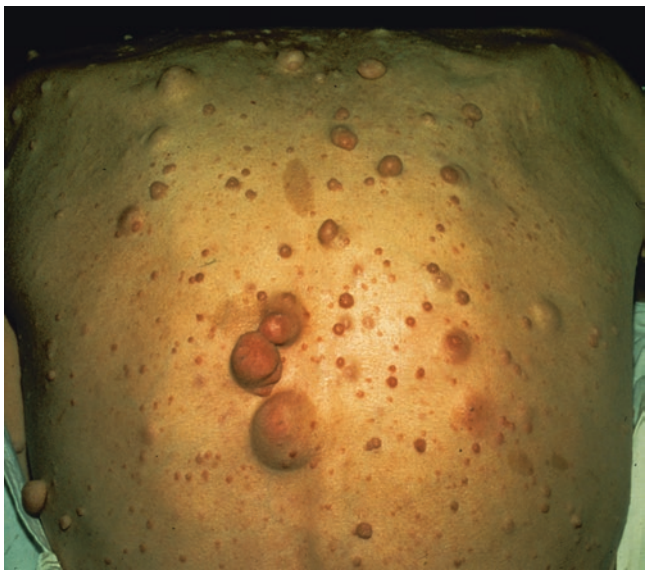

Fig. 16.3 Diffuse cutaneous neurofriboma (Courtesy Dr Frank Judisch collection U of Iowa)

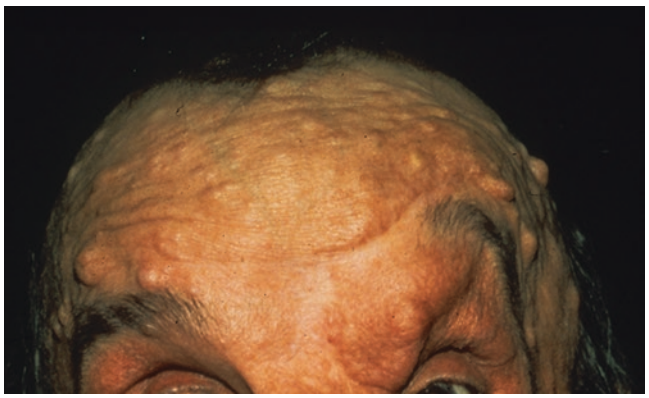

Fig. 16.4 Diffuse cutaneous neurofibroma (Courtesy Dr Frank Judisch collection U of Iowa)

present in 30–50 % of NF1 patients. Neurofibromas are benign Schwann cell tumors that arise from the fibrous tissue surrounding peripheral nerve sheaths and are composed of Schwann cells, fibroblasts, perineural cells, and mast cells, classified according to their appearance and location: focal or diffuse cutaneous, subcutaneous, nodular or diffuse plexiform and spinal [35]. The multiple cutaneous tumors of NF1 in most cases appear in late childhood/adolescence and gradually increase in size and number through adulthood. They are usually skin-colored, and are either semiglobular or pedunculated (Figs. 16.3 and 16.4) [33].

Optic gliomas are the most common intracranial tumor (see Ophthalmic Manifestations); however other low grade gliomas may also be found in addition to other radiographic abnormalities.

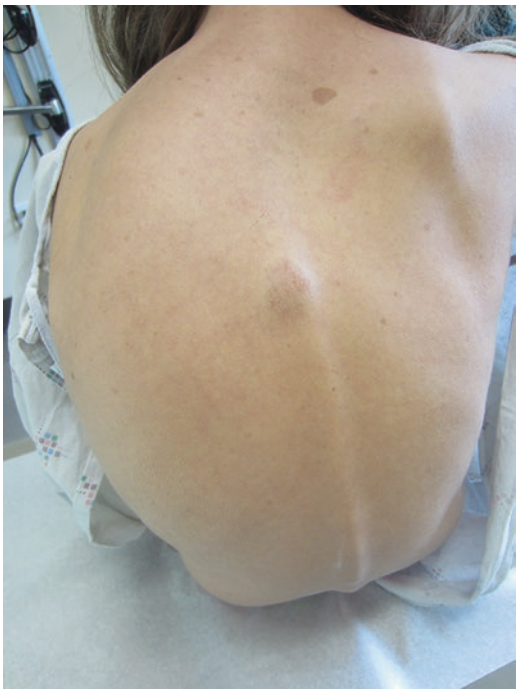

Fig. 16.5 Multiple café' au lait macules with plexiform neurofibroma

Plexiform neurofibromas, arise from multiple nerve fascicles, and tend to grow along the length of the nerve. The diffuse proliferation within the nerve sheath produces a grossly thickened and tortuous nerve [9]. They usually have a soft consistency, often described as like a "bag of worms" [8]. They may involve multiple nerve branches and plexuses potentially causing significant morbidity. These lesions can appear in the skin as an irregularly bordered patch or finely papillated plaque, sometimes with coarse terminal hair growth overlying (Fig. 16.5). Since plexiform neurofibromas extend into surrounding structures including skin, fascia, muscle, bone, and internal organs, they may cause pain. The neurofibromas may become large and disfiguring. Enlargement of a particular part of the body with neurofibromatosis is called elephantiasis neuromatosa, representing a diffuse proliferation outside the nerve sheath [9]. Approximately 50 % of patients with NF1 develop plexiform neurofibromas, and they are most often internal without associated cutaneous manifestations. They tend to be slow-growing, although occasionally rapid growth has been noted (particularly in early childhood) [36, 37].

Patients with plexiform neurofibromas and persistent pain lasting greater than 1 month, significant sleep disruption, new or unexplained neurologic deficit, or rapid increase in neurofibroma size should prompt evaluation for a malignant peripheral nerve sheath tumor (MPNST) [35, 37, 38]. A malignant peripheral nerve sheath tumor, (previously described as "Malignant schwannoma," "Neurofibrosarcoma," and "Neurosarcoma") is a cancer of the connective tissue surrounding nerves. Given its origin and behavior it is classified as a sarcoma. These tumors usually arise from pre-existing plexiform neurofibromas but a minority (36 %) arise de novo [38, 39]. The lifetime risk for an MPNST in patients with neurofibromatosis type 1 is 8–13 % [38]. About half the cases are diagnosed in people with neurofibromatosis. The median age of diagnosis of this tumor in NF1 is 26 years, with a 5-year survival rate of 21 % (lower than observed in sporadic cases of MPNST) [38].

Besides MPNST and optic pathway gliomas, NF1 remains a risk factor for development of other tumors and malignancies. There is a predilection for low-grade gliomas in the brainstem and cerebellum, as well as the tectum (dorsal midbrain). Compared to sporadic occurrences of these tumors in children without NF1, there is a possibility of spontaneous regression. Therefore, treatment is typically reserved for symptomatic tumors or concerning radiographic progression. The reported incidence of malignant transformation of neurofibromas ranges between 2.4 % and 16.5 % [40, 41]. Malignant transformation occurs most commonly in neurofibromas of large nerve trunks and only rarely in cutaneous neurofibromas [42]. There is an increased risk for both gastrointestinal stromal tumors and a 3.5-fold incidence in rates of breast cancer (with increased likelihood of diagnosis before age 50 years) [43]. There are several reports of rare NF1 associations with juvenile xanthogranuloma and juvenile myelomonocytic leukemia, a rare malignancy. Juvenile xanthogranulomas present as small pink papules, gradually becoming yellow/orange in color over time and eventually spontaneous involute, over the time course of several years. NF1 patients with juvenile xanthogranuloma are at significantly higher risk (20–32 times higher) of developing juvenile myelomonocytic leukemia than the general population [44].

Academic difficulties and school failure are the most common reported complication of NF1, with ~50 % of children performing poorly on tasks in reading, spelling, and mathematics. Formal neuropsychologic testing identifies an intellectual disability (FSIQ < 70) in ~7 %. An additional 20 % were diagnosed with a specific learning disability. Other neurocognitive problems are more prevalent, as almost 2/3 demonstrate difficulties with attention, with 38 % meeting criteria for a diagnosis of attention deficit-hyperactivity disorder (ADHD). The most consistent areas of difficulty were within the domains of visuospatial/perceptual skills, executive functioning, and attention. Language was less significantly impaired, and memory was relatively preserved [45]. NF1 patients also have a higher incidence of autism spectrum disorders, behavioral abnormalities and psychosocial issues [35].

Macrocephaly in the absence of hydrocephalus, is present in 30–50 % of children with NF1. MRI of the brain identifies diffuse enlargement of both grey and white matter (including

corpus callosum), suggesting that macrocephaly is driven by megencephaly. There is no apparent correlation between brain volume and cognitive ability [46]. There is also evidence that optic pathway gliomas are associated with macrocephaly significantly more often when compared to NF1 patients without optic pathway gliomas [47].

Headaches are another common neurologic manifestation, with 61 % of individuals reporting recurrent headaches (90 % of these with one or more headaches/month), and the majority of these individuals reported onset before the age of 10 years. One-third of individuals with recurrent headache had migraineous features (nausea, photo/phonophobia, throbbing/pulsatile quality, and/or visual scotoma). Migraine was more common with adolescents, but was also seen at a high rate in children <10 years (25 %). The majority of individuals did not have intracranial pathology that could potentially account for headache symptoms, with <3 % having either tumor or hydrocephalus. The majority of these individuals did have non-specific radiographic changes that were felt not to be related [48].

Seizures have been reported in ~10 % of individuals, with confirmed epilepsy in 6 % [49, 50]. The majority of these cases present during childhood (77 %). At least one quarter of those with seizures had intracranial tumors (dysembryoplastic neuroepithelial tumor, low-grade glioma) other than optic pathway gliomas, and some of these neoplasms were new findings compared to prior neuroimaging. The majority of seizures are focal in onset, although some individuals have had a primary generalized epilepsy syndrome (including childhood absence epilepsy, juvenile myoclonic epilepsy) [49].

Myelin vacuolization (also called spongioform myelinopathy, formerly 'unidentified bright objects' or UBOs) is often incidentally identified on MRI brain, and registers as T2 hyperintense signal, most commonly in the brainstem, basal ganglia, thalamus, and cerebellum. They increase in number in early childhood with a natural history of spontaneous remission in adolescence; this finding is considered rare after the age of 20 years. These do not evolve into tumors, and as such, do not exert any mass effect. These generally do not correspond to clinical symptoms, and the incidence is similar in individuals with NF-1 (~70 %) irregardless of the presence of seizures [50]. T2 hyperintense lesions in other locations (cortical, juxtacortical) should prompt consideration of low grade tumor or developmental dysplasia rather than presumed myelin vacuolization [50, 51]. The number and distribution of T2 hyperintensities does not correlate with cognitive disability; however, well defined, discrete lesions in the thalamus (seen in ~8 % of children with NF1) are associated with global intellectual dysfunction, with mean FSIQ 18 points lower than the general NF1 population [52].

The osseous manifestations of NF1 may consist of either intraosseous neurofibromatosis or erosive defects caused by the pressure of adjacent neurofibromas on bone. Scoliosis affects 10 % to 26 % of patients [53]. The most severe form, dystrophic scoliosis, occurs in fewer than 10 % of patients but is marked by earlier onset, rapid progression and need for early spinal fusion with potential for spinal cord compression [54–56]. Spinal dislocation has been described [57]. As a result of spinal cord compression, patients may suffer from bladder and bowels dysfunction as well as limb paralysis [58]. Although nonspecific bone lesions such as increased length of long bones may occur, decreased height is more of a concern with 14 % of NF1 patients two standard deviations below the mean height for chronological age [59, 60].

NF1 has been associated with congenital bowing of the tibia and subsequent pseudoartbrosis or "false joint" formation from repetitive fracture and poor healing [61]. This long bone tibial dysplasia is typically identified in infancy and manifests as anteriolateral bowing of the leg secondary to cortical thinning and pathologic fractures with weight bearing [62].

Cardiovascular disease is an important consideration in the evaluation of NF1 patients. Vasculopathy, hypertension and congenital heart disease are the principal considerations. Vasculopathy, which includes stenosis, aneurysm and arteriovenous malformations, ranks as the second leading cause of death in NF1 [63]. Renal artery stenosis, the most common vasculopathy, is estimated to occur in at least 1 % of patients. Therefore, any NF1 patient with hypertension should have consideration for renal arteriography [64]. Cerebrovascular disease is another important vasculpathic consideration with pathology resulting from stenosis or occlusion. Patients with sudden onset neurologic changes or a history of headaches, weakness, seizures or involuntary movements should be evaluated for cerebrovascular disease [64]. The underlying histopathology lesion for both the renal artery stenosis and the cerebrovascular lesions show fibromuscular dysplasia with intimal thickening and proliferation of Schwann sells without atherosclerosis [63, 64].

Hypertension in NF1 patients is most frequently caused by renal artery stenosis. Other possible differential considerations are coarctation of the aorta and pheochromocytoma. Pheochromocytomas occur in 0.1–5.7 % of patients with neurofibromatosis [65]

Congenital heart disease occurs at a higher frequency for NF1 patients than noted in the general population. Pulmonary artery stenosis represents 25 % of the congenital heart disease lesions [64]. Murmurs require cardiology and echocardiography evaluation [64]

Other clinical features of NF1 include hamartomas of the gastrointestinal tract which can cause gross hemorrhage, occult blood loss with chronic anemia and pain [66, 67]. Additionally, neurofibromas have been demonstrated in the bladder, mouth, larynx, renal artery and vagina [68, 69].

Table 16.3 Ocular manifestations of neurofibromatosis

Orbital
General
– Plexiform neurofibroma
– Neurilemoma (schwannoma)
– Proptosis
– Displacement of the globe
– Pulsation of the globe synchronous with pulse but no bruit
– Enlargement of the optic foramen
– Underdevelopment of the orbital bones
– Absence of the greater wing of sphenoid
– Optic nerve gliomas
– Neurofibromas of the ciliary nerves
Lids
– Ptosis
– Cafe-au-lait spots
– Neurofibroma of the eyelid
Extraocular
Conjunctiva
– Neurofibromata
– Thickening of the conjunctival nerves
Sclera
– Nodular swelling of the ciliary nerves
Intraocular
Anterior segment
– Nodular swelling of the corneal nerves
– Medullated/myelinated corneal nerves
– Posterior embryotoxon
– Unilateral keratoconus
– Glaucoma (congenital secondary)
– Dense abnormal tissue in the chamber angle
– Defects of Schlemm Canal
– Focal iris (Lisch) nodules/hamartomas
– Neurofibroma of the iris
– Congenital extropion uveae
– Iris neovascularization
Media
– Cataract
– Neurofibroma of the ciliary body
Choroid
– Choroidal ganglioneuroma
– Diffuse neurofibroma of choroid
– Diffuse and nodular involvement with thickening consisting of neurofibroma, fibroblasts, spindle cells containing pigment, ovoid corpuscles of convoluted nerve fibers
– Uveal malignant melanoma
– Choroidal nevi (multiple)
– Near infra-red detected choroidal lesions
Retina
– Hamartoma of the retina
– Cafe-au-lair spots of the retina
– Sectorial retinal pigmentation
– Sectorial chorioretinal scar
– Myelinated/medullated nerve fibers
– Typical peripheral retinoschisis
– Congenital hypertrophy of the RPE
Optic nerve
– Optic nerve drusen
– Hamartoma of optic disc
– Neurofibroma of the optic disc
– Primary optic atrophy due to tumor pressure
– Secondary atrophy due to papilledema
– Glioma of optic nerve head
Other
– Extraocular muscle palsies
– Strabismus
– Juvenile xanthogranuloma

Ophthalmic Manifestations

The effects of neurofibromatosis on the eye and ocular adnexae are diverse, involving virtually every conceivable structure (Table 16.3) [4, 6, 70]. Symptoms depend on the location and extent of the tumors.

Skin, Lids and Orbit

Eyelid abnormalities consisting of punctate neurofibroma, plexiform neurofibroma or café au lait spots of the lids occur in 25 % of NF1 patients [71]. The skin of the affected lids often has a brawny and bronzed appearance. Plexiform neurofibroma of the lid results in a characteristic enlargement producing an S-shaped deformity and proptotic appearance (Fig. 16.6) [72]. Patients may have significant facial asymmetry. Elephantiasis can result from involvement of the eyelids. "Box-like enlargement of the sella turcica" has been associated with thickening of the lids due to plexiform neurofibroma [73]. Other associated cranial orbital anomalies abnormalities include bony defects of the sphenoid bone and absence of the orbital roof. The defects in the bony walls of the orbit may be congenital or may be attributable to a secondary erosion by a neurofibroma [4]. Plexiform neurofibromas of the orbit can produce enlargement of the involved orbit. A non-expansile pulsating exophthalmos synchronous with the radial pulse and not associated with a bruit is characteristic. Pulsating exophthalmos not associated with carotid-cavernous fistula most often arises as a result of neurofibromatosis [73]. Proptosis in NF1 represents congenital absence/dysplasia

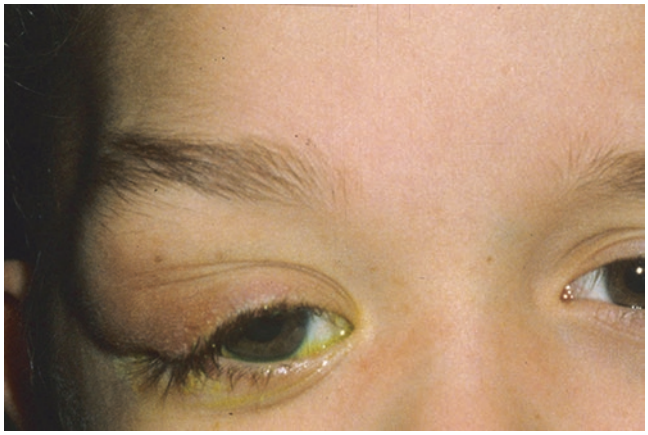

Fig. 16.6 Plexiform neurofibroma

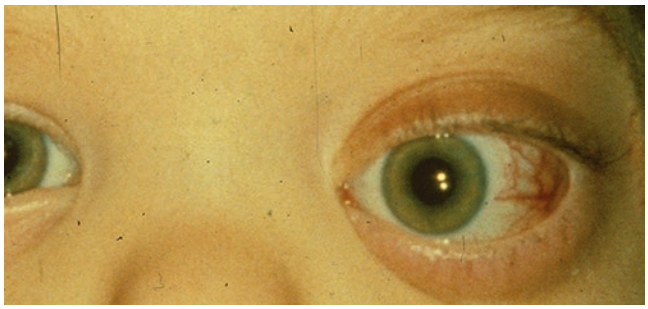

Fig. 16.7 Proptosis and strabismus from orbital tumor (Courtesy Dr Frank Judisch collection U of Iowa)

of the greater wing of the sphenoid bone, optic glioma or orbital neurofibroma (Fig. 16.7) [72]. Sphenoid wing dysplasia is most often detected in asymptomatic individuals as a unilateral defect affecting the orbital plate and frontal bone, although some patients have pulsating exophthalmos with cerebral herniation into the orbit [60, 62].

Orbital tumors not only produce proptosis but may result in decreased visual acuity, visual field defects, optic disc edema and atrophy, relative afferent pupillary defects and secondary strabismus.

Anterior Segment

Involvement of the anterior segment is common in neurofibromatosis. Hamartomatous conjunctival lesions have been described as painless salmon-pink growths on the bulbar surface which may infiltrate the cornealscleral limbus [73, 74]. Prominent corneal nerves are present in up to 25 % of patients, with posterior embryotoxin less frequent [72, 73]. Lisch nodules, melanocytic hamartomas, are the most characteristic iris findings [73]. They are typically multiple, bilateral and up to 2 mm in diameter (Figs. 16.8 and 16.9). These are present in 92 % of in NF1 patients over the age of 6 years [71]. The presence of Lisch nodules is correlated to age. They are found in 5 % of NF1 patients younger than 3

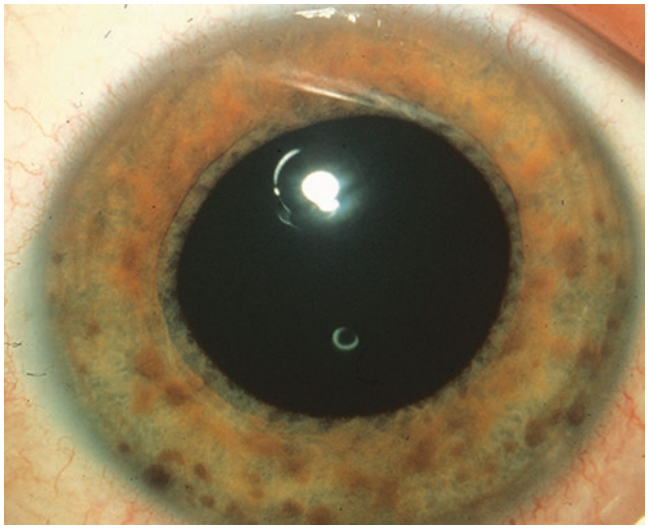

Fig. 16.8 Lish nodules (Courtesy Dr Frank Judisch collection U of Iowa)

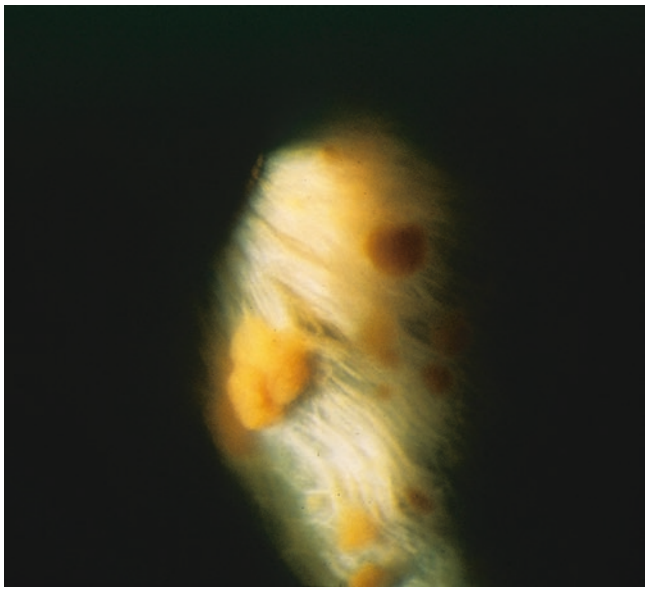

Fig. 16.9 Lisch nodules, high magnification (Courtesy Dr Frank Judisch collection U of Iowa)

years of age, 42 % of 3–4-year-olds, 55 % of 5–6-year-olds and virtually all adults over 21 years of age [75]. Their absence, particularly in children, does not exclude the diagnosis of neurofibromatosis.

Multiple juvenile xanthogranuloma lesions are transiently present in almost 40 % of children with NF1. They are difficult to diagnose and are often missed by clinicians other than dermatologists since the lesions disappear before 5 years of age [76]

Segmental neurofibromatosis, also called mosaic or localised neurofibromatosis, describes a person in which the signs for NF1 are limited to a particular area of their body. This affects one in 36,000 patients. Segmental neurofibromatosis

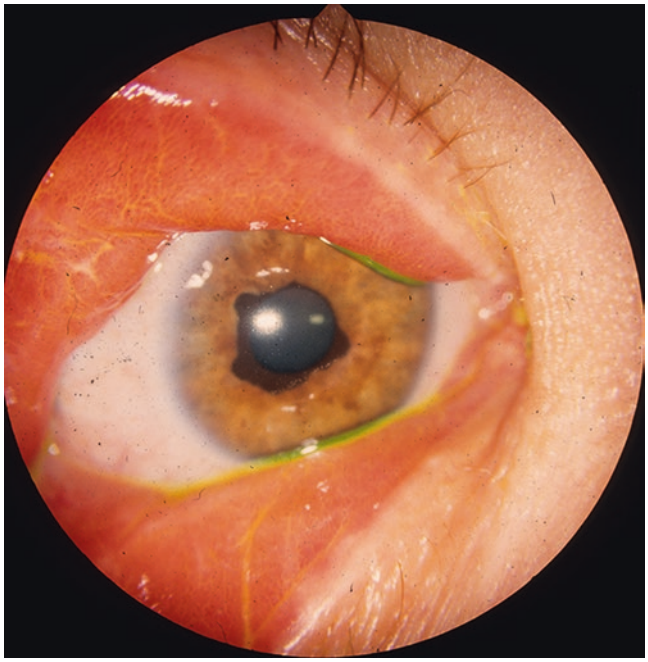

Fig. 16.10 Pupillary ectropion uveae

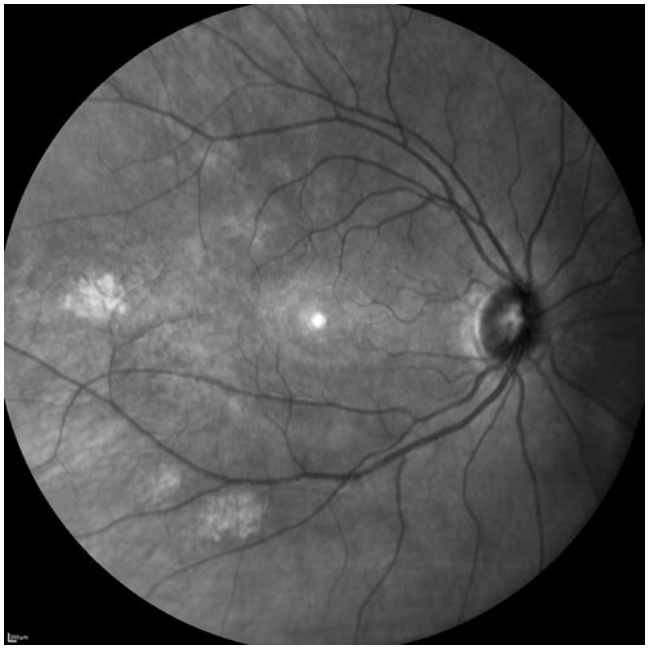

Fig. 16.11 Choroidal lesion posterior pole with near infrared reflectance OCT (Courtesy of Dr Alex V. Levin)

is generally thought to result from a postzygotic NF1 gene mutation [77]. In segmental NF1 the iris hamartomas are unilateral and ipsilateral to the side of cutaneous involvement when the eye is in the affected segment.

Glaucoma is infrequent in NF1 patients. It may be present at birth or as a juvenile glaucoma. Congenital ectropion uveae increases glaucoma risk and warrants continued observation for the development of glaucoma and disorders of neural crest origin (Fig. 16.10) [78]. Unilateral glaucoma has been documented in approximately 50 % of patients with plexiform neurofibroma of the ipsilateral upper lid and face [79]. The triad of unilateral buphthalmos and hydophthalmos, homolateral plexiform neuroma of the eyelid, and homo lateral facial hemi-hypertrophy has been termed the Francois syndrome [80, 81]. Glaucoma may be present at birth before any abnormality of the lid is observed [82]. Distinctive angle findings have been described as avascular dense, opaque, light brown tissue (resembling a Barkan membrane) covering and obscuring the angle structure in neurofibromatosis and childhood glaucoma [79].

Three main theories have been postulated to explain the glaucoma associated with neurofibromatosis: (1) obstruction to the outflow of aqueous humor by neurofibromatous tissue or by a developmental anomaly in the chamber angle; (2) closure of the angle by tumor involving the ciliary body and anterior choroid; and (3) a secondary fibrovascular membrane in the iridocorneal angle and the formation of peripheral anterior synechiae (neovascular glaucoma) [4, 79, 83].

Posterior Segment

Choroid and ciliary body neurofibromatosis changes may be found at routine autopsy in individuals without NF1 ocular symptoms [73]. Choroidal hamartomas may be single or multiple flat ill-defined lesions varying from yellow-white to light brown scattered throughout the posterior pole [71, 84]. Reports show the number of lesions varying from 1 to 18 and occurring in up to 51 % of patients studied [71]

Bright patchy choroidal lesions visible by infrared light confocal scanning laser ophthalmoscopy, iridocyanine-green fundus angiorgraphy and more recently infrared reflectance optical coherence tomography (OCT) have been found to be highly specific to NF1 patients [85–88] (Fig. 16.11). Interestingly, these lesions are not visible by traditional ophthalmoscopy, autofluorescence, fluorescein angiography or red-free testing [87]. The lesions increase in number over time and have an increased tendency to accumulate in the posterior pole between the arcades with an earlier appearance than Lisch nodules [86, 88]. They rarely occur in non NF1 subjects and typically one a solitary lesion would be found as compared to multiple lesions in NF1. There is no visual consequence from these choroidal lesions, but it has been suggested that they represent a new diagnostic criterion for NF1 [87, 88]

Uveal involvement may show diffuse neurofibroma thickening, consisting of a mixture of spindle-shaped Schwann cells and fibrocytes with variable number of melanocytes, ganglion cells and ovoid bodies [89]. The ovoid bodies consist of concentric layers of Schwann cells with nerves present [90, 91]. A limited number of eyes with diffuse

neurofibromatosis of the uvea have demonstrated a marked increase of plump dendritic melanocytes with the uveal melanocytes over shadowing the neurofibromatous elements. This has suggested these patients may have a higher incidence of malignant melanoma of the uvea than the general population [4].

A number of disparate retinal lesions occur in NF1. Lesions include large retinal astrocytic hamartomas, multiple retinal capillary hemangiomas, and combined hamartomas of the retina and retinal pigment epithelium, which may result in rubeotic glaucoma, vitreous hemorrhage, and retinal detachment [92]. Astrocytic hamartomas may cause retinal dialysis and retinal detachment [84]. Retinal vasoproliferative tumors are uncommon benign vascular tumors in NF1 that may result in vision loss secondary to retinal fibrosis, subretinal exudation and neovascular glaucoma [93]. Myelinated nerve fiber layers have also been reported in patients with neurofibromatosis but it is not clearly established that the frequency of occurrence is greater than the normal population [4, 73, 92].

Optic disc "tumors" have been described in NF1 patients [94–96]. These mulberry like masses involving the optic nerve head are not true glial neoplasms but histologically a hamartomatous malformation composed mainly of fibrillary astrocytes and frequently exhibiting dystrophic secondary dystrophic calcification [4]. Pathologically the lesion is a neuroma containing many cystic spaces and clefts consisting of groups of neurocytes and neurofibrils with areas of degeneration. Papilledema may be present as a result of increased intracranial pressure [73]. Optic atrophy develops when glioma occurs within the nerve or chiasm or it may result from long-standing papilledema or nerve compression by non intraneural tumor [73].

Optic pathway gliomas (OPGs) are the most common type of intracranial malignancy in patients with NF1 and typically consist of low-grade pilocytic astrocytomas [97]. Although considered a usually slow-growing, relatively benign neoplasm (astrocytoma) and considered by some to be a hamartoma, evidence suggests that optic pathway gliomas fall on a continuous scale from benign to malignant differentiation [98, 99]. NF1 OPGs appear more indolent and are more often located along the optic nerves as opposed to sporadic OPGs found more frequently in the chiasmal or postschiasmal regions [100, 101]. Most of these tumors develop in the first 6 years of life in approximately 15 % of children with NF1. Fifty to 75 % of patients are asymptomatic at time of diagnosis and approximately 30–50 % develop visual symptoms with the majority having a benign course [73, 97, 100, 102–104]. When symptomatic, OPGs can cause vision loss, visual field loss, proptosis and precocious puberty [60]. Chiasmal tumor involvement is associated with precocious puberty (12–40 % of children) from tumor expansion and hypothalamic encroachment [60, 101]

Strabismus, including congenital esotropia, partially accommodate esotropia, alternating esotropia, overacting inferior oblique muscles, and rotary nystagmus occur in approximately 10 % of patients with NF1 [103]

Diagnosis

Clinical criteria (Table 16.2) can establish a diagnosis of NF1 without confirmation by molecular genetics. Histopathology remains important for characterization of masses and other cutaneous manifestations. MRI and other functional imaging studies remain important adjuncts to evaluate for diagnostic findings, characterize/categorize abnormal findings, and potentially monitor growth. Neurofibromas are benign tumors consisting of Schwann cells, axons, fibroblasts, perineural cells, and mast cells [39, 105]. Cutaneous and dermal neurofibromas have characteristic appearances and typically appear during late childhood or early adolescence, rarely cause pain or neurologic deficits but may pose local discomfort or cosmetic disfiguration [106, 107]. Diagnoses are by means of clinical appearance or histopathology.

Although usually present at birth, plexiform neuromas develop from multiple nerve fascicles with growth along the length of the nerve in an unpredictable growth pattern and if located more internally may remain undetected for many years [36, 107]. The development of pain or a new neurologic deficit could represent either growth of an existing plexiform neurofibroma, but could also be the heralding signs of transformation to a malignant peripheral nerve sheath tumor (MPNST). This tumor typically presents with pain and/or rapid growth, with 38 % occurring internally without any cutaneous signs. MRI and PET scan may be useful in distinguishing the two; although a histologic diagnosis remains the gold standard. Specifically, MRI may be used to determine volumetric measurements of plexiform neurofibromas permitting tumor growth calculations, response to treatment or with monitoring for transformation into MPNST [36, 37].

Pediatricians in particular need a heightened awareness of the multiple skeletal associations with NF1. These include scoliosis, congenital bone defects leading to pseudoarthrosis, short stature, macrocephaly and sphenoid wing dysplasia [35]. Careful assessment of linear growth, head growth, spinal curvature and symmetry as well as early identification of limb anomalies with anterolateral bowing or repeated fractures are necessary.

Cardiovascular abnormality associations require specific diagnostic testing. NF1 patients should have a cardiac examination and blood pressure measurement at the time of diagnosis. Any sign of murmur or hypertension warrants a cardiologist evaluation with consideration of echocardiography [64]. Examination for possible renal artery stenosis as a cause of hypertension is necessary since this occurs in at least

1 % of patients with NF1, potentially requiring renal arteriography [64]. Additionally, since pheochromocytoma occurs at a higher rate in NF1 patients than the general population, catecholamine testing may be necessary [108]. Intracranial vascular disease evaluation should be considered for children with onset of headache, seizures, weakness, involuntary movements or any sudden onset neurologic deficit [63, 64].

Every patient with NF1 must have a complete ophthalmology examination. The characteristic skin lesions involving lids and face, café au lait macules, cutaneous and plexiform neurofibroma changes and proptosis or strabismus, should be recognizable through direct examination. Intraocular pressure should be measured to monitor for glaucoma. Biomicroscopy using the slitlamp will establish the presence of prominent corneal nerves and/or Lisch nodules. Careful dilated fundus examination should identify optic nerve changes such as edema or atrophy and presence of retinal lesions. Fundus photography, angiography and ocular coherence tomography (OCT) may need to be utilized to make an accurate diagnosis of characteristic lesions. Optic pathway gliomas demand special attention and consideration. Any evidence of visual acuity change, visual field loss or endocrine dysfunction would warrant MRI evaluation of the orbits and brain. Baseline MRI testing attempting to detect asymptomatic optic pathway gliomas is not indicated [101]. MRI studies for identification of unidentified bright objects [50, 51, 109] and OCT for identification for choroidal abnormalities may become instrumental in the diagnosis of NF1 [85–88]. Asymptomatic patients can be evaluated yearly. This is especially important for children less than 6 years of age when vision changes may not be recognized and they are at greatest risk for developing optic pathway glioma [97, 101].

Management

The skin freckling and café au lait macules may be followed since there is no tendency for malignant transformation. For those concerned with the appearance, cosmetic makeup and dermabrasion are available, but there is no strong recommendation for laser removal [107]. Neurofibromas may cause significant skin irritation and pruritus treated by antihistamine, mast cell stabilizers and emollients [107, 110]. Patients with cutaneous neurofibromas causing cosmetic disfigurement and discomfort may have removal by an experienced surgeon, but should be aware of the risk for increased scarring and tumor recurrence [107, 111]. Additionally, removal of subcutaneous neurofibromas and spinal neurofibromas may result in neurologic deficit with both sensory and motor components [107, 112].

Plexiform neurofibromas are more difficult to treat because of their diffuse infiltrative nature which may prevent successful resection. Local recurrence is common due to incomplete resections. Neurologic deficit related to surgical treatment remains a risk. There is evidence that early removal may prevent complications later in life and prevent the greater growth demonstrated in young children [36, 113]. Radiotherapy is contraindicated due to a risk for inducing malignant peripheral nerve sheath tumors [38]. Treatment for MPNST consists of wide surgical excision with postoperative radiotherapy. This regimen does not improve long-term survival rates but does delay the time for local recurrence. Chemotherapy as a second treatment option is controversial [114].

Treatment of neurologic manifestations is symptomatic, with standard anti-seizure and migraine/headache medications tailored to the clinical situation (e.g. seizure or headache type). Individuals with neuropathic pain symptoms may be treated with either gabapentin or pregabalin as first-line agents. There should be a low threshold for screening for ADHD symptoms, with early implementation of behavioral and pharmacologic treatments. All children with a diagnosis of NF1 deserve a 504 plan to ensure early evaluation of learning difficulties within the school. If educational difficulties arise, complete psychometric testing should be completed to best tailor the child's individual education plan.

Patients with scoliosis may benefit from early brace treatment to prevent progression when there is mild change and corrective surgery for more severe cases. Dystrophic scoliosis, recognized as the most severe form, demonstrates rapid progression and the need for early spinal fusion [54]. Pseudoarthroses frequently respond poorly to surgical management with patients progressing to limb amputation. Bisphosphonate therapy when used early in the disease progression has demonstrated positive effect [53]. An exercise regimen directed at strengthening bone may prevent some of the long-term loss of bone mineral density and predisposition for osteoporosis and fractures [53, 115]. Sphenoid wing dysplasia with pulsating proptosis may require surgical reconstruction [116].

The cardiovascular manifestations of congenital heart disease, hypertension and vasculopathy are treated as directed by the underlying diagnosis. Specific findings of ischemia, stenosis, hypertension, cardiac disease, cerebrovascular disease and pheochromocytoma direct the further investigation and treatment modalities.

Optic pathway glioma is typically diagnosed and considered for treatment when an NF1 patient has vision, visual field or endocrinologic signs and symptoms [101]. When indicated, the optic pathway glioma is treated with chemotherapy (combination of carboplatin and vincristine) [117]. Radiation therapy is discouraged because of concerns for radiation-induced second malignancies and vascular stenosis [100, 118]. Surgical excision of an optic nerve glioma generally results in

the sacrifice of all vision in that eye [119, 120]. Optic pathway gliomas may also occur in the brain stem, diencephalon and cerebellum (3.5 %) of NF1 patients [107, 118]. These tumors show a more indolent course with potential for spontaneous regression, but must be followed carefully for aggressive tumor characteristics. Surgery is not recommended unless there are excessive growth characteristics or deterioration of the patient's clinical state [107, 121].

Neurofibromatosis Type 2

Definition

The central or type 2 form of neurofibromatosis (NF2) is an autosomal dominant multiple neoplasia syndrome characterized by tumors of the eighth cranial nerve (usually bilateral), meningiomas of the brain, and schwannomas of the dorsal roots of the spinal cord.

Neurofibromatosis type 2 is caused by mutation in the (*NF2*) gene (22q12.2) encoding neurofibromin-2, which is also called merlin [134]. Approximately 50 % are familial and demonstrate autosomal dominant inheritance. Of the de novo cases, 25–33 % result from somatic mosaicism, which may result in atypical clinical presentations or inability to detect a mutation in leukocytes (mutations confirmed in tumor). Among mosaics, recurrence risk to offspring appears low if no mutations are identified in leukocytes [135]. Genetic testing is 93 % sensitive, combining sequencing and deletion/duplication analysis [136].

History

Neurofibromatosis type 2 was previously called central neurofibromatosis or bilateral acoustic neurofibromatosis. Despite an initial NF2 description in 1882 (a patient with deafness and tumors of the brain, dura matter and skull), it was clinically incorporated within the diagnosis of the more common neurofibromatosis type 1 or peripheral neurofibromatosis for decades [122–124].

In 1920, three generations of a single-family were reported with vestibular schwannomas demonstrating the heritable nature of NF2 [125]. In 1930, 38 members of a single-family across five generations were found to have acoustic neuromas. By 1970 more than 100 members of this same family were affected demonstrating autosomal dominant transmission [126, 127]. NF1 and NF2 were localized to two different chromosomes by genetic linkage analysis in 1987 firmly establishing the existence of two separate disease entities [128–130].

Epidemiology

The incidence of neurofibromatosis type 2 is 1 in 25,000 live births [131]. It has wide phenotypic variability and nearly 100 % penetrance by 60 years of age [132, 133]. NF2 has few of the hallmarks of the peripheral or type 1 form of neurofibromatosis.

Systemic Manifestations

Diagnostic criteria for NF2 include presence of either bilateral vestibular schwannomas, or an affected first degree relative and unilateral vestibular schwannoma, or two of the following : schwannoma, glioma, meningioma, ependymoma, posterior subcapsular cataract (Table 16.4) [137]. With distinct features from NF 1, more than 6 café-au-lait macules are uncommon, learning disabilities are not a feature and malignant tumors are not increased in frequency in NF2. Vestibular schwannomas present with tinnitus, hearing loss and trouble with balance. In the setting of NF2, these tumors arise early—often in the second decade of life, as opposed to occurring later in life which is typical of idiopathic presentations of this tumor. Schwannomas can also affect the other cranial nerves as well as cutaneous nerves. When affecting cutaneous nerves, skin-colored to slightly hyperpigmented papules and plaques with increased overlying hair growth are the presenting signs (Fig. 16.12) [138].

Spinal tumors are present in ~2/3 of individuals. Most often, these are schwannomas of the dorsal root seen in the intravertebral canal. Multiple tumors are often identified with surveillance imaging, although many remain asymptomatic. Other tumors include intramedullary astrocytomas or ependymomas (present in 5–33 %). 50–80 % of patients

Table 16.4 Findings in NF2

Ophthalmological lesions
Cataracts 60–81 %
Epiretinal membranes 12–40 %
Retinal hamartomas 6–22 %
Neurological lesions
Schwannomas 24–95 %
Intracranial meningiomas 45–58 %
Spinal tumours 63–90 %
Cutaneous lesions
Skin tumours 59–68 %
Skin plaques 41–48 %
Subcutaneous tumours 43–48 %
Intradermal tumours rare

Modified from Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. Lancet 2009;373:1974–86

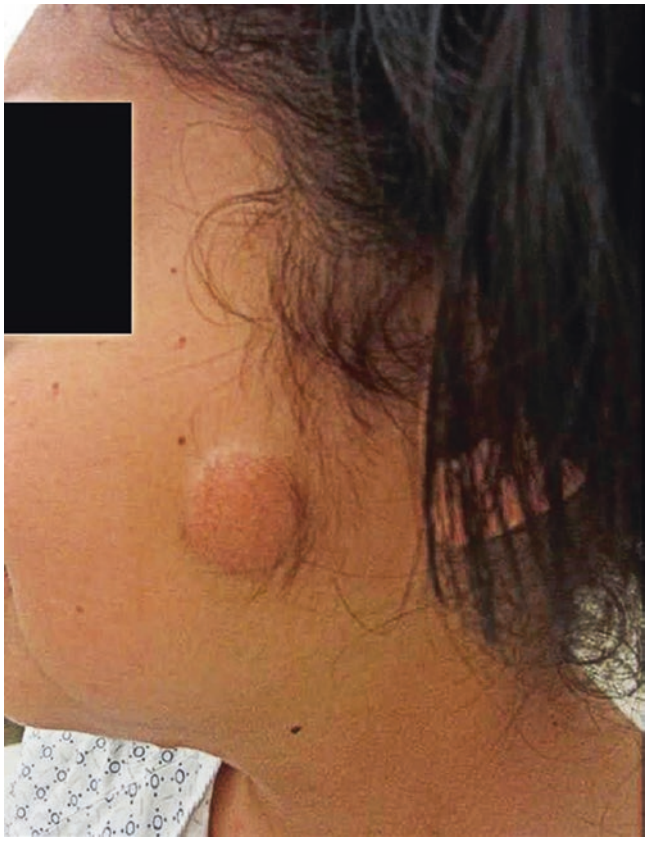

Fig. 16.12 Soft skin-colored nodule with overlying hypertrichosis consistent with schwannoma in NF2

will have one or more meningiomas, most typically with an intracranial location, although they can occur in the spine [139]. Symptoms correspond to size and location, but symptoms can include headache, visual loss, or focal weakness.

Mononeuropathy without tumor involvement may be seen, and common features include facial droop, oculomotor palsy, or a foot/wrist drop, and may be more common with childhood presentation [140]. In contrast, an axonal polyneuropathy has been demonstrated in nerve conduction studies in adults with NF2, although the contribution of this finding to clinical well-being and function is uncertain [141].

Ocular Abnormalities

Ocular abnormal findings include cataracts, epiretinal membranes, and retinal hamartomas. Lisch nodules, iris hamartomas that are frequently found in NF1, are typically not found in NF2 [142].

Cataracts are present in 60–81 % of NF2 patients [133, 141, 143, 144]. The cataracts are characteristically posterior subcapsular, capsular or peripheral cortical opacifications with onset under 30 years of age [145, 146]. The cataracts frequently predate symptoms of bilateral acoustic neurofibromatosis [142]. The association of peripheral cortical lens opacities with NF2 has been found to be statistically significant being present in approximately 38 % of patients [145]. Although lens opacities are an important marker for NF2, the majority do not interfere with vision such that 10–25 % of patients might need cataract extraction [144, 145, 147]. The cataract association is strong enough that NF2 should be considered in young persons without NF1 but with mild skin findings of NF or CNS tumors with posterior capsular opacities. Additionally, the presence of posterior capsular opacities in a relative of persons with NF2 is suggestive of NF2 [148].

Epiretinal membranes are present in 12–40 % of NF2 patients [146, 147]. These are characterized as translucent, semi-translucent or gray white lesions with well demarcated borders located in the posterior pole. Dysplastic Muller cells might be a major component of NF2-associated epiretinal membrane [149]. The epiretinal membranes are typically not a cause of significant vision impairment [150]

Retinal hamartomas are present in 6–22 % of NF2 patients [144, 146, 148]. They consist of slightly raised masses frequently identified in the macula that often reduce visual acuity [144, 146, 148]. They are characterized by enhanced pigmentation and varying amounts of thickened, grey–white retinal and epiretinal tissue [145].

Combined pigment epithelial and retinal hamartoma (CEPRH) and intrascleral schwannomas have also been described in NF2 [149, 151].

There are multiple considerations for potential visual loss in NF2. Progressive cataract, damage to the optic pathways, optic sheath meningiomas, macular hamartomas and corneal opacities secondary to fifth or seventh cranial nerve damage are prime considerations. Fifth cranial nerve lesions resulting corneal hypoesthesia and seventh cranial nerve damage may cause lagophthalmos and decreased lacrimal secretion [152].

Diagnosis

NF2 should be considered in any child presenting with meningioma, vestibular schwannoma, or cutaneous symptoms such as neurofibroma or schwannoma, especially if they have fewer than 6 cafe-au-lait patches and therefore do not fulfill the diagnostic criteria for NF1 [140]

Historically, four separate diagnostic criteria evolved to assist in making the diagnosis of NF2: the NIH Consensus Development Conference [153], the Consensus Development Panel of the NIH [154] the Manchester Group [133] and the National Neurofibromatosis Foundation (NNFF) criteria [137]. None of the criteria were adequate in making the diagnosis in individuals with negative family history of NF2 and without bilateral vestibular schwannomas [155].

The Baser criteria (2011) was developed incorporating a diagnostic system that utilizes genetic testing and weighted characteristic clinical features that occur before 30 years of age. The Baser criteria have been found to have increased diagnostic sensitivity to 79 % (9–15 % greater than previous sets of criteria) while maintaining 100 % specificity at the age of onset of the first characteristic sign of NF2 [156].

Multispecialty evaluation by dermatology, neurology and ophthalmology is necessary for both initial diagnostic evaluation and ongoing clinical monitoring monitoring of NF2 patients.

Management

Early detection of vestibular schwannomas is important and this is best done with MRI, though auditory brainstem evoked response testing may also be helpful. Management of these tumors may involve surgery or stereotactic radiation. Auditory brainstem implants may be helpful in restoring hearing [157]. The other associated tumors—meningeomas and other schwannomas—are managed surgically [138].

NF2 patients require ophthalmology evaluation and monitoring for visual acuity status with special attention to cataract formation and posterior segment epiretinal membrane formation.

Sturge-Weber Syndrome (Encephalo-Trigeminal Angiomatosis)

Definition

The Sturge-Weber Syndrome (SWS, encephalo-trigeminal angiomatosis) is a congenital vascular disorder characterized by the following features: leptomeningeal vascular malformations (usually over the posterior parietal and occipital lobes), facial capillary malformation (port-wine birthmark—PWS) most often in the cutaneous distribution of the first and second divisions of the trigeminal nerve, ipsilateral choroidal vascular malformation which may lead to glaucoma [158]. Partial forms of SWS may occur with only eye findings, or only CNS involvement [159, 160]. SWS has been classified into three types based on the presence or absence of these vascular malformations [161].

Type I: individual has a facial port-wine birthmark, leptomeningeal angioma, and may have glaucoma
Type II: individual has a facial port-wine birthmark, no leptomeningeal angioma, and may have glaucoma
Type III: individual has leptomeningeal angiomatosis, no facial port-wine birthmark, and rarely, glaucoma

A somatic mosaic mutation of the *GNAQ* gene is the underlying genetic etiology of Sturge-Weber syndrome. As the gene mutation is not present in the germline in affected individuals, the inheritance pattern is sporadic [166]. There have been no reported cases of familial recurrence or parental consanguinity [167, 168].

History

The triad of findings which bear the eponyn of Sturge-Weber Syndrome was described clinically by Sturge in 1879 when he described a patient with epilepsy, buphthalmos and a facial capillary malformation with suspected vascular brain anomalies [162]. The underlying brain vascular abnormalities and intracranial calcifications were further clarified by Kalischer, Durck, Volland, Krabbe and Parkes Weber [163, 164]. There may be isolated single symptom forms—facial angioma, meningeal angioma, or isolated choroidal angioma, and incomplete forms exhibiting two of three complete signs have been described [159, 160].

Epidemiology

Sturge Weber syndrome is a rare neurocutaneous disorder which has an incidence of 1/50,000 live births with no racial predilection and equal male to female distribution [165].

Systemic

The combination of cutaneous and cerebral angiomas is thought to result from maldevelopment of the vasculature at 4–8 weeks gestational age, when the ectoderm that will form the upper part of the face closely apposes the neural tube that will form the occipital lobe and adjacent cerebrum [158]. Morgan notes that the development of the blood supply to the brain in the primordial vascular system splits into an inner layer which supplies the brain and the retina and an outer layer which supplies the meninges, choroid, and face. Morgan feels that this common derivation of the meningeal, choroidal, and facial vessels may explain the congenital vascular malformation of SWS [160]

The territory of the ocular branch of the trigeminal nerve is classically used to describe the distribution of the majority of PWM in SWS; however, embryoinic development of facial vasculature occurs independently of neural innervation of the face. Interestingly, a recent article by Waelchli et al. challenges the classic teaching that the V1 distribution is a good description of the location of PWM in SWS and thoughtfully proposes using a forehead distribution (bordered inferiorly by a line from upper eyelid to top of the ear) as a more accurate way

to predict infants at risk for SWS [169]. The proposed forehead distribution covers territory from all three branches of the trigeminal nerve but corresponds well to embryonic vasculature development. In order to remain consistent with other published texts and majority of literature on SWS we will utilize the branches of the trigeminal nerve as anatomic landmarks.

Nearly all patients with SWS have a PWM in the distribution of the ocular branch of the trigeminal nerve (V1) (Fig. 16.13). Patients with V1 PWM have an approximate 8–10 % chance of developing SWS [170]. Unilateral V1 is most common PWM location but ipsilateral V2 and V3 and contralateral dermatomes may additionally be affected. When this is the case, risk of SWS is elevated beyond 8–10 % and presentation tends to be more severe.

The cutaneous feature of the SWS is the "port-wine birthmark," which is a capillary malformation. These lesions are present at birth as flat, vascular patches. They tend to evolve overtime to a deep red to purple color and surface can thicken, become irregular, or nodular with age. Histopathologic examination of PWM shows a normal numbers of ectatic vessels in the superficial dermis. The nasal mucosa and buccal mucosa may also be affected, and localized hemiphypertrophy of the involved tissues may develop over time [4]

The cerebral vascular malformation in SWS is leptomeningeal angiomatosis, demonstrated as meningeal enhancement on contrast MRI of the brain. Progressive calcification of the cortex underlying the angiomatosis can occasionally be seen as early as infancy [4]; however, by age 20 years, most patients have cortical calcifications that appear radiographically as double densities resembling "railroad tracks." [171]

The vascular malformation results in progressive cerebral changes due to impaired blood flow, with chronic hypoperfusion and hypometabolism. Perfusion studies suggest venous stasis results in decreased arterial perfusion, and there can be significant progression of this process over the first year of life [170]. Functional imaging through PET and magnetic resonance spectroscopy (MRS) show a broader distribution of abnormalities than might be predicted by the delineation of the angiomatosis alone, and these functional disturbances can fluctuate with the degree of underlying seizure control [172]. Chronic changes have been recognized radiographically with both cortical and subcortical atrophy [173]. There are increasing reports of associated dysplastic lesions of the cortex adjacent to the malformation (focal cortical dysplasia type IIa, polymicrogyria), which have epileptogenic potential independent of chronic perfusion abnormalities [174].

The most common neurologic manifestations include seizures, "stroke-like episodes," headache, hemiparesis, visual field cuts, and cognitive disability. In a patient with facial PWM, if the child has normal development, neurologic examination, absence of seizures, and normal MRI brain with contrast after 1 year of age, it is unlikely that there is any cerebral involvement.

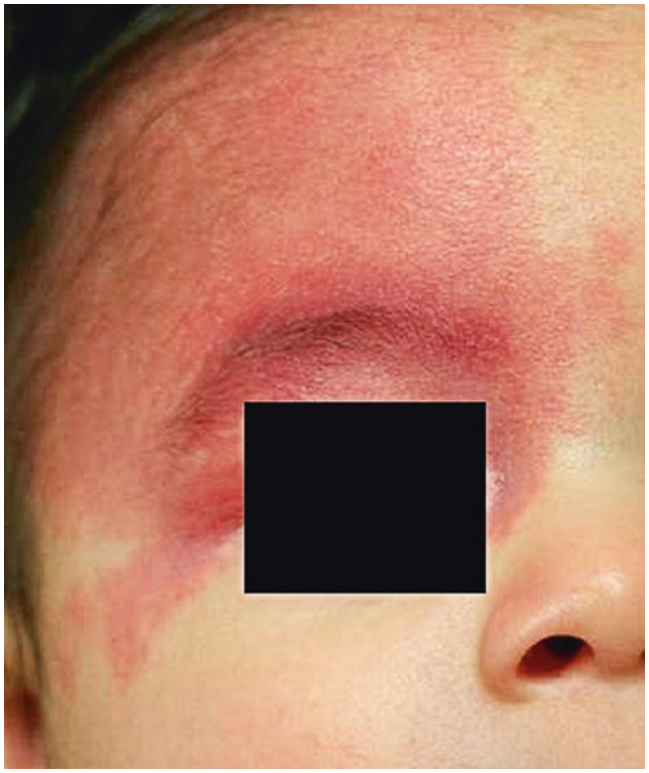

Fig. 16.13 Port wine birthmark V_1 and some V_2 distribution

Seizures are reported in 80 % (71 % with unilateral and 87 % with bilateral PWM) [175]. Approximately 75 % of those develop within the first year of life (range birth to 23 years) [175]. The development of seizures at <6 months of age correlates with development of a more severe hemiparesis [176]. Seizures are most commonly described as focal clonic seizures +/− impairment of consciousness. Progression to generalized convulsion may occur, and other seizure types (e.g. atonic) are reported less frequently.

Recurrent headaches are reported in 44 % of patients and over half of these were consistent with the International Headache Society classification for migraine. There is also a proclivity towards complicated migraine, with 58 % of those with migraine reporting an associated neurologic deficit [177]. Headaches often begin in early childhood (mean onset = 8 years), and duration can be prolonged with a median duration of 12 h. Migraines are five-fold more likely in individuals who experience stroke-like events [178].

"Stroke-like events" in SWS differ from classic acute arterial ischemic strokes, in that symptom progression may be more gradual, and symptoms are potentially reversible. Recurrent thrombotic venous occlusion has been postulated as the underlying mechanism. An episode starts with subacute to acute onset of contralateral weakness, sensory loss, cognitive

impairment or visual field loss. The symptoms may last hours to days, and recovery may be gradual (weeks) but potentially incomplete. The consequence of multiple events can be a stepwise decline in function. These events are distinct from postictal deficits after a seizure, which should result in complete return to neurologic baseline within minutes to a few hours. Mild head trauma has been reported as a potential trigger for stroke-like events, most prevalent in toddlers [179]. Both seizures and headache can co-occur with stroke-like events, with repeated descriptions of headache preceding stroke-like events and/or stroke symptoms preceding onset of seizures.

Neurodevelopmental effects are frequent and include emotional/behavioral difficulties, learning disabilities, and intellectual disability. Approximately 50–60 % of individuals meet diagnostic criteria for intellectual disability (FSIQ<70) [180–182]. This statistic underestimates the prevalence of *any* cognitive effects, which include milder attention deficits or specific learning disabilities despite intelligence scores in the normal or borderline range [175]. In a survey of 171 SWS individuals, 58 % were involved in special education, while 83 % were noted to have some developmental or academic problem. Progressive functional declines have been observed, mostly with recurrent stroke-like episodes or status epilepticus. However, there has been no observed association between lower IQ scores with increasing age [180] suggesting that the progressive aspect of cognitive disability may occur prior to the age where neuropsychologic can be performed reliably. Bilateral angiomatosis and earlier presentation of treatment-resistant seizures are both risk factors for more severe intellectual disability [175, 183].

Other viscera in which angiomas may develop include the lung, thymus, testes, lymph nodes, pituitary gland, and liver, and gastrointestinal tract [184–186].

Ophthalmologic

The characteristic cutaneous facial lesion seen in SWS is the PWM which is present at birth. The PWS is a vascular lesion at the level of the dermis [186–188]. It begins as a well-defined pink smooth macular lesion which blanches with pressure, helping to distinguish PWM from capillary hemangioma [189]. With time, the area changes color from pink to red to purple with associated hypertrophy of the involved skin [190].

SWS patients develop PWM along the trigeminal nerve distribution V1 through V 3, with the most frequent distribution involving the ophthalmic V1 upper lid distribution [191, 192]. Adjacent conjunctiva may also be involved [160]. Episcleral hemangioma and iris heterochromia may also be present with PWM and when found have a high correlation with glaucoma (45 % and 50 % respectively) [189]. Several cases of SWS have been associated with oculocutaneous melanosis [193]. Up to 37 % of SWS patients have bilateral PWM facial lesions [194]. Additionally, 40–50 % of patients with SWS have choroidal hemangiomas, and 50 % of all choroidal hemangiomas occur in SWS patients (Table 16.5 for ocular findings) [7].

Choroidal hemangiomas may be discrete or diffuse. The discrete lesions are yellowish, elevated, circular areas which disappear or decrease with scleral depression, in contrast to the diffuse "tomato catsup" hemangioma which is often flat, involving the posterior pole and more difficult to observe. The diffuse type occurs more commonly in SWS patients, and the age of onset of ocular symptoms with the diffuse hemangioma is noted earlier (median, 7.6 years) than with the discrete or solitary type (38.7 years) [194]. In SWS, choroidal hemangiomas are typically unilateral, and ipsilateral to the angiomatous malformation of the skin [195]. The examiner may be able to see beyond the lesion with the indirect ophthalmoscope and note the border of the striking color change. The appearance of an optic nerve buried in a "sea of tomato catsup" is described as a pathognomonic fundus picture in SWS (Fig. 16.14) [196]. In unilateral disease there is a dramatic color difference between the two fundi with the

Table 16.5 Ocular manifestations of SWS

Orbital
General
– Proptosis
– Lids
– Ptosis
– Port-wine birthmark of eyelid
Extraocular
Sclera
– Nevoid marks or vascular dilation of the episclera
– Large, anomalous vessels in the episclera
– Dilation and tortuosity of episcleral vessels
– Episcleral hemangiomas
Conjunctiva
– Conjunctival telangiectasia
– Conjunctival hemangiomas
– Dilatation and tortuosity of conjunctival vessels
– Large anomalous vessels in the conjunctiva
Intraocular
Anterior segment
– Increased corneal diameter
– Iris discoloration
– Telangiectasia of the iris with heterochromia
– Dilation and tortuosity of iridic vessels
– Sluggish pupils
– Anisocoria or other disturbances in pupil reaction
– Deep anterior chamber angle
– Glaucoma
– Ectopia lentis

(continued)

Table 16.5 (continued)

Choroid
– Choroidal hemangioma
– Angioid streaks
Retina
– Dilation and tortuosity of retinal vessels
– Retinal arteriovenous aneurysm
– Varicosity of retinal veins
– Glioma
– Retinal detachment
– Central retinal vein occlusion
Optic nerve
– Arteriovenous angiomas
– Papilledema
– Optic atrophy
– Optic nerve cupping
– Optic nerve drusen
Other
Strabismus
Nystagmus
Loss of vision (any degree)
Cortical blindness
Abnormal visual field due to lesion in visual pathway
Anisometropia

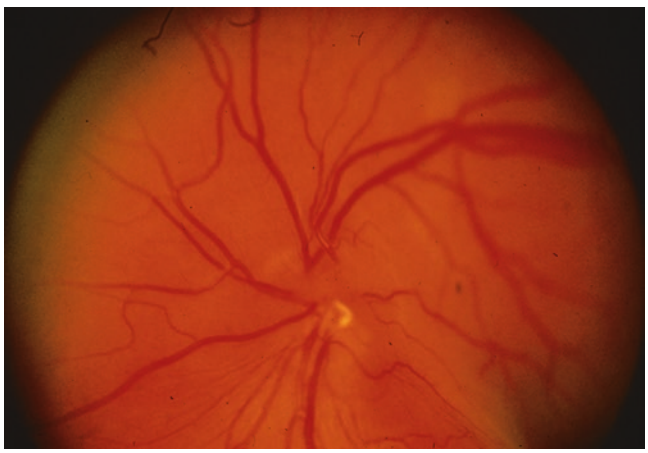

Fig. 16.14 Diffuse choroidal hemangiomas. Note absence of choroidal markings (Courtesy Dr Frank Judisch collection U of Iowa)

involved eye seen as a bright red fundus reflex compared to the normal contralateral fundus. Bilateral choroidal hemangiomas may be difficult to appreciate.

Patients with diffuse choroidal hemangiomas are at risk for developing secondary retinal detachment with shifting subretinal fluid layers [195, 197]. They may also develop visual loss from changes in refractive error, foveal distortion, and exudative retinal detachment [198].

Histologically, the diffuse hemangioma engorgement of pre-existing vessels is intermixed with the vascular tumor, presenting the picture of diffuse hemangiomatosis of the choroid [199]. The choroidal hemangioma may induce changes in the adjacent and overlying choroid and in the overlying retina and retinal pigment epithelium (RPE). In 11 eyes enucleated for suspicion of malignant melanoma, the eyes were found to have irregular pigmentation over and at the margin of the tumor caused by compressed choroidal melanocytes and hyperplastic RPE. Additionally, fibrous tissue proliferation from hyperplastic RPE was observed in half of the diffuse hemangiomas [200]. This fibrous tissue is thought to be responsible for the grayish-white appearance of many of these lesions [199]. Ossification in association with hyperplastic RPE was observed in 64 % of diffuse hemangiomas [200]. Breakdown of the blood ocular barrier at the level of the RPE leads to cystic changes in the outer layers of the overlying retina and retinal detachment, and eventually to degeneration of the entire photoreceptor cell layer [199].

Glaucoma occurs in approximately 68–71 % [189, 201] of patients and is more common when the PWS involves the eyelids or when there is episcleral hamangioma, iris hterrochromia or choroidal hemangioma [168, 189]. Stevenson and Morin reviewed 50 patients with PWM and found that when PWM involves the area of both the first and second sensory branches of the trigeminal nerve, there is a 15 % chance of diagnosing definite glaucoma, and a 30 % chance of diagnosing a patient as a glaucoma suspect [202]. The Great Ormond Street Hospital experience with 216 PWM patients demonstrated that glaucoma was more common in bilateral PWM compared to unilateral PWM patients, 47.2 % versus 12.2 % [189]. They also showed that the incidence of glaucoma in PWS patients with episclaeral hemangioma was 45 %, iris heterochromia patients 50 % and those with choroidal hemangioma 40 % [189].

In SWS patients, glaucoma develops in a bimodal pattern with approximately 60 % of cases appearing in early childhood with a higher risk of developing buphthalmos, and a later childhood or early adult form which does not develop buphthalmos [4, 168, 201, 203–205]. The early form is attributed to immature or anomalous angle anatomy with trabeculodysgenesis with an anterior insertion of the longitudinal muscle of the ciliary body on the trabecular meshwork and incomplete cleavage of the chamber angle with persistence of the uveal part of the meshwork [204–206]. The later onset glaucoma is related to increased venous pressure and possibly anomalous angle anatomy changes [204–206]. Phelps described 16 of 21 SWS patients with glaucoma and episcleral vascular hamartoma, in which 11 had elevated episcleral venous pressure [207]. Vascular malformations in the episclera and limbal conjunctiva may result in an elevated episcleral venous pressure, impeding the outflow of aqueous from the anterior ciliary veins [205, 207–209].

Glaucoma mechanisms also include occlusion of the anterior chamber angle by peripheral anterior synechiae (PAS) and malformation of the anterior chamber angle [4,

168]. PAS most often occurs in persons with choroidal hemangioma and retinal detachment with development of secondary neovascularization and rubeosis. Cibis and co-workers reviewed the histolopathology of trabeculectomy specimens from three eyes with SWS and suggested that a premature aging of the trabecular meshwork Schlemm's canal complex is the primary cause for the later onset juvenile glaucoma [206].

Diagnosis

SWS is suspected in any patient with PWM along the facial distribution of V1-V2. Clinical investigation and diagnostic confirmation frequently involves dermatology, radiology, neurology and ophthalmology services. A complete ophthalmologic evaluation with frequent consideration for ancillary ultrasound and ocular coherence tomography (OCT) testing is necessary to determine ocular associations and potential vision loss from glaucoma or choroidal hemangioma changes. The central nervous system concerns require neurologic investigation with consideration for EEG for seizure evaluation and computerized tomography and/or magnetic resonance imaging for leptomeningeal angiomas. The PWS needs early evaluation and timely treatment by dermatology to prevent chronic more disfiguring changes.

Treatment

It is well-established that individuals with facial disfigurement have an altered social experience resulting in negative psychological consequences thus providing significant motivation for treatment of facial PWM in SWS [210]. Additionally, early treatment of PWM can prevent the superficial thickening and nodularity that tends to occur over time. Pulsed dye laser (PDT) is the treatment of choice for PWM. Pulsed dye lasers (PDL) emit a wavelength of light between 585–595 nm that can penetrate up to 1.2 mm [211]. This wavelength targets superficial blood vessels causing intravascular coagulation and subsequent vessel involution. Side effects of PDL include postoperative bruising that persists for 1–2 weeks and transient pigmentary alterations. There is a low risk of scarring. It is controversial as to when exactly laser treatment should be initiated for this condition, but with most agreeing on at least early childhood if not infancy given the progressive nature of this lesion. Rarely does laser treatment completely fade the cutaneous malformation. A widely accepted goal of therapy is 70 % lightening and prevention of thickening/nodularity. On-going, intermittent treatment for maintenance is needed.

Treatment of seizures associated with SWS remains symptomatic, and choice of medication does not differ significantly from other causes of epilepsy. A rescue medicine such as rectal valium (Diastat™) should be available for clustering or prolonged seizures (>5 min). Migraine treatments are also symptomatic, and consist of both preventive medications and abortive medications. A survey of patients with SWS indicated that both categories of medicine are used effectively in this population. Those taking preventive medications were less likely to report a negative impact of headaches on quality of life (42 % vs 85 %). Approximately 22 % of migraineurs with SWS reported using triptans, and overall reported that triptans were more effective as an abortive than over-the-counter analgesics (42 % vs 20 %) [212]. The safety of triptans in the SWS population has not been evaluated. Triptans could potentially precipitate a stroke, and some experts advise against triptan use in individuals experiencing neurologic deficits (weakness, sensory loss, aphasia) during their migraine, although there is insufficient data to determine the absolute risk. 2/16 individuals in the Kosoff study reported reversible unilateral weakness with a migraine in which a triptan was used.

Treatment with low-dose aspirin (3–5 mg/kg/day) remains controversial as there have been no randomized controlled trials for this treatment. Anti-platelet therapy has been proposed to reduce recurrent microthrombosis and improve perfusion. A retrospective survey of families indicates a reduction in monthly stroke-like events and seizures in children who were taking daily aspirin [213]. Of 26 individuals reporting stroke-like events before and after aspirin use, there was a reduction from a mean number of monthly events from 1.1 to 0.3 ($p = 0.014$). There was a statistically significant reduction in the number of reported seizures (from 3/month to 1/month), even though the majority of these families subjectively felt there was no change in seizure burden. In cases of medically-resistant epilepsy and/or progressive cognitive decline, hemispherectomy is an option, with noted improvements in cognitive outcome and seizure burden [214].

Medical management of SWS associated glaucoma is difficult and often unsuccessful. Aqueous suppressants are more an adjunct to surgery in the early onset glaucoma patients and often the initial treatment modality in the later onset glaucoma group. Oral propranolol has also been used to produce a temporary intraocular pressure lowering treatment for SWS glaucoma patrients, but is not indicated as a primary treatment modality [215]

Surgical treatment should probably be individualized based on the gonioscopic appearance of the anterior chamber angle at the time of examination under anaesthesia. Numerous surgical procedures have been advocated, including goniotomy, trabeculotomy, full-thickness filtration surgery, partial-thickness filtration surgery (trabeculectomy), combined trabeculotomy-trabeculectomy, argon laser trabeculoplasty, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser goni-

otomy, seton procedures, and transpupillary thermotherapy (infrared diode laser) [216].

Goniotomy and trabeculotomy are considerations for the early onset group. A combined trabeculectomy and trabeculotomy may have theoretical advantages, since it should provide treatment for both a congenitally abnormal angle and increased episcleral venous pressure [205, 217]. Cibis and co-workers site the success of trabeculectomy, trabeculotomy, and goniotomy in controlling lOP as proof that a primary block in the trabecular meshwork and Schlemm's canal system is the main cause of SWS glaucoma [206]. SWS patients with infantile glaucoma have also been successfully treated with combined trabeculectomy and cyclocryotherapy [218].

In view of the expulsive hemorrhage risk with open procedures in SWS glaucoma, goniotomy or trabeculotomy should be considered as a primary procedure. Cibis and coworkers have anectotally noted a poor response to goniotomy and have done trabeculotomies as the primary procedure for SWS glaucoma [206]. YAG laser goniotomy has been employed in an eye with juvenile primary developmental glaucoma associated with SWS [219]. Cycloablative procedure, either with cryotherapy or laser, can eliminate the risks of open surgical procedures. Induction of a low intraocular pressure preoperatively and careful cauterization of the dilated subconjunctival and episcleral vessels would seem to be prerequisites for avoiding complications of hemorrhage, expulsion or prolapse of intraocular contents as much as possible.

Complications of glaucoma surgery in SWS patients are significant. Ciliary processes, lens zonule and vitreous prolapse into the trabeculectomy wound has been described [220]. Cilioretinal artery occlusion has been reported with glaucoma drainage device surgery in SWS [221]. Expulsive hemorrhage, choroidal effusion, prolonged persistence of flat anterior chambers and excessive anterior chamber hemorrhages are well documented serious complications in open eye surgery in SWS glaucoma cases [206, 222–224]. This had led same surgeons to take measures to preplace sutures and scleral flaps and posterior sclerotomies in order to permit rapid closure with prevention of hemorrhage, effusion or expulsive hemorrhage although this is less common in children. One recent report has demonstrated that this risk may be very low and preventive measures are not necessary [225].

Management of the choroidal hemangiomas presents a therapeutic challenge for the treating ophthalmologist. These vascular malformations frequently produce an exudative retinal detachment leading to vision loss, intractable secondary glaucoma, and increased potential for enucleation [4, 168]. Treatment modalities, including diathermy, photocoagulation, cryotherapy, radiotherapy, proton beam stereotactic radiotherapy, photodynamic therapy (PDT) and plaque radiation therapy, have produced favorable results treating exudative retinal detachment associated with choroidal hemangioma especially when initiated prior to the development of significant exudation [6, 195, 197, 216, 226–233]. Treatment with argon laser over the area of tumor may be effective in reducing or eliminating associated retinal detachment, even those involving the macula [234]. Bevacizumab has also been effective in treating serous retinal detachment associated with choroidal hemangioma [232].

PDT is suggested as the treatment of choice for discrete choroidal hemangioma but has good short-term results in limited case reports with the diffuse choroidal hemangioma form as well (2002, [235]). In eyes where the exudative retinal detachment precludes photocoagulation, treatment by percutaneous radiotherapy has resulted in successful reattachment [236, 237].

Potential treatment complications include radiation retinopathy, optic neuropathy, macula ischemia, and subretinal fibrosis in addition to the secondary formation of choroidal effusion after laser treatment for choroidal hemangioma [195, 227].

Tuberous Sclerosis Complex

Definition

Tuberous sclerosis complex (TSC) is a multisystem disease characterized by disordered proliferation, migration, and differentiation due to dysregulation of the mammalian Target of rapamycin (mTor) pathway. Common manifestations include hamartomas and other abnormalities in the skin, brain, eye, kidney, heart, lung, and liver.

History

In 1880 Bourneville described the case of a 15 year-old girl who had seizures since childhood, psychomotor delay, and an eruption vascular papules on her nose, cheeks, and forehead [238]. At autopsy, multiple sclerotic nodules were observed in the cerebral cortex and kidney, which Bourneville associated with skin lesions he had observed [4]. In 1808, Bourneville published another paper about a 4 year-old boy who had intractable seizures, intellectual disability, and a heart murmur who was found to have tubers of his heart, brain, and kidneys, at autopsy [239]. Although tuberous sclerosis bears the eponym "Bourneville's disease," it was not until 1908 that Vogt established the classic triad of epilepsy, low intelligence, and angiofibromas of TSC (although less than 1/3 of patients have all three symptoms) [7, 240]

The term "epiloia" has often been used in the past to designate this triad. The term was coined by Sherlock as a contraction of the words epilepsy and anoia, meaning

mindlessness [4, 8]. Although obsolete now, an attempt was made by Gorlin in 1981 to suggest a more useful interpretation of the term epiloia as an acronym for the disease with *epi*lepsy, *lo*w *i*ntelligence, and *a*denoma sebaceum (the term "angiofibroma" is now preferred for these lesions) [241]. In 1920 van der Hoeve first established that retinal tumors are present in some cases of TSC and called these "phakomas," now termed astrocytic hamartomas [2, 4].

Epidemiology

The current estimated birth incidence is 1/6000 person, with a population prevalence of approximately 1/20,000 [242]. The disease shows no sexual or racial predilection.

Tuberous sclerosis is a single gene disorder that may be inherited in a dominant fashion from an affected parent (~1/3) or arise sporadically as a *de novo* mutation (~2/3). 85 % of cases have an identifiable mutation in the *TSC1* (31 % 9q34) and *TSC2* (69 % 16p13.3) genes, which code for the proteins hamartin and tuberin, respectively. Mutations cause constitutive activation of the mammalian target of rapamycin complex 1(mTORC1), which result in multi-system hamartomas in addition to the other sequelae described in this disorder [243, 244]. Although the penetrance of the gene is high, there can be variable expressivity within a family with some individuals having multiple or severe findings and others expressing only a single sign.

Somatic mosaicism is present in ~5 % of individuals without a known mutation (1 % of all individuals with TSC). If the gonadal cell line carries the mutation, these individuals could have affected children [245]
Although not absolute, *TSC2* mutations and sporadic inheritance have been associated with more severe multisystem disease.

Clinical Diagnosis

The diagnostic criteria for TSC was most recently revised at the 2012 International Tuberous Sclerosis Complex Consensus Conference (Table 16.6). A diagnosis can be established either by genetic or clinical criteria. For a clinical diagnosis, definite TSC diagnosis requires presence of two major or one major plus ≥2 minor features. Possible TSC diagnosis is made by one major or ≥2 minor features [242].

Genetic testing can also provide a definite diagnosis, as 85 % will have a known pathogenic mutation in either the TSC1 or TSC2 gene. Genetic testing may yield a variant of unknown significance or no identifiable mutation, and clinical criterial would be necessary to establish the diagnosis.

Systemic Features

Cutaneous manifestations are frequently the first signs of TSC and occur in nearly all patients. Four different cutaneous manifestations are independent major criteria for a diagnosis of TSC: hypopigmented macules, angiofibromas, a shagreen patch, and periungual fibromas. Hypopigmented macules are usually present at birth and occur in 90–100 % of TS patients (Fig. 16.15). These can be difficult to appreciate in lightly pigmented infants, and so may not become obvious until months or years of life as the surrounding normal pigmentation darkens over time in these individuals. They can present in numerous shapes and sizes including 1–2 mm macules called "confetti" macules (a minor feature) or larger lesions. These may have one rounded and one tapered end, resembling the leaf of an Eastern Mountain ash tree, from which these characteristic "ash leaf" macules take their name. Hypopigmented macules and patches, sometimes called nevus depigmentosus, are not an infrequent

Table 16.6 Updated diagnostic criteria for tuberous sclerosis complex 2012 [242]

Genetic diagnostic criteria	Major features	Minor features
TSC1 or TSC2 DNA mutation (Identification of mutation serves as independent diagnostic criterion)	1. Hypomelanotic macules (≥3, at least 5-mm diameter. Poliosis may count as hypomelanotic macule)	1. "Confetti" skin lesions
	2. Angiofibromas-major feature in child (≥3) or fibrous cephalic plaque	2. Dental enamel pits (≥3)
	3. Ungual fibromas (≥2)	3. Intraoral fibromas (≥2)
	4. Shagreen patch	4. Retinal achromic patch
	5. Multiple retinal hamartomas	5. Multiple renal cysts
	6. Cortical dysplasias	6. Nonrenal hamartomas
	7. Subependymal nodules	*Angiofibromas, multiple with adult onset, considered a *minor feature*
	8. Subependymal giant cell astrocytoma	**Bone cysts no longer a diagnostic criterion
	9. Cardiac rhabdomyoma	
	10. Lymphangioleiomyomatosis (LAM)	
	11. Angiomyolipomas (≥2)	

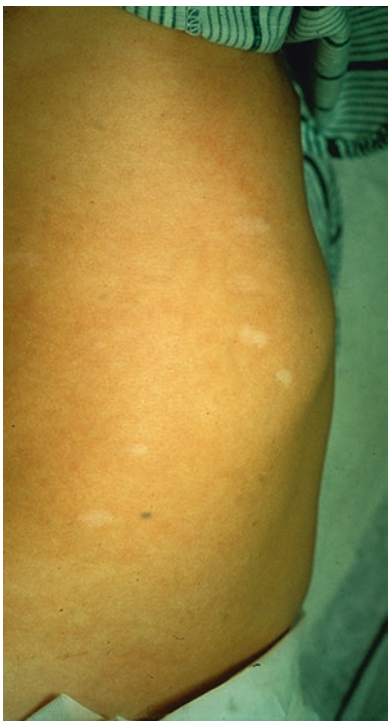

Fig. 16.15 Hypopigmented macules in TSC (Courtesy Dr Frank Judisch collection U of Iowa)

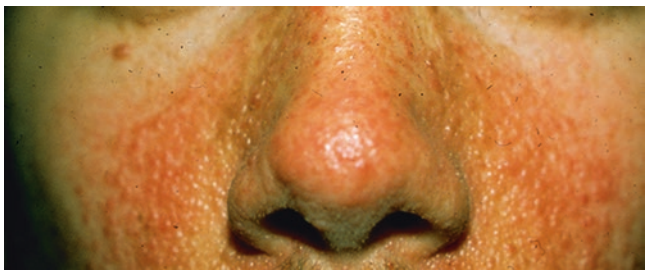

Fig. 16.16 Angiofibroma in TSC (Courtesy Dr Frank Judisch collection U of Iowa)

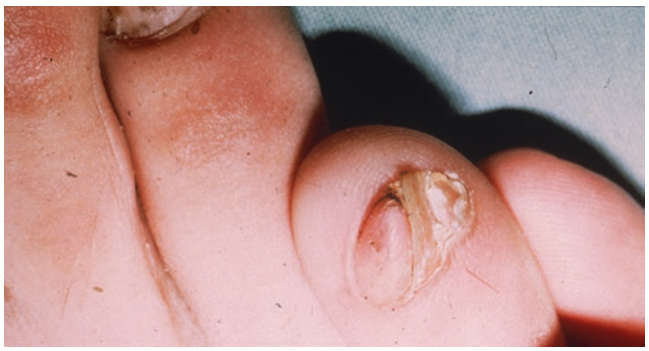

Fig. 16.17 Periungual fibromas

occurrence in healthy children (approximately 1–4 % of children have at least one); however, more than three hypopigmented macules is highly specific for TSC and therefore has been adopted as a major criterion for the disease [242, 246]

Unlike hypopigmented macules, angiofibromas are not present at birth but develop over the first 2–10 years of life and occur in approximately 75 % of TS patients [247]. Angiofibromas were called "adenoma sebaceum" until it was discovered that these tumors were neither adenomatous nor derived from sebaceous glands. The prototypical angiofibromas are numerous red-brown firm shiny dome-shaped papules located on bilateral cheeks and forehead (Fig. 16.16). In mosaic TSC, facial angiofibromas may be unilateral. A variant of angiofibromas is the fibrous plaque of the forehead which histologically resembles an angiofibroma but arises as a single, slowly growing plaque.

Another cutaneous manifestation of TSC is a connective tissue nevus or shagreen patch. These occur in about half of TS patients and typically present around 2 years of life. The shagreen patch most often manifests as an uneven firm skin-colored, pink, or brown plaque with depressions at follicular orifices resulting in an appearance likened to that of pig skin or an orange peel (peau de' orange). Shagreen patches are commonly in the lumbosacral area.

The final cutaneous finding that is a major criterion for TS diagnosis is periungual fibromas or Koenen tumors (Fig. 16.17). Periungual fibromas in association with TSC were first described by Richard Kothe in 1903; however, it was not until Koenen published a paper on a family of TSC patients with pictures of periungual fibromas that this finding was definitively linked with TSC [247]. These are skin-colored, firm papules found on the skin around the nails. Periungual fibromas are more commonly found on toes than fingers and on occasion can present at a linear distortion of the nail plate without visible tumor. Periungual fibromas are found in 15 % of TSC patients and develop later than other cutaneous manifestations, with onset in late childhood and extending throughout adulthood [248]

Multiple randomly distributed dental enamel pits and gingival fibromas are also common in TSC patients and are both minor criteria for TSC diagnosis [249]

Several other cutaneous lesions have been associated with TS but are not part of the diagnostic criteria. These include poliosis (a circumscribed patch of depigmented hair), soft fibromas in flexural areas, cafe-au-lait spots (tan patches of skin, and port-wine stains (capillary malformations).

Neurologic manifestations of TSC include frequent epilepsy and intellectual disability. The most common anatomic findings, which are all considered major diagnostic criteria, include areas of cortical dysplasia (i.e. tubers), subependymal nodules, and subependymal giant cell astrocytomas (SEGA).

Epilepsy occurs in ~85 % of individuals with TSC, although periods of remission are possible [250]. A broad range of seizure types may be seen, with an elevated risk for development of infantile spasms.

Intellectual disability occurs in 50–60 % of individuals with TSC. Other neurodevelopmental disabilities are also more frequently seen, including specific impairment of attention, executive function, other learning disabilities, and/or behavior problems. Autism spectrum disorders have been reported in ~40 %. The presence of bilateral tubers and seizure onset < 6 months are risk factors for intellectual disability [251] as is the development of infantile spasms [252].

The cortical/subcortical tubers are T2-hyperintense lesions on brain MRI, often multifocal in distribution. They are present in >70 % of patients with TSC. Pathologically, these reflect areas of disrupted cortical architecture with a mixture of dysplastic neurons and astroglial cells, disoriented pyramidal cells, and reactive astrocytes [253]. Functionally, there is abnormal expression of excitatory glutatmate receptors [254]. This combination of abnormal architectural and physiologic features predisposes the risk for seizures, although some tubers remain physiologically quiescent. The disrupted connectivity (cortico-cortical and cortico-subcortical networks) may also underlie neurodevelopmental disabilities, which correlate with increased tuber burden. Tubers with cystic qualities are more likely to be associated with TSC2 mutations, the development of infantile spasms, and refractory epilepsy [255]

Subependymal nodules are benign hamartomatous growths of the lateral and third ventricle wall. These were first associated with TSC in two separate reports published in 1881 by Bourneville and Hartdegen [256]. It is now known that these are present in 90 % of TSC patients and are detectable prenatally via ultrasound or MRI [257, 258]. Nodules can transform to subependymal giant cell astrocytmas (5–20 %), which are slow-growing tumors most commonly detected in childhood or adolescence. SEGAs occur predominantly near the foramen of Monro, and mass effect can cause obstructive hydrocephalus as the primary complication [259]. Progressive calcification of the tubers or subependymal nodules over time is often incidentally noted.

The heart, lungs, and kidneys can also be affected in TSC. Cardiac rhabdomyomas are a major criterion for diagnosis and can be seen prenatally or after birth by echocardiography or MRI. They are often largest in the neonatal period. When detected they confer at least an 80 % risk of having TSC [260, 261]. Fortunately, cardiac rhabdomyomas do not often have major functional ramifications and they have the propensity to involute in the first years of life. Rarely, they can be associated with outflow obstruction and congestive heart failure in the neonatal period and the incidence of cardiac arrhythmias including Wolff-Parkinson-White syndrome is significantly higher in TSC patients [262]. Lymphangioleiomyomytosis (LAM) is the major criterion for TS diagnosis associated with pulmonary manifestations. LAM is an infiltration of all lung structures with benign appearing smooth muscle cells resulting in cystic changes in lung parenchyma, subsequent pneumothoraces, and symptoms of progressive dyspnea [263]. This condition occurs in about 30 % of TSC patients, at a five to ten fold higher incidence than sporadic LAM [264–266].

Angiomyolipomas and multiple renal cysts are the major and minor criterion, respectively, for TSC involving the kidneys. Angiomyolipomas, as their name implies, are benign tumors composed of vascular, smooth muscle, and adipose tissue. They are often asymptomatic and can occur in organs other than the kidney. Interestingly, TSC patients can have multiple renal cysts due to a contiguous gene deletion syndrome resulting from loss of both *TSC2* and polycystic kidney disease 1 (*PKD1*) genes as they are immediately adjacent on chromosome 16 [267]. More commonly, however, cysts occur as single or multiple small asymptomatic lesions. Over time, these benign lesions can grow enough to cause life-threatening bleeding and can replace enough normal renal parenchyma to cause end-stage renal disease. Malignant angiomyolipoma and renal cell carcinoma are also possible. Overall, renal disease is the second leading cause of early death in TSC patients.

Ophthalmic Features

The ophthalmic manifestations of TSC may be divided into retinal and non-retinal findings (Table 16.7). Retinal lesions are the most frequent findings. Four different retinal lesions have been described: a flat, grey, non-calcified translucent hamartoma, a raised multnodular (mulberry) calcified hamartoma, an “in between” transitional retinal hamartoma with features of the first two hamartoma types and a punched out or depigmented achromic patch (non-astrocytic hamartoma) typically noted in the midperiphery [268–271]. Hyperpigmented areas thought to be congenital retinal pigment epithelium hypertrophy may also be present [272]

Astrocytic hamartomas of the retina are the most common finding being present in 30–50 % of patients and it is common to find multiple lesions in the same patient [268, 270, 273, 274]. Flat non calcified glial hamartomas of the retina have a smooth, spongy appearance with fuzzy borders. They are gray-white and may be mistaken for retinoblastoma. In the absence of other systemic evidence of TSC, observation over time may be necessary to rule out this malignancy [5]

The raised hamartomas appear condensed and have an irregular surface (Figs. 16.18 and 16.19). These lesions are

white and resemble a mulberry. The lesions are frequently multiple and vary in size from 0.25 to 4.0 disc diameters [268, 274]. Retinal hamartomas vary in number from one to a dozen or more in the two eyes and can occur anywhere in the fundus, although there seems to be a predilection for the posterior pole, along the arcades and adjacent to the optic nerve [5, 274].

These lesions are not related to the surrounding vasculature and cause little reaction in the adjacent retina. If there is growth, it is extremely slow and the general impression is that these lesions are congenital or present very soon after birth and are stable over time [8, 268, 275].

In general, although the earlier conception that flat hamartomas develop into multi-nodular hamartomas over time is incorrect, there are reports of astrocytic hamartoma transformation with more aggressive growth causing exudative retinal detachment and neovascular glaucoma [268, 276, 277]. Vitreous seeding rarely occurs with retinal hamartomas, but can result in overlying vitreous inflammation and hemorrhage [278, 279].

The astrocytic hamartomas in TSC differ from those found in neurofibromatosis type I in that the TSC hamartomas are intraocular and do not involve the orbit, the optic nerve or produce increased glaucoma risk [5].

The actual prevalence of retinal hamartoma in the general population is not known, but suspected to be very low. The rarity of this lesion in non-TSC patients was demonstrated by a study which performed perinatal ocular examinations on 3573 healthy full-term newborns with only two astrocytic hamartomas noted in this population [280]. Diagnostically, the presence of two retinal hamartomas is necessary to meet the major diagnostic criterion.

Retinal hamartomas have similar histologic features to the tubers located in the brains of TSC patients [268, 274]. Histologically, the retinal hamartomas are composed of large, fusiform astrocytes separated by a coarse and nonfibrillated, or finer and fibrillated, matrix formed from the astrocytic cell processes. The retinal tumors are generally sparsely vascularized or nonvascularized [9]. Microscopically, these are astrocytic hamartomas of the nerve fiber layer, and fluorescein angiographic studies have demonstrated associated abnormal vessels [7, 281].

Retinal achromic patches have been determined a minor diagnostic feature [242]. Retinal achromic patches are basically areas of hypopigmentation on the retina. These patches have been noted to occur in 39 % of TSC patients [268, 282]. Incidence in the general population is estimated at 1 in 20,000 [245].

The non-retinal ocular findings of TSC represent a collection of diverse physical features. Sectorial hypopigmentation of the iris [268, 283] as well as more subtle hypopigmented

Table 16.7 Ocular manifestations of tuberous sclerosis

Orbital
General
– Proptosis
– Fibrous dysplasia of orbit
Lids
– Adenoma sebaceum (angiofibroma)
– Poliosis (hypopigmented lashes)
– Nevus flammeus
Sclera
Conjunctiva
– Small pediculate whitish-gray tumors on palpebral conjunctiva
– Subconjunctival nodules
Anterior Segment
– Corneal opacities with subepithelial haze
– Lens opacities
– Depigmented sectors of iris
– Hypopigmented iris spots
– Coloboma of iris
– Megalocornea
– Posterior embryotoxon
Media
– Vitreous cloudy
– Vitreous hemorrhage (from hamartoma)
Choroid
– Diffuse angiomatosis
– Angioid streaks (single finding)
– Coloboma of choroid
– Punched-out chorioretinal defects
Retina
– Retinal mushroom-like tumor of grayish-white color
– Yellow-white plaques with small hemorrhages and cystic changes
– Neurofibrilloma
– Neurocystoma
– Retinal glioneuroma
– Glial hamartoma
– Pigmentary changes
– "Ash-leaf" patches
– Atypical retinitis proliferans
– Retinal telangiectasis
– Retinal angioma
– Exophytic retinal astrocytoma
Optic Nerve
– Optic atrophy
– Papilledema
– Pseudopapilledema
– Disc drusen
– Glial hamartoma anterior to the lamina cribosa (giant drusen)
Other
Glaucoma
Nystagmus
Strabismus
Phthisis bulbi
Progressive external ophthalmoplegia

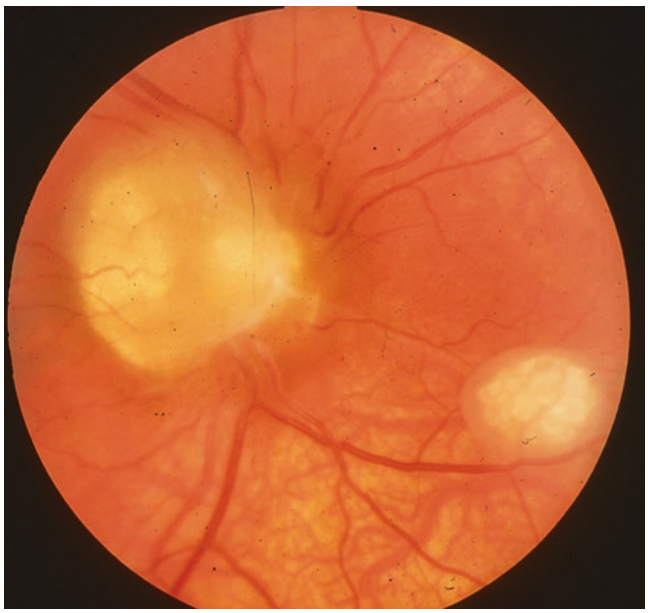

Fig. 16.18 Astrocytic hamartoma (Courtesy Dr Frank Judisch collection U of Iowa)

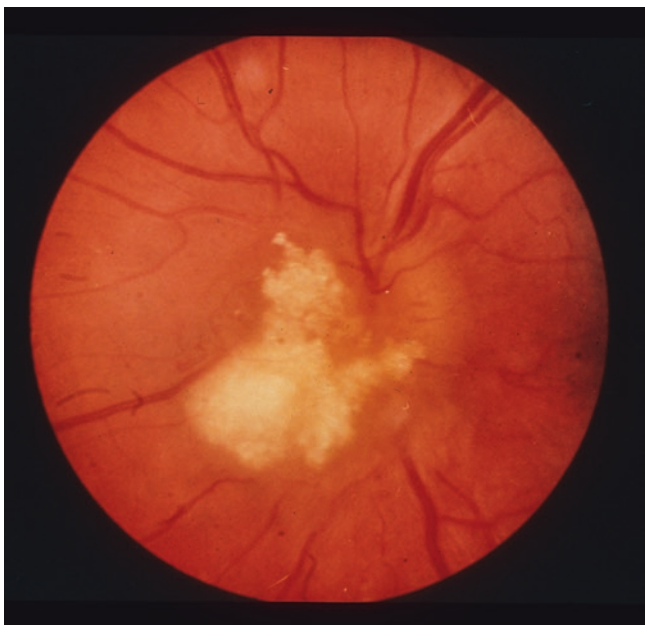

Fig. 16.19 Astrocytic hamartoma (Courtesy Dr Frank Judisch collection U of Iowa)

iris spots have been reported [271, 284]. Lens colobomas [268] megalocomea [285] posterior embryotoxon [286], poliosis, with hypopigmented lashes set amongst normally pigmented lashes [287] strabismus [268, 272] and isolated cases of progressive external ophthalmoplegia may occur [288].

Cutaneous angiofibromata may develop with the, formation of small salmon-colored nodules in the lid and under the conjunctiva (39 %) [268, 287, 289–291]. Retinitis pigmentosa has been associated with optic disc hamartoma, however, it is uncertain whether these patients had TSC or isolated hamartoma [292–294].

In general, the ocular lesions found in TSC do not interfere with vision development or function. The unfortunate development of a large hamartoma of the central macula would be an exception with the potential for significant vision loss [5]. Vision loss in TSC patients is more likely to result from disruption of the visual pathway. Intracranial tumors (tubers) can damage the optic nerves, chiasm or visual pathways from direct compression [5]. Additionally, posterior fossa tumor involvement can produce hydrocephalus and increased intracranial pressure leading to papilledema and optic atrophy [5, 270, 295].

Diagnosis

The updated genetic and diagnostic clinical features are listed in Table 16.6 [242, 246].

The current consensus is that "identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue" or presence of two major or one major and two or more minor feature indicates a definite TSC diagnosis. One major feature or two or more minor features is a possible TSC diagnosis. Since TSC has great variability of disease expressivity, patients with neurologic (epilepsy) or neurodevelopmental conditions (learning disorders and developmental delay) without specific etiology should be considered for investigation [296]. Evaluation of first-degree relatives, parents and siblings of TSC patients requires participation by multiple specialties including pediatrics, dermatology, ophthalmology, and radiology [297].

Treatment

The 2012 International Tuberous Sclerosis Complex Consensus Conference published updated guidelines for screening and management and a summary of their recommendations by the Tuberous Sclerosis Alliance appears in Table 16.8—www.tsalliance.org [297].

Neurologic treatment of seizures remains largely symptomatic and a broad array of anti-seizure medications may be used; however, there is a specific indication for the use of vigabatrin in the treatment of infantile spasms due to tuberous sclerosis. Using vigabatrin in TS yields spasms remission rates as high as 95 %, which is significantly higher than remission rates seen with standard steroidal treatments or for spasms due to other etiologies [298]. For cases of medically refractory epilepsy, surgical resection of a tuber has been

Table 16.8 Pediatric surveillance and management of tuberous sclerosis syndrome [242]

	Newly diagnosed or suspected	Diagnosed definite or suspected tuberous sclerosis
Genetics	+ testing/counseling	+ testing/counseling
Brain	MRI EKG	MRI EKG
Kidney	MRI abdomen, renal fxn	MRI abdomen, renal fxn
Lung	Baseline pulmonary fxn	Specific testing per findings
Skin	Dermatology evaluation	dermatology evaluation
Teeth	baseline dental exam	dental evaluation every 6 months
Heart	EKG baseline	EKG every 1–3 years
Eye	Complete examination for baseline	Yearly examination

successfully pursued in cases where the seizure burden is primarily attributable to a single focus.

Everolimus, an mTor inhibitor, is a non-surgical option for decreasing the volume of SEGAs, thereby reducing the likelihood of obstructive hydrocephalus. The majority of patients have a >30 % volume reduction that appears sustainable for up to 3 years (longer follow-up not available) [299]. MTor inhibitors are also clinically used for treatment of renal angiomyolipomas, lymphangioleiomyomatosis, and facial angiofibromas. Discontinuation of therapy can result in regrowth of tumors and other lesions. There are small case series supporting a potential decrease in seizure burden while taking everolimus [300]; further investigation via randomized controlled trial is ongoing.

Topical rapamycin has been used with success to reduce cutaneous angiofibromas [301]. Older modalities used for treatment of these lesions include pulsed dye laser and curettage.

The ocular lesions are not largely progressive and require no treatment [4]. Patients with significant drusen may often have visual field deficits. However, if the hamartomas do not involve either the macula or the optic disc, the patient will generally have no ocular complaints [4]. Rarely, portions of a calcified retinal phakoma may break off and float freely in the vitreous [4]. Panzo and co-workers described an unusual case of a serous detachment of the fovea and decreased vision with parafoveal exudates from a retinal astrocytoma with subsequent spontaneous resolution and return of central vision in a patient with TSC [302]. Also, vitreous seeding by a peripapillary retinal astrocytic hamartoma in a patient with TSC is an uncommon event, however, such a diagnosis was verified by vitreous biopsy and the use of a millipore filter and a modified Papanicolaou staining technique [303]

Careful ophthalmoscopy by an experienced observer should be an integral part of the evaluation of anyone suspected of having TSC [304, 305]. Mild but definite ophthalmologic signs of TSC are often uncovered by careful examination of parents after birth of a child with obvious disease [306]. However, approximately half of the retinal lesions in Harley and Grover's series were observed by the pediatrician and neurologist prior to the ophthalmological survey [307]. A major ophthalmology function involves assessment of visual function, screening for treatable conditions and monitoring the ophthalmology associated lesions found in TSC patients. Seizure patients treated with vigabatrin pose a special situation requiring formal visual field testing, electroretinogram evaluation and retinal nerve fiber layer assessment with optical coherence tomography directed towards estimating drug toxicity effects. Vigabatrin monitoring requirements have been difficult to perform and some experts contend that more frequent assessment, including those treated with vigabatrin, is of limited benefit and not recommended unless new clinical concerns arise [299].

von Hippel-Lindau

Definition

The combination of retinal, brain and spinal cord tumors is called "von Hippel-Lindau disease" (VHL). This rare, autosomal dominant genetic condition predisposes individuals to both benign and malignant tumors. In addition to central nervous system and retinal capillary hemangioblastomas (RCA), the most common tumors are clear cell renal carcinomas, pheochromocytomas, pancreatic neuroendocrine tumors, pancreatic cysts, endolymphatic sac tumors and epididymal papillary cystadenomas and broad ligament cysts of the uterus [308]

Von Hippel Lindau is due to a mutation in the *VHL* gene located at the chromosomal locus 3p25.3. This is transmitted in an autosomal dominant fashion. Approximately 80 % of *VHL* mutations are familial and 20 % are *de novo*. The mutation detection rate with current molecular genetic testing approaches 100 % in familial cases. The overall detection rate exceeds 90 %, although mutations may not be detected in sporadic cases with mosaicism. *VHL* has been described as a tumor suppressor gene; more specifically, with the absence of *VHL*, hypoxia inducable factor (HIF) may constitutively stimulate angiogenesis via increased levels of VEGF or PDGF-β, and this increases the predisposition to vascular tumors [315]. For individuals with a documented family history consistent with dominant inheritance, a presumptive clinical diagnosis can be made with only one of the

following: retinal angioma, spinal or cerebellar hemangioblastoma, pheochromocytoma, renal cell carcinoma, or multiple pancreatic and renal cysts.

Some phenotype-genotype correlations have been described regarding the penetrance of particular tumor types. VHL has been clinically subcategorized into type 1 (low risk for pheochromocytoma) and type 2 (high risk for pheochromocytoma). Type 2 VHL was more likely to be associated with specific missense mutations. Furthermore, individuals with deletions overlapping a particular region at the 5' end of the gene appear to have a reduced risk for renal cell carcinoma [308].

History

In 1904 a German ophthalmologist, Eugen von Hippel, described two cases which he had observed over a period of several years to the Heidelburg Congress and established "angiomatosis retinae" as a clinical entity [8, 309]. In 1926, the Swedish neurologist Arvid Lindau noted that many of his patients with hemangiomatous cysts of the cerebellum also had retinal angiomatosis [310]. The eponym "von Hippel-Lindau disease" has been applied to the disorder in which the angiomatous process involved both the retina and the central nervous system, while the term "von Hippel's disease" has been reserved when only the retina is involved [4]. Although the term von Hippel-Lindau disease was first used in 1936, its use became common only in the 1970s [311, 312].

Epdemiology

VHL prevalence is estimated at 1/53,000 and annual birth incidence at 1/36,000 with over 90 % penetrance by the age of 65. Men and women are equally affected. The age at diagnosis varies from infancy to age 60–70 years, with an average patient age at clinical diagnosis of 26 years [313, 314].

Systemic Manifestations

Von Hippel-Lindau (VHL) disease includes numerous benign and malignant tumors of the CNS, kidneys, neuroendocrine and genitourinary systems. These tumors specifically include: hemangioblastomas of the brain, spinal cord, and retina; renal cysts, clear cell renal cell carcinoma, pheochromocytoma, pancreatic cysts, neuroendocrine tumors, endolymphatic sac tumors, epididymal and broad ligament cysts.

Central nervous system (CNS) hemangioblastomas are the most common tumor type in VHL, seen in 60–80 % of all patients, and if present, multiple hemangioblastomas commonly develop (~90 %) [316]. CNS hemangioblastomas have a benign histology, but can cause a variety of neurological signs and symptoms based on their anatomic location. Cerebellar hemangioblastomas may be associated with headache (75 %), gait ataxia (55 %), dysmetria (29 %), and vomiting (28 %) [317]. Brainstem involvement may result in dysphagia, decreased sensation, or hyperreflexia. The most common symptom associated with spinal hemangioblastomas is pain, although focal weakness or sensory loss may occur to compression at the level of the peripheral nerve root. Many of the spinal tumors are associated with syrinx. Symptoms are often mediated by an enlarging cyst either causing mass effect or obstructive hydrocephalus. In fact, 70 % of symptomatic brainstem or cerebellar hemangioblastomas and 90 % of spinal hemangioblastomas were associated with peritumoral cysts, which can account for 4–12 times the volume of the tumor [318, 319]. Serial monitoring of these tumors show that growth can be stalltutory, with alternating periods of growth and relative quiescence.

Renal cell carcinoma is seen frequently in patients with VHL, occurring in approximately 70 % by age 60 years and is the leading cause of death in this syndrome [311, 312]. Pheochromocytomas may cause diaphoresis, palpitations and hypertension, or may be asymptomatic.

Pancreatic lesions are often asymptomatic cysts but may cause endocrine or exocrine insufficiency, and rarely, malignant behavior has been observed [320]

Endolymphatic sac tumors are seen in 10–15 % of individuals and can cause variable hearing loss, vertigo, tinnitus, or unexplained balance difficulties. Hearing loss is typically gradual; however, intralabyrinthine hemorrhage can result in sudden hearing loss [316]. To assist in the diagnosis of small tumors, symptomatic individuals should get MRI brain with thin slices through the internal auditory canal; those with suspected hemorrhage may benefit from CT head.

Cysts of the epididymis are commonly observed in VHL but rarely led to symptoms, unless bilateral, which can result in infertility.

Ophthalmic Features

Retinal capillary hemangioblastoma (also called retinal angioma, hemangioma or retinal hemangioblastoma) is the hallmark ocular lesion seen in VHL. RCHs are present in 37 % of VHL patients with bilateral ocular lesions in 58 % of patients and multiple lesions in the same eye approximately 30 % of the time [321, 322]. The histopathological appearance of the RCA is identical to the hemangioblastoma found in the central nervous system [312]

The retinal lesions become visible ophthalmoscopically between ages 10 and 35 years, with an average age of onset

of 25 years, about a decade before the peak occurrence of cerebellar tumors ([5, 311, 322–324]. Patients with RCA have a 25 % risk of developing CNS hemangioblastomas [325]

The most common RCA site is the midperiphery, with some apparent preference for the temporal and inferior portions of the retina [4]. Tumors located in the juxtpapillary retina, optic papilla, or intraorbital portion of the optic nerve are less common [4, 326–328].

Whether these angiomas arise de novo or develop from embryonic rests of partially undifferentiated angioblastic elements has not been firmly established [7] Histopathologically, the RCAs consist of relatively well-formed capillaries [329]. Electron microscopic studies have confirmed that the vessels of this tumor have endothelial cells, pericytes, and rarely multilaminar pericytes with smooth muscle differentiation. The endothelium has been noted to have fenestrations, which possibly explains the basis of the extravagated exudate that is characteristic of the larger tumors [329, 330].

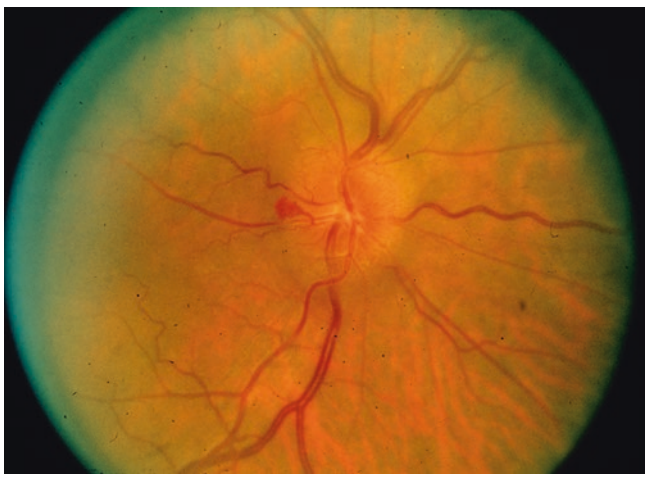

Fig. 16.20 Retinal capillary hemangioblastoma adjacent to temporal disc (Courtesy Dr Frank Judisch collection U of Iowa)

Although the retinal lesions may be detectable at an earlier age, they usually do not produce symptoms before the third decade of life [311, 324]. Progression of identified lesions and the appearance of new retinal lesions has been observed in individuals with VHL studied over several years [323]. Progression of the retinal angiomas is highly variable, but when untreated, tumor enlargement, hemorrhages, exudates, gliosis, and retinal detachment often develop, which may result in total visual loss with glaucoma and phthisis bulbi [8].

In the early stages the angioma is a small nodule with a well defined paired vascular supply (Figs. 16.20 and 16.21) [328]. This transforms into a larger (2–3 disc diameters), rounded, yellow to red tumor in the retina, usually with large, dilated, and tortuous afferent and efferent vessels [8]. The hallmark of the mature tumor is a pair of markedly dilated vessels running between the lesion and the disc, indicating the occurrence of significant arteriovenous shunting (Fig. 16.22) [5]. Because of the shunting, the color of the retinal vein often approaches that of the retinal arteriole [4]. These vessels have been shown to leak fluorescein, and transudation of fluid into the subretinal space causing lipid accumulation [5, 322, 331]. A macular star may develop, or the exudates may assume a circinate pattern (Fig. 16.23) [4]. The deposition in the macula of large amounts of lipid-like material is a well-known complication of angiomatosis retinae, even when the angiomatous malformations are confined

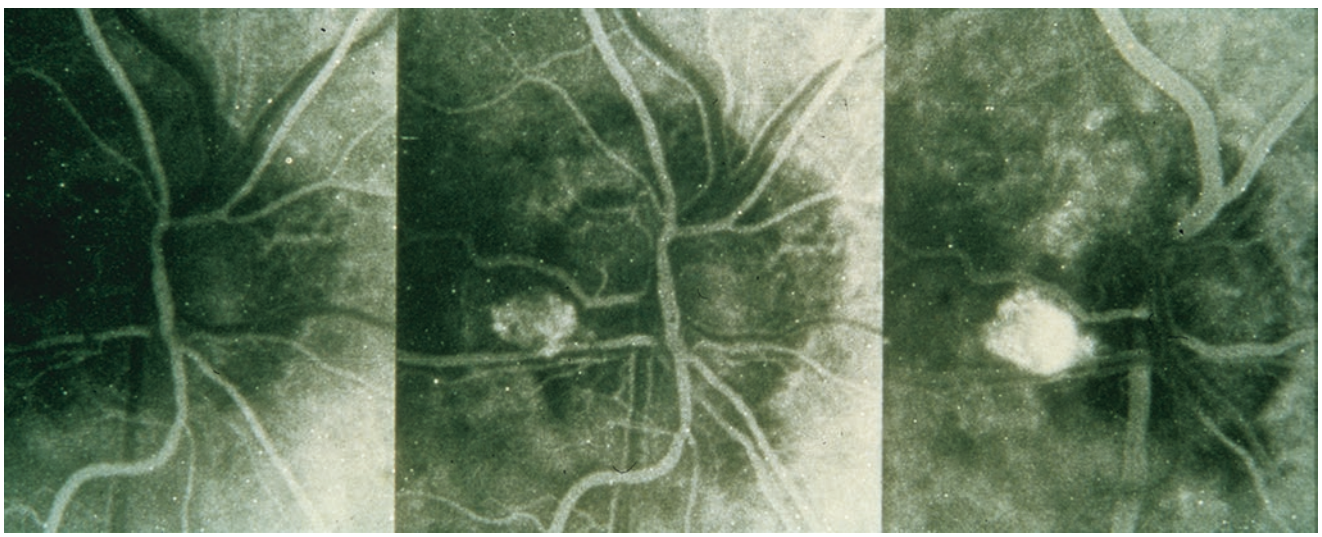

Fig. 16.21 FA of same eye shown in Fig. 16.24 (Courtesy Dr Frank Judisch collection U of Iowa)

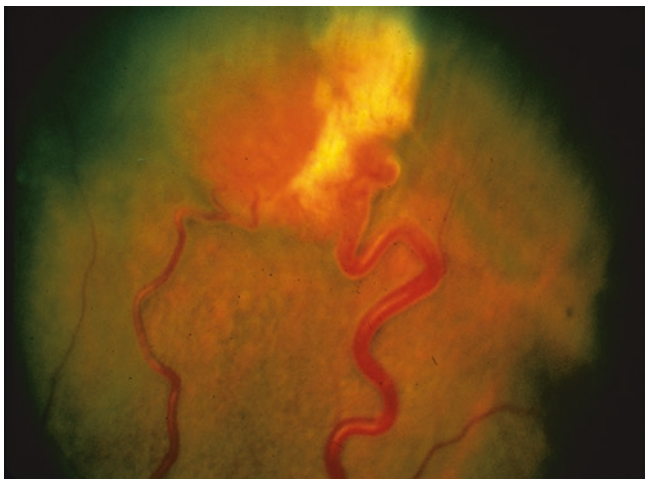

Fig. 16.22 Retinal capillary hemangioblastoma (Courtesy Dr Frank Judisch collection U of Iowa)

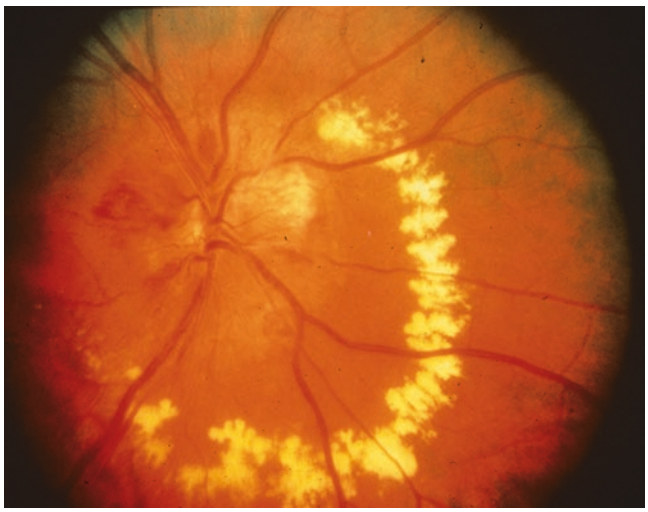

Fig. 16.23 Retinal capillary hemangioblastoma with circinate exudate (Courtesy Dr Frank Judisch collection U of Iowa)

to the periphery of the retina [332]. If the condition is left untreated, the usual course is continued exudation into and beneath the retina, leading to extensive retinal detachment and ultimately to neovascularization [4, 5, 322, 331].

The secondary ophthalmic complications commonly include retinal exudates and hemorrhages, fixed retinal folds and organized fibroglial membranes, retinal detachment, rubeosis iridis, peripheral anterior synechiae, and chronic retinal detachment [9]. Additionally, VHL patients may develop uveitis with resultant iris bombe and secondary glaucoma or rubeosis iridis may develop secondary to chronic retinal detachment or uveitis [333]. Left untreated, phthisis is a common result.

Although the retinal periphery is most commonly affected, angiomas of the iris have been described.

Table 16.9 Ocular manifestations of von Hippel-Lindau disease

Orbital
– Proptosis
Intraocular
Anterior Segment
– Angiomatosis of the iris
Media
– Vitreous hemorrhage and vascular proliferation
– Vitreous membrane formation
Retina
– Angiomatosis with (feeder vessels)
– Juxtapapillary retinal angiomatosis
– Secondary retinal hemorrhages and exudates
– Retinitis proliferans (less frequent)
– Retinal detachment (late sequelae)
– "Macular star" lipid-like material in macula
– Cystic degeneration
– "Twin" retinal vessels
Optic Nerve
– Angiomata of optic nerve
– Papilledema
Other
Secondary glaucoma

Additionally, hemangioblastomas involving the retrobulbar optic nerve or posterior visual pathway are uncommon, but angiomatous lesions have been described at the optic disc, the juxtapapillary retina, and near the macula [322, 327, 334, 335]. Hemangioblastomas of the optic nerve may rarely enlarge, ultimately resulting in profound visual dysfunction [331, 335]. Papilledema may be the initial sign of tumors of the cerebellum producing increased intracranial pressure [5, 336].

The pathogenesis of vision loss in VHL patients is multifactorial, but retinal detachment usually plays a prominent role. The retinal detachments can be rhegmategenous or nonrhegmatenous. Such detachment can occur as the direct result of proliferation of neovascular tissue into the vitreous or as the indirect result of bleeding from the retinal angiomas into the vitreous. It can also occur secondary to subretinal exudation or hemorrhage [332]. Fibrous proliferation into the vitreous cavity is reported but uncommon [337]. Vision loss may also result from macular edema, macular holes, glaucoma, uveitis and optic atrophy. Table 16.9 presents a summary of the ophthalmic manifestations of VHL.

Diagnosis

The clinical diagnosis of VHL has traditionally depended on family history and the presence of RCH, CNS hemangioblastoma or visceral lesions (visceral lesions include: renal

cysts and renal carcinoma, pancreatic cysts, pheochromocytoma, islet cell tumors, epididymal cystadenoma, and endolymphatic sac tumors). Diagnosis is now primarily confirmed by genetic testing.

Treatment

Following initial diagnosis, an individual diagnosed with von Hippel-Lindau (VHL) disease should undergo careful neurologic, ophthalmologic, audiologic and medical evaluation. Ophthalmologic evaluation should be undertaken to evaluate for retinal hemangioblastomas. Hearing should be tested to assess symptomatic endolymphatic sac tumors. Medically, blood pressure measurement should be screened to evaluate for pheochromocytoma, and urine catecholamine metabolites should be included if age ≥5 years). If the patient is ≥16 years, a screening abdominal ultrasound should be performed. An initial brain and spine MRI would be indicated for abnormal neurologic signs/symptoms or if the age at diagnosis is ≥16 years. A genetics consultation may be warranted.

On-going surveliance recommendations include: yearly neurologic, ophthalmologic and blood pressure evaluation starting at 1 year of age;

Beginning at age 5 years: annual blood or urinary fractionated metanephrines, and audiology assessment every 2–3 years.

Starting at age 16 years: annual abdominal ultrasound and every *other* year MRI of the abdomen, brain, and total spine (w/wo contrast).

No standard guidelines exist for the management of lesions seen in VHL. Complete resection of CNS hemangioblastomas is curative, and is the goal for symptomatic tumors. Asymptomatic tumors may be observed clinically and radiographically. Stereotactic radiosurgery has been explored with small asymptomatic hemangioblastomas, although the long-term benefits are unknown as initial lack of progression may represent a quiescent phase. Overall mortality rates for surgery of CNS hemangioblastomas is 10 %, with higher rates if the brainstem is involved [338]

For renal cell lesions, monitoring only is recommended for lesions smaller than 3 cm. Early surgery is recommended for lesions suspicious for renal cell carcinoma is recommended. Nephron-sparing or partial nephrectomy may be possible without compromising survival [339]. Cryoablation and radiofrequency ablation therapy may be used for small lesions [340, 341]

Pheochromocytomas are surgically removed, sometimes laparoscopic approach is possible. It is important to have preoperative alpha-adrenergic blockade, and optional beta-adrenergic blockade for 7–10 days.

Pancreatic cysts are common but generally do not need surgical removal.

Pancreatic tumors are often indolent, but they can cause metastatic disease. Surgery is considered when the risk of metastases is high, which include the following criteria [342]

- A tumor of ≥3 cm;
- A mutation in exon 3; or
- A tumor with a doubling rate <500 days

Endolymphatic sac tumors may warrant surgical removal, but there is a potential surgical risk of total deafness. Early intervention of small tumors has been shown to preserve function [343]. Epididymal or broad ligament papillary cyst adenomas typically do not require surgery, unless symptomatic or threaten fertility.

Tobacco and industrial toxins should be avoided since they are considered a risk factor for cancer. Contact sports should be avoided if abdominal lesions are present.

Treatment of the RCH depends on size and location. Small peripheral lesion <500 μm in size may be observed if non-vision threatening. Juxtapapillary RCH are more likely to need treatment to prevent vision loss [344]. Cryo-therapy for larger (up to 4 mm) lesions and laser photocoagulation is recommended for smaller lesions (up to 1.5 mm). Photodynamic therapy has also been successful for larger lesions [345]. Photodynamic therapy, proton beam therapy and anti-angiogenesis therapy have shown variable success treating RCH [346–351].

In general, treatment is more likely to be successful if implemented before development of subretinal fluid, macular edema, exudate, or exudative detachment.

Incontinentia Pigmenti

Definition

Incontinentia pigmenti (IP) is a rare X-linked inherited disease that presents in the skin, nails, teeth, central nervous system (CNS), and eye. The syndrome was named for the characteristic skin hyperpigmentation that occurs as the disease progresses.

IP is an X-linked dominant neurocutaneous syndrome expressed predominantly in females. The majority of cases are associated with a mutation in the *IKBKG* gene (formerly known as *NEMO*), and no other gene associations are known [358]. The gene product (IKK-gamma) activates NF-κB, which helps to protect the cell against pro-apoptotic factors as well as regulates expression of genes important in immune function, inflammatory response, cell adhesions, and stress reaction. Skewed X-inactivation in females is common, conferring a survival advantage to cells inactivating

the X chromosome harboring a mutation [359]. Genetic testing identifies a mutation in ~75 % of females. There is a mutational hot spot with 2/3 of affected girls having a deletion of exons 4–10. Sequencing identifies an additional 9 % of mutations [360]. In those without an identifiable mutation, skin fibroblasts or analysis of leukocytes for skewed X-inactivation may also be pursued to corroborate a clinical diagnosis.

The disease was previously characterized as lethal for males in the perinatal period; however, there are now greater than 60 reported cases. Classic IP in males may be due to Kleinfelter syndrome (XXY) or somatic mosaicism due to a post-zygotic, spontaneous *IKBKG* mutation [361, 362]. Additionally, some males may have an allelic variant of the *IKBKG* gene that is compatible with survivability, which is clinically associated with hypohydrotic ectodermal dysplasia with immunodeficiency (HED-ID).

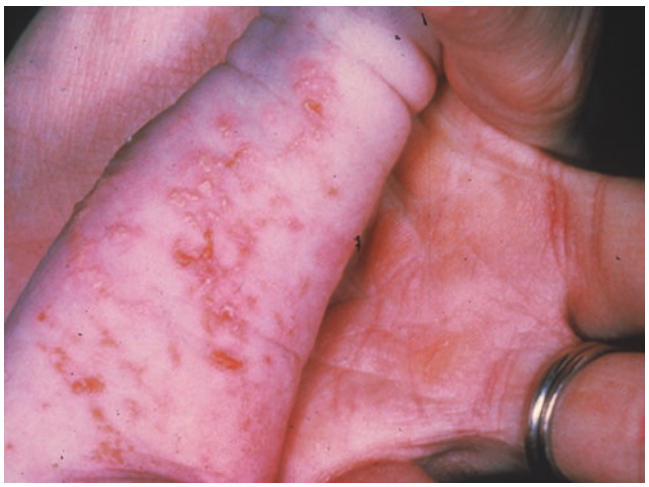

Fig. 16.24 Blaschko-linearly distributed erythema and blisters (Courtesy Dr Frank Judisch collection U of Iowa)

History

Garrod described the first case of IP in 1906 in a child with pigmentary changes, developmental delay, and tetraplegia [352, 353] however, it was not until Bloch presented the disease at the Swiss Society for Dermatology in 1926 that the syndrome was named incontinentia pigmenti [354]. Bloch named the disease because of the pathologic finding of pigmentary incontinence (where melanin granules 'drop out' from the epidermis and are found free in the dermis or within dermal macrophages) that results in the clinical finding of skin hyperpigmentation. Sulzberger published a follow-up report of the same case in 1928 and together are remembered eponymously (IP is also known as Bloch-Sulzberger syndrome) [355, 356]. Interestingly, Bloch's initial case was t a 1 year old girl who was first admitted to the eye clinic with a diagnosis of a glioma with secondary retinal detachment; she was subsequently referred to Bloch's dermatology clinic for the differential diagnosis of a peculiar skin pigmentation [357].

Systemic Features

Cutaneous manifestations of IP are the most characteristic clinical findings and evolve through four roughly consecutive, but often overlapping, morphologic stages. Stage 1 is the vesiculobullous stage and presents as widespread Blaschko-linearly distributed erythema and blisters in an otherwise healthy female infant (Fig. 16.24). Lines of Blaschko represent pathways of epidermal migration and proliferation during embryogenesis. Vesiculobullous lesions are typically present in the first days to weeks of life, although occasionally stage 1 occurs in utero and has nearly resolved at time of birth and therefore may be missed clinically. In

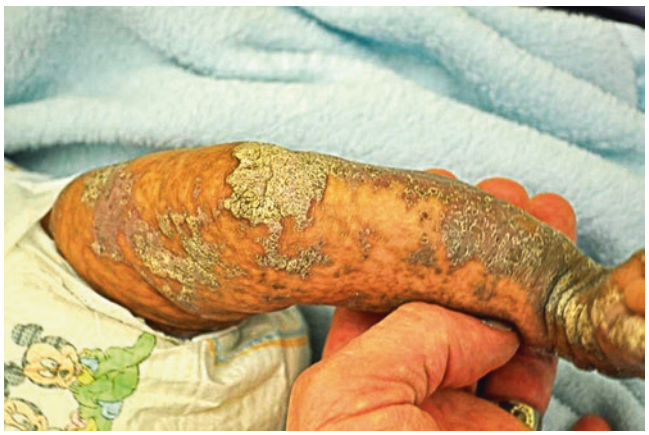

Fig. 16.25 Blaschko-linear verrucous plaques in Stage 2 Incontentia Pigmenti

stage 2 the vesiculobullous lesions are replaced by hyperkeratotic papules coalescing to form verrucous plaques. This stage may be present at birth and evolve over the first several months of life (Fig. 16.25). Stage 3 is characterized by 'whorls and swirls,' of grayish-brown hyperpigmentation which replace the lesions of stage 2. This can occur at weeks to months of age and persists for months to years (Fig. 16.26). The name "incontenentia pigmenti" reflects the pathologic appearance of skin at this stage. These hyperpigmented lesions are most marked on the trunk and intertriginous sites and may not fade until adolescence. Finally, in the second and third decade of life, linear hypopigmented atrophic and alopecic streaks appear in the affected areas, often most obviously visible on posterior extremities, especially on the lower legs. These remain throughout adulthood.

In addition to the characteristic cutaneous findings, patients may also present with other ectodermal abnormalities

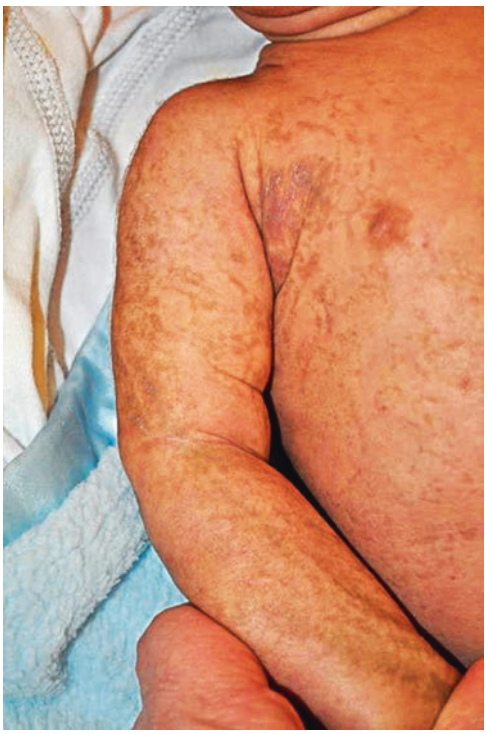

Fig. 16.26 Blaschko-linear hyperpigmentation in Stage 3 Incontentia Pigmenti

including: dystrophic nails, alopecia, abnormal "wooly" hair, small and/or abnormally shapedteeth, hypodontia, breast hypoplasia and supernumerary nipples [363, 364].

Neurologic features are present in 30 % of individuals with IP [365] and if present, most commonly present in the neonatal period. Neonatal encephalopathy with or without seizures have been reported in the first week of life. The pathophysiology is incompletely understood, but likely due to a microangiopathy [366] with associated ischemia and possible hemorrhagic transformation. While many cases suggest greater involvement of the small vessels, there are reports of large vessel strokes, with broader territories of both cortical and subcortical injury [366, 367]

MRI brain findings often show periventricular leukomalacia, although there can be multiple, scattered foci involving cortex, basal ganglia and subcortical white matter [368]. Some early radiographic findings may be reversible [369] or chronic and asymptomatic [370] but early injury typically results in necrosis and encephalomalacia with clinical sequelae. Many of the clinical findings can be attributed to the extent and location of injury, resulting in findings such as spasticity, intellectual disability, hemiparesis, or epilepsy. Other MRI findings include volume loss of the corpus callosum or generalized atrophy. The co-existence of other hemispheric or multifocal white matter abnormalities in these individuals suggest that the decreased volume is due to loss of white matter rather than a developmental hypoplasia [368]. Individual cases of cerebellar hypoplasia [371] focal polymicrogyria [372, 373], or heterotopic grey matter [374] suggest that some pathologic features develop prenatally.

The neonatal period appears the highest risk for stroke, but recurrence may happen later in infancy and childhood. A predilection for white matter injury remains for childhood strokes as well. Neonatal strokes in IP may present with non-lateralized findings such as encephalopathy or coma. However, focal findings may occur, including focal clonic seizures. Seizures occur in ~25 % of individuals with IP [375, 376]. Seizures frequently correlate with acute cerebrovascular injury, although recurrent seizures (epilepsy) eventually occur in almost half of those with acute seizures. Significant motor disability (i.e. cerebral palsy) is seen in 11 % [365, 376] and intellectual disability in 8 % [375, 376]. The risk for intellectual disability is higher in sporadic cases compared to familial cases [363]

Ophthalmic Features

Ocular abnormalities have been reported in 20–77 % of IP patients [358, 365, 375–380]. In a recent literature review looking at IP patients with associated neurologic findings, ocular abnormalities were present in 45 % of the study cohort [368]. The primary ocular findings is peripheral retinal non-perfusion with proliferative vitreoretinopathy. Secondary findings include retinal detachment, strabismus, cataract, and optic nerve atrophy. Iris hypoplasia and corneal changes have also been reported [381, 382]. The most common finding is retrolental mass or membrane suggestive of persistent hyperplastic primary vitreous (Fig. 16.27) [383]. The primary causes of severe visual dysfunction in patients are the retinal vascular abnormalities, ranging from peripheral retinal avascularity to neovascular and fibrous proliferation with traction retinal detachment (Figs. 16.28 and 16.29) [375, 378, 384].

Many of the earlier reported cases were enucleated because the ophthalmologist could not certainly rule out glioma or other neoplasm on clinical grounds since the ocular lesions resembled developmental and inflammatory conditions considered in the differential diagnosis of leukocoria [385, 386]. The less severe of these masses suggest lesions described by Mann as congenital retinal folds [386]. Pigmentation changes in the conjunctiva have been described as very similar to the cutaneous lesions typical found in IP [387].

Although ophthalmic manifestations associated with IP affect all segments of the globe, the primary site of ocular involvement is the retina [388]. Various abnormalities have been described: intraretinal vascular anomalies, including avascularity of large areas in the periphery; neovascular proliferation with extension from the retina into the vitreous,

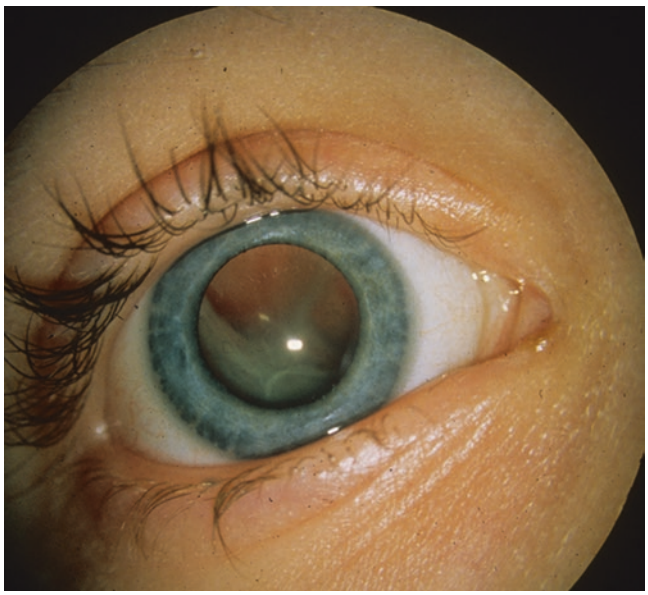

Fig. 16.27 Retrolental fibrosis/mass in patient with IP and ROP (Courtesy Dr Frank Judisch collection U of Iowa)

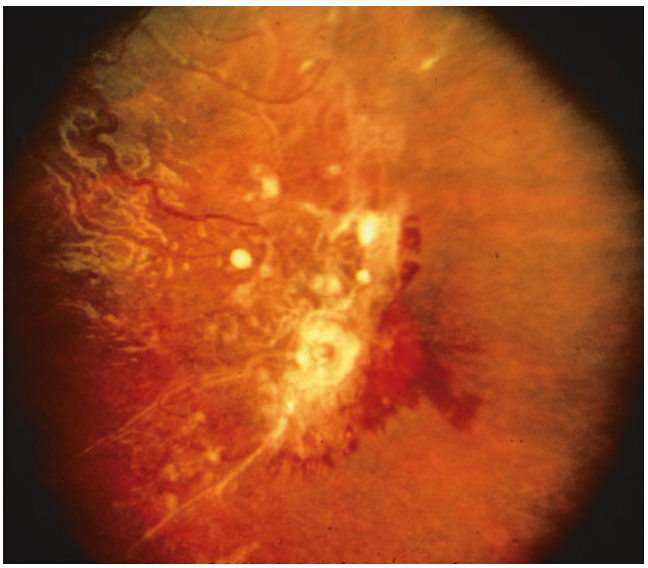

Fig. 16.29 Retinal vascular tortuosity and vessel closure with non perfusion telangiectasia and fibrosis (Courtesy Dr Frank Judisch collection U of Iowa)

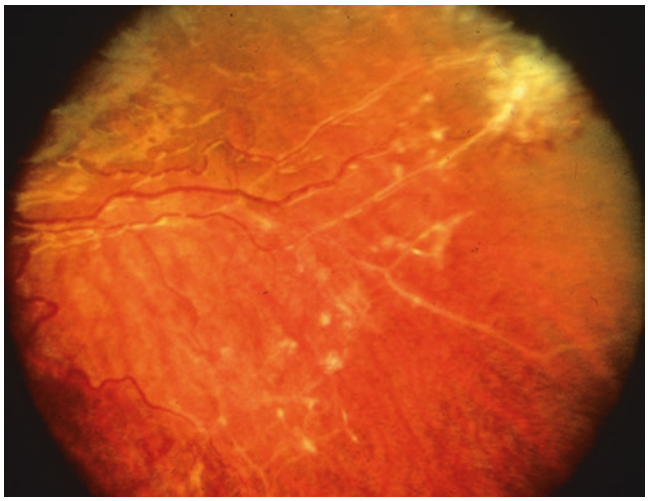

Fig. 16.28 Retinal vascular tortuosity and vessel closure with non perfusion and telangiectasia (Courtesy Dr Frank Judisch collection U of Iowa)

secondary hemorrhages, and arteriovenous shunting; and the formation of a mass of fibrous tissue and dysplastic retina in the peripheral fundus [5]. Patients with peripheral vascular changes have shown avascularity at the periphery of the temporal retina [389, 390]. Although the natural history of the ocular changes in IP is not clearly defined, it is postulated there is a progression from retinal avascularity with hypoxia, through reactive neovascular proliferation, to cicatrization with development of retinal detachment and dysplasia as fibrovascular membranes in the vitreous contract [5]. The retinal changes in IP have a striking similarity to the vascular lesions of early retinopathy of prematurity. Both have abnormal arteriovenous connections and intraretinal microvascular anomalies at the temporal equator [388]. The vascular ischemic areas may be difficult to appreciate or clinically absent without fluorescein angiography testing [384, 391].

Diagnosis

The diagnosis of IP is typically made clinically, however, adjunctive testing may include skin biopsy (which will show suggestive, but not pathonomonic findings of spongiotic eosinophilic dermatitis when completed in stage 1), complete blood count with differential (which will show eosinophilia in stages 1 and 2) and molecular genetic testing.

Patients with suspected IP need to be seen by a pediatric ophthalmologist or a retina specialist at birth and then at least monthly for the first 3–4 months. After this period, exams are recommended at quarterly intervals up to 1 year and every 6 months up to age 3 [379]. The frequency of examinations may be modified by positive retinal findings requiring more frequent observation or need for treatment. Visual prognosis is improved for a child with no ophthalmologic findings during the first year of life [392, 393].

Treatment

There are no efficacious treatments for the skin lesions of incontinentia pigmenti, other than standard, supportive wound care for blisters and treatment for any secondary infections. Affected children should be seen early on by a

pediatric dentist, with referral recommended at age 6 months or when teeth erupt, whichever occurs first. Dental management may include dental implants. If the degree of hypodontia interferes with speech and/or eating, referral to speech pathologist is indicated.

Children with IP may present with leukocoria secondary to the fibrovascular mass. This has resulted in enucleation because of the possibility of malignancy. However, ophthalmoscopic differentiation of IP pseudoglioma from retinoblastoma should be possible for an experienced observer [5]. Since there has been no known association of malignant tumors of any kind with IP, confirmation of the diagnosis by dermatology consultation and skin biopsy should save these children from unnecessary enucleation.

When retinal findings are present it is not possible to predict whether the lesions will remain stable or progress slowly or rapidly towards retinal detachment and loss of vision [378, 394]. Photocoagulation treatment has been used in the presence of abnormal vessels that leak fluoroscein with exudative and fibrotic reaction in the surrounding retina and vitreous of IP patients [388]. Several early reports described photocoagulation of the avascular retina in IP patients when there was evidence of progression of retinal vascular proliferative changes [388–390]. These early reports of photocoagulation in IP patients were not uniformly successful and the value of photocoagulation in the patients was uncertain. However, most types of proliferative retinal vasculopathy can now be successfully managed with ablation of the hypoxic retina and several recent studies have reported the benefits of laser photocoagulation or cryotherapy in ischemic regions of the retina in order to stop the progression of vasculopathy in IP patients [395–397].

Non-retinal manifestations, such as strabismus and amblyopia may also need treatment. These problems are usually present before the age of two [379].

Resource for families:

Incontinentia Pigmenti International Foundation (IPIF)

30 E 72nd St., New York, NY, 10021. www.ipif.org. Email: ipif@ipif.org. Phone: 212-452-1231

Wyburn-Mason Syndrome

Definition

Wyburn-Mason syndrome (WMS), also called Bonnet-Dechaume-Blanc syndrome, is a congenital, non-heritable, sporadic condition characterized by arteriovenous malformations of the retina, visual pathways, midbrain and facial structures. Although considered one of the phakomatoses, a minority of the reported arteriovenous malformation patients have skin involvement [398].

Wyburn-Mason is a sporadic condition without reported familial recurrence or a known candidate gene.

History

Unilateral retinal arteriovenous malformation was first described by [399]. Over the next 50 years a succession of authors [400, 401] described case reports with combinations of retinal or retinal and cerebral arteriovenous malformation until 1932 when the full spectrum of retinal, cerebral and facial skin vascular changes were described in two separate reports by Brock and Dyke and authors Krug and Samuels [402, 403]. In the English literature, however, the syndrome is attributed to Bonnet, Dechaume, and Blanc for reporting the association of retinal vascular malformations with ipsilateral cerebral arteriovenous malformations and facial nevi [404] and Wyburn-Mason for his 1943 description of "arteriorvenous aneurysm of mid-brain and retina, facial naevi and mental changes" in a clinical patient series report [405]. A major review by Schmidt, Pache and Schumacher suggest using the term *congenital retinocephalic vascular malformation syndrome* for this disorder to avoid confusion with the many names associated with this disorder [398].

Epidemiology

The prevalence is not known but the condition is congenital and very rare. The most extensive review of retinal arteriovenous malformations identified 121 patients in the literature [398]. The sex ratio is even [398].

Systemic Manifestations

Cerebral lesions most commonly appear along tracts of the visual pathway including the optic chiasm, tracts, and radiations, with the highest frequency of lesions seen in the orbit. However, AVMs may also occur in the thalamus, hypothalamus, or suprasellar area [406]. These vascular malformations can remain asymptomatic for several years. Even with symptomatic AVMs, the clinical presentation may vary widely depending on the location and number of vascular lesions. The predilection for the optic pathway may lead to associated visual field cuts (e.g. homonymous hemianopia), optic pallor, afferent pupillary defect, or decreased visual acuity. Other symptoms may include headache, retro-orbital pain, focal weakness, and occasionally seizures. Rupture of an AVM results in subarachnoid or intraparenchymal hemorrhage, with associated symptoms due to mass effect from hemorrhage or ischemia (vasospasm may occur with subarachnoid

hemorrhage). In a review of 27 patients, six had a reported history of cerebral hemorrhage [406]. Unruptured cerebral AVMs may also become symtpomatic either from ischemia due to a vascular steal phenomenon or from mass effect.

In this syndrome, arteriovenous malformations may also rarely occur in the facial skin, mouth, nasopharynx, lung, and bone. AVMs occuring on the facial skin appear as red/brawny telangiectatic patches, often over the upper and or mid facial structures. Cutaneous AVMs frequency are feel warm on palpation and sometimes a bruit may be appreciated. The differential diagnosis of this cutaneous lesion is simple capillary malformation such as port wine stain or nevus simplex versus complex/sydromis vascular malformation such as Struge Weber syndrome or Klippel Trenauny syndrome. Oronasopharyngeal involvement has also been reported with spontaneous bleeds (epistaxis, oral bleeds) as well as facial asymmetry. Orbital involvement can cause proptosis, and may also have an accompanying bruit.

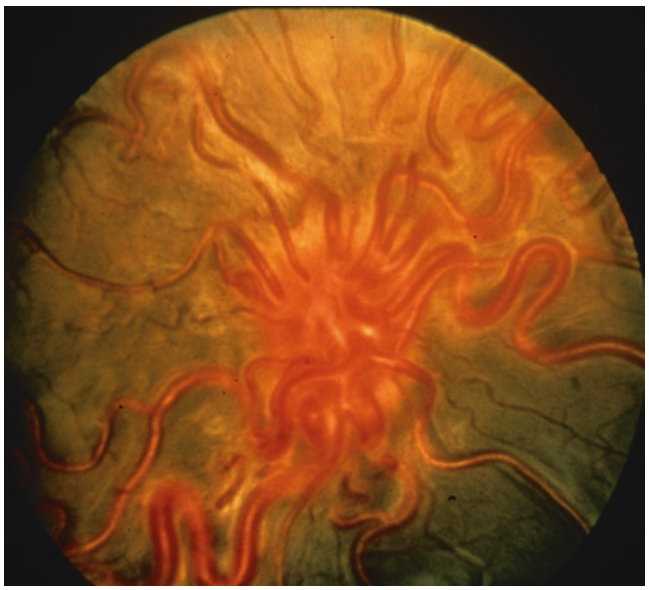

Fig. 16.30 Retinal arteriovenous malformation (Courtesy Dr Frank Judisch collection U of Iowa

Ophthalmic Manifestations

The retinal arteriovenous malformation (AVM) appearance is the most important ocular clue for making a diagnosis of WMS. The typical retinal lesion consists of a markedly dilated and tortuous artery connected directly to a similar-appearing vein (Fig. 16.30). There is no apparent intervening capillary bed. Some authors refer to these vascular malformations as "arteriovenous aneurysms." Archer et al. proposed that the term "retinal arteriovenous communication" be employed [407]. Other authorities have suggested using the term "racemose hemangioma," since a definite arteriovenous communication cannot always be demonstrated [4]. The direct communication between the artery and vein permits arteriolar blood to pass into the venous system, and it is often impossible to determine where one ends and the other begins unless fluorescein angiographic studies are performed [4]. Fluorescein angiography demonstrates a rapid transit of dye through the arteriovenous communication and no leakage in the better compensated patients [408]. Thus, this condition is often asymptomatic and nonprogressive[409].

Archer et al. classified retinal arteriovenous anastomoses into three groups, as follows [407]:

- Group I is characterized by small arteriole-venule anastomoses, which may be subtle and difficult to clinically detect. These vessels are usually isolated to a sector or quadrant of the retina.
- Group II represents direct artery-to-vein communication without intervening capillary or arteriolar elements causing hyperdynamic flow through low-resistance veins. This group may represent an exaggerated form of the abnormalities included in group I and is likewise geographically segmented within the fundus. Complications can range from edema to hemorrhage.
- Group III includes malformations characterized by markedly convoluted, dilated, and tortuous retinal vessels extending throughout the entire fundus, making it virtually impossible to differentiate between arterial and venous components. These eyes are usually severely vision impaired, typically leading to earlier diagnosis in childhood. Patients in this group are at higher risk for systemic vascular involvement.

The diagnosis of WMS may be made without the characteristic retinal lesion [410]. Wyburn-Mason's original series described retinal arteriovenous malformation in 14 of the original 20 patients having intracranial arteriovenous malformations [405].

The retinal lesion of WMS is congenital and symptoms usually appear before age 30. While the intracranial malformation may hemorrhage, the retinal lesion is usually stable. Occasionally, retinal hemorrhage or exudation may occur [4, 7]. In the involved area, the retinal vessels are often increased in number, size, and tortuosity. The vessels in the vascular malformation do not pulsate normally. Hemorrhage from the retinal lesions is rare. Unlike the lesions of angiomatosis retinae, these vascular malformations have no particular propensity to cause an exudative retinal detachment [4].

The ophthalmoscopic appearance of the retinal arteriovenous malformation may vary from small, abnormal vessel

communications to extensive involvement of the entire fundus. The retinal lesion is almost always unilateral and there appears to be some preference for the inferotemporal retina [409]. Vision, therefore, may be normal or severely reduced depending upon the location of the lesion in the retina. Peripherally situated lesions usually cause little or no difficulty, in contrast to those situated near the posterior pole [4]. In the review by Schmidt at al, for patients with both retinal and cerebral arteriovenous malformation, 48 % were blind (NLP or LP) and 27 % had reduced acuity (20/30–20/200) [398].

The retinal lesions are generally described as nonprogressive [6, 411] however, these lesions are not always static. Retinal arteriovenous malformations have been documented to undego spontaneous regression [412], develop spontaneous thrombosis with resolution of the abnormal communication [413] or conversely demonstrate enlargement in size [414–416]. Patients may present with either acute or gradual vision loss. The former occurs secondary to spontaneous hemorrhage, and the latter is due to loss of nerve fibers from mechanical compression of the optic nerve, chiasm or optic tract [417].

Mild proptosis of the affected eye is often present and is reducible by applying pressure. It is believed that the proptosis results from an increased size of the retrobulbar blood vessels in and around the optic nerve [409, 402]. The optic foramen may be greatly enlarged [410, 411, 418, 419]. Additionally, an orbital AVM may produce an ipsilateral, occasionally pulsatile, exophthalmos [398, 404]. Exotropia, esotropia, cranial nerve palsys and nystagmus have also been described in WMS patients [4, 398]. Optic atrophy is an uncommon finding but has been reported with both orbital and optic pathway AVMs [409, 420–422]. Homonymous hemianopsia or hemianopia in one eye with a blind second eye is present in 25 % of WMS patients with cerebral AVMs [398].

Conjunctival vessel injection occurs in almost 30 % of WMS patients [398]. Iris vessels may also be abnormally dilated [423].

Glaucoma in WMS has been reported sporadically. Effron et al. described a child with WMS who developed rubeosis iridis and neovascular glaucoma secondary to a retinal AVM with central retinal vein occlusion and signs of retinal and choroidal ischemia [416]. Glaucoma cases secondary to presumed increased venous pressure on the episcleral vessels as well as case reports of presumed increased retrobulbar vascular pressure with increased intraocular pressure have been described [424, 425].

Histological examinations of the retina have shown that the dilated and tortuous vessels occupy the greater part of the thickness of the retina, and the remainder of this tissue being degenerate and cystic, while the optic nerve may be occupied by a tangle of blood vessels [403, 426–428]. Cystic degeneration of the choroid with absent chriocapillaris has been described in a rhesus monkey with a retinal AVM [429]. Pathologic specimens have shown that the vascular malformation may extend from the retina past the optic nerve to the chiasm and optic tract, and to the midbrain and cerebellum [403, 428]. Not surprisingly, compression on the optic nerve may be associated with loss of nerve fibers and decrease in the number of ganglion cells [428]. It may be impossible to distinguish arteries from veins since all these vessels demonsrtate fibro- muscular medial coats of variable thickness and wide, almost acellular, fibro-hyaline adventitial coats [428]. See Table 16.10 for ocular findings in WMS.

Table 16.10 Ocular manifestations of WMS

Orbital
General
– Pulsating proptosis
– Exophthalmos
– Intraorbital AVM
– Enlarge optic foramen
– Proptosis
Lid
– Ptosis
Extraocular
Conjunctiva
– Congestion bulbar conjunctiva
– Abnormally dilated conjunctival vessels
Intraocular
Anterior segment
– Reduced corneal reflex/corneal opacities
– Pupillary abnormalities (anisocoria, sluggish pupils, or other disturbances of pupil reaction, RAPD)
– Abnormally dilated iris vessels
Retina
– Retinal arteriovenous aneurysm
– Varicosity of retinal veins
– Tortuosity of retinal veins
Optic nerve
– Optic nerve arteriovenous angioma
– Optociliary shunt vessels
– Papilledema
– Optic atrophy
Other
Strabismus
– Esotropia
– Exotropia
Nystagmus
Loss of vision
Homonymous hemianopsia
External ophthalmoplegia
Ocular ischemia
Neovascular glaucoma

Diagnosis

The ocular diagnosis of WMS is primarily made through direct ophthalmoscopy of the retina. Ocular coherence tomography provides dramatic imagery [430]. Ocular and orbital ultrasound may be useful ancillary tests. If the diagnosis is suspected based on retinal findings and neurologic symptoms, MRI of the brain along with MR angiography of the head are the first-line diagnostic tests to evaluate for cerebral involvement. Conventional angiography may be indicated to better delineate arterial supply and can be useful for surgical planning.

Management

WMS Specific ocular treatment is generally not necessary and not indicated since the retinal lesions are frequently not progressive. Macular hemorrhage, vitreous hemorrhage, central retinal vein occlusion and neovascular glaucoma may warrant conservative management with photocoagulation and vitrectomy in selected cases [398]. Certainly, asymptomatic retinal AVM's should not be treated. However, if the lesion undergoes vascular degeneration with hemorrhage or lipid exudation, photocoagulation may be of benefit [417].

Surgical treatment of cerebral and cutaneous AVMs may include ligation, embolization, radiotherapy, and stereotactic cryosurgery. The decision to treat or observe a cerebral lesion is individualized and must take into account the patient's symptoms, location, and whether or not progressive changes have been observed. There is the potential for neurologic sequelae, particularly when attempting to access deep lesions (e.g. thalamus, midbrain). Other techniques, such as radiotherapy, can be associated with endocrine abnormalities if the hypothalamic-pituitary axis is targeted [406].

Klippel-Trenaunay and Klippel-Trenaunay-Weber Syndromes

Definition

Klippel-Trenaunay is a congenital syndrome (KTS) characterized by cutaneous capillary malformations (aka port-wine birthmark), lymphatic maformations, venous abnormalities, and hemi-hypertrophy of bones and soft tissues, usually involving one of the extremities.

KTS can occur in isolation or in combination with other syndromes. The disorder clinically resembles Sturge-Weber syndrome (SWS) and both entities have been noted in some patients [18]. When lesions include arteriovenous malformation, patients with such findings are said to have Klippel-Trenaunay-Weber syndrome [431]. Klippel-Trenaunay syndrome can be associated with hydrocephalus, cerebral calcification, AVMs and hemimegalencephaly [432–434]. Klippel-Trenaunay syndrome can also be present within the group of anomalies referred to as phakomatosis pigmentovascularis.

Klippel Trenaunay syndrome is generally thought to occur sporadically, but some clinical manifestations have been found to cluster in families, suggesting a possible autosomal dominant inheritance pattern [434].

A novel angiogenic factor gene (*AGGF1*) was initially identified as a candidate gene in a KTS patient with a t (5;11) chromosome translocation [446]. There has been at least one additional study showing an association of two specific polymorphisms within the *AGGF1* gene in a large case-control study [447]; however, further characterization of potential pathogenic mutations in this gene via sequencing and deletion/duplication analysis has not been published. While *RASA1* mutations have been found in Parkes Weber syndrome, these are not reported in Klippel-Trenaunay syndrome (without AV fistulas) [448, 449].

History

The initial report of an association between limb hypertrophy and vascular dilation was in 1869 by Trelat and Monod [435]. Klippel and Trenaunay described a specific triad of symptoms of cutaneous hemangiomata, hemihypertrophy, and varicosities in 1900 and published their neurocutaneous syndrome as "naevus variqueux osteo-hypertrophique" [436]. In 1907 Parkes Weber described essentially the same triad of symptoms with the additional finding of arteriovenous fistula [437]. This resulted in renaming KTS as Klippel Trenaunay Weber syndrome (KTWS) when the arteriovenous fistula was included in the findings of cutaneous hemangioma, hemihypertrophy and varicosities. It has been argued, however, that KTS and KTWS are different disorders in that KTS is predominantly a slow flow venous malformation and KTWS is always associated with a high flow arteriovenous fistula and does not demonstrate the lymphatic formations found in KTS [438–440]. In order to clarify the nomenclature it is proposed that when arteriovenous fistula is present in a patient with KTS, it should be termed Parks Weber syndrome, without the arteriovenous malformation it is KTS [438, 441]. KTS is also known as angioosteohypertrophy syndrome, congenital dysplastic angiectasis, osteohypertrophy nevus flammeus, and elephantiasis congenital angiomatosa [442].

Epidemiology

Klippel-Trenaunay syndrome is a rare condition, affecting about one in every 20,000–40,000 (2–5/100,000 live births)

children. Children of all ethnic groups can be born with Klippel-Trenaunay syndrome, and it affects males and females in equal numbers [443].

The origin of most cases of KTS is unknown. It was initially suggested that venous changes developed as a consequence of a deep venous obstruction that resulted in edema and hypertrophy of the limb [444] but it is now well accepted that venous abnormalities are not the causative insult. Baskerville et al. found that few patients with KTS have true atresia of the deep veins [445]. They hypothesized that embryonic mesodermal changes resulting in increased angiogenesis lead to increased vascular flow causing tissue hypertrophy and vascular changes.

Systemic Manifestations

The classic triad of KTS includes capillary malformation, venous varicosity, and bone and soft tissue hemihypertrophy of the affected limb or limbs. In addition to capillary and venous malformations, lymphatic disease is also common manifesting as superficial and deep lymphatic malformations and/or lymphedema. When combined with an arteriovenous malformation (AVM), the eponym for the disease is KTW or Parkes-Weber. In most cases a single limb is affected, with leg involvement being the most common. Limb length discrepancy has several orthopedic complications including compensatory scoliosis and hip dislocation.

The cutaneous vascular birthmark is often the first manifestation of KTS, usually presenting at birth or shortly after in a single extremity. The cutaneous besthunt was previously classified as a simple capillary malformation; however, the birthmark of KTS also usually contains components of lymphatic and venous malformation. The characteristic morphology of this lesion is a well demarcated geographic vascular patch with a tendency to thicken and develop lymphatic blebs over time [450, 451]. By adolescence, all patients have developed prominent venous varicosities that can be large, tortuous, and are susceptible to phlebolith formation and many develop significant soft tissue and/or boney overgrowth.

Complications of KTS include phleboliths, DVTs/pulmonary embolisms [452] coagulopathy, high output heart failure (if significant AVM is present), stasis dermatitis and ulcers, cellulitis, and bleeding. Rarely, long standing vascular malformation can result in dilated vascular channels within internal organs imparting a risk of life threatening bleeding or hemarthrosis when a joint is involved. Additionally, chronic lymphedema can predispose patients to the development of angiosarcomas [453]

Klippel-Trenaunay syndrome and Sturge Weber syndrome can, rarely, co-exist in the same patient when findings for both syndromes are met. When KTS is associated with a widespread pigmentary nevus, this presentation may fall under the category of what has been termed phakomatosis pigmentovascularis, and includes 4 subtypes [454]. Those which could include a presentation of KTS and/or Sturge Weber syndrome include phakomatosis cesioflammea, spilorosea, cesiomarmorata and unclassifiable subtypes. Phakomatosis cesioflammea includes dermal melanosis (or blue spots, previously termed "Mongolian spots") and capillary malformation. Phakomatosis spilorosea includes nevus spilus (aka speckled lentiginous nevus) and capillary malformation. Phakomatosis cesiomarmorata includes dermal melanosis and widespread reticulated capillary malformation. The association of these pigmented and vascular nevi was thought to be related to the phenomenon of twin spotting, but more recent evidence suggests that these seemingly disparate clinical findings may actually arise from the same post-zygotic mutation in the affected tissues [454].

Ophthalmologic Manifestations

Among the phacomatoses, KTS is one of the least likely to involve ocular structures. Since KTS is relatively rare, the ophthalmic manifestations have been gleaned from the medical literature often involving single case reports or small series of patients (Table 16.11). The majority of reported ocular findings have been vascular malformations involving the eye and orbit, with the ocular findings ipsilateral to the involved limb [435]. The abnormal findings have included orbital varix [455] retinal varicosities [435] angiomas of the choroid, conjunctiva and sclera [435, 456, 457] conjunctival telangiectasias [458, 459] and severe vitreoretinopathy [460]

Regional hypertrophy of the orbital contents has been described [455, 461]

Optic nerve enlargement may occur in KTS without inevitable visual deterioration [461]. However, bilateral visual loss in a patient with KTWS and enlargement of both optic nerves has resulted from biopsy proven optic nerve meningiomas [462]. Glaucoma occurs, but is less frequent in KTS than in the SWS [461]. Histopathology findings in the autopsy of neonate with KTS and congenital glaucoma demonstrated multiple anomalous angle structures. There was an absence of the scleral spur, the ciliary muscle inserted directly into the trabecular meshwork, the iris root inserted anteriorly, and an apparent continuous layer of material similar to Barkan's membrane was present. Additionally, the retina was dysplastic with extensive gliosis of the inner retinal layers and multiple astrocytic proliferations of the retinal nerve fiber layer [463]

Diagnosis

Klippel-Trenaunay syndrome may be suspected in children who have an extensive port wine stain, but the diagnosis may not be confirmed until the child is walking and lymphatic

Table 16.11 Ocular manifestations of KTWS

Orbital External
General
– Venous angioma (congenital varix)
– Proptosis
– Regional hypertrophy of orbital contents
Lids
– Ptosis
Extraocular
Conjunctiva
– Telangiectasias
– Angioma
Sclera
– Angioma
– Melanosis
Intraocular
Anterior Segment
– Anomalous angle structures
– Iris coloboma
– Heterochromic irides
Lens
– Cataracts
Choroid
– Choroidal angioma
– Chorioretinal scar
Retina
– Retinal varicosities
– Tortuosity of retinal vessels
– Central retinal vein occlusion
– Retinal holes
– Retinal dysplasia
– Astrocytic proliferations of the retinal NFL
Optic nerve
– Optic nerve enlargement
– Optic nerve hypoplasia
– Tilted disc with telangiectatic vessels
Other
Glaucoma
– POAG
– Congenital
Strabismus

blebs, varicose veins and limb hypertrophy are more obvious. Generally, a child has to have all three symptoms to be diagnosed with Klippel-Trenaunay syndrome. The diagnosis is confirmed with characteristic findings of complex vascular malformation on MRI with and without contrast of the affected segment of the body.

Treatment

Treatment considerations for KTS are specific for the type and severity of symptoms and physical findings. Associated glaucoma is similar to that seen for SWS with simpler treatment modalities [464].

For the systemic sequelae of KTS, custom-made compression garments are the mainstay of treatment, to support the malformed venous and lymphatic systems. In childhood, compression garments require updating every few months to accommodate growth. Additional considerations may include pain management and vascular laser for the cutaneous capillary malformation. Unfortunately, pulsed dye laser is has a less durable effect on the capillary malformations in this setting given the presence of underlying malformations which are not impacted by the laser. Phleboliths can cause significant pain and patients are often put on a trial of low dose aspirin to reduce associated discomfort and swelling. A recent retrospective cohort study by Nguyen et al. supports the use of aspirin for this purpose suggesting improvement in aching and shooting pain, as well as decreasing swelling in the majority of patients [465]. Periodic measurement of coagulation parameters including d-dimer, fibrinogen, and platelet count is advised. Coagulopathies often respond to a low-dose aspirin as well; however, occasionally patients, especially those who have developed embolic phenomenon, require other anticoagulation regimes including long-term low molecular weight heparin, warfarin or inferior vena cava filter placement [466]. Some individuals may be candidates for procedural interventions of large and symptomatic venous varicosities but this is dependent on the vascular anatomy of the affected limb, including patency of the deep venous system to allow for sufficient venous return if superficial veins are removed. Such interventions could include sclerotherapy, venous stripping and phlebectomy. One study of 20 patients who underwent surgical intervention for symptomatic varicose veins showed that all patients had initial improvement but 50 % had recurrence with an average follow-up time was 5 years [467]. Epiphysiodesis is indicated if limb length discrepancy is projected to exceed 2 cm at skeletal maturity. Physical therapy and occupational therapy can also be useful.

Ataxia Telangiectasia

Definition

Ataxia telangiectasia (AT) is a rare inherited disorder with ocular, immunologic and neurologic symptoms, in addition to radio-sensitivity and a predisposition for malignant transformation.

Ataxia telangiectasia is an autosomal recessive disorder caused by inactivating mutations of the *ATM* gene. *ATM* is located on chromosome 11 (11q22.3). This gene encodes a protein kinase playing a key role in the control of double-strand-break DNA repair [470]. *ATM* mutations are identifiable

in 90 % of affected individuals through sequencing of genomic DNA, but increased to 95 % through sequencing of cDNA. Additional duplication/deletion analysis increases the detection rate another 1–2 % [471]. Historically, peripheral blood karyotypes have been used for diagnosis as a 7;14 chromosome translocation is typically seen in 5–15 % of lymphocytes in affected individuals. Gene carriers do not have neurologic symptoms, but may have an increased risk of developing cancer.

History

The first description of this disorder was in 1941 [468]. He described the condition as cerebellar ataxia beginning in early childhood, associated with ocular apraxia, choreoathetosis, oculocutaneous telangiectasia, immune dysfunction, chromosomal instability, and hypersensitivity to x-rays, with a high incidence of respiratory infections and neoplasias [469].

Epidemiology

The prevalence of ataxia telangiectasia in United States is 1:40,000–1:100,000 live births.

Systemic Manifestations

Neurologic features typically present at age 1–4 years. Usually, the initial manifestation is ataxia that becomes apparent when the child starts to walk between ages 1–2. Many children then experience a transient gait improvement between 2–4 years where developmental progression supercedes disease progression. Gait and truncal ataxia is reported in 87 %, and progressive decline leads to use of a wheelchair in late school age or early adolescence. This gait decline is concordant with the observation of progressive cerebellar atrophy. While ataxic gait is typically wide-based, the characteristic gait in AT is narrow based and affected by other factors including difficulty reproducing patterned movement (apraxia), slow movements and decreased postural responses.

The next most common neurologic findings include dysarthria (82 %), dysmetria (75 %), and abnormal eye movements (80 %). Common eye movement abnormalities include oculomotor apraxia, difficulty with saccadic initiation, and saccadic intrusion with smooth pursuit. Extrapyramidal features develop in many individuals, including choreoathetosis (59–95 %), dystonia (16 %), and parkinsonism/bradykinesia (69 %) ([472]. Interestingly, there are no corresponding radiographic changes in the basal ganglia among patients with extrapyramidal symptoms.

Additional neurologic findings of myoclonus or intention tremor are reported in 25 % each. Excessive drooling is also frequently noted. Intelligence can be underestimated due to the effects of the movement disorder and bradykinesia resulting in slow verbal and motor responses; however, IQ is generally well preserved and many individuals complete high school or college. Additional barriers to academic achievement include difficulties with reading due to oculmotor apraxia and saccadic intrusions. Acquired postnatal microcephaly is noted in 17 %, and is generally proportional to other growth parameters.

If early ataxia is not recognized, the diagnosis may not be pursued until the mucocutaneous manifestations become apparent at age 3–6 years old. Conjunctival telangectasias are typically first to develop and are the most striking; however, cutaneous telangectasias (Fig. 16.31) with special predilection for the sun-exposed areas including ears, eyelids, malar cheeks, and neck also occur. Cutaneous telangectasias can be subtle.

Additional cutaneous manifestations occur later in childhood and these include: loss of subcutaneous fat, sclerotic skin, skin atrophy, and graying hair. Sad, mask-like facies are characteristic with end-stage cutaneous changes. Many affected individuals also develop non-infectuous cutaneous granulomas and nevoid pigmentary changes, especially café-au-lait macules, as a result of localized chromosome instability.

The majority of patients also have growth retardation while approximately one in three patients will have developmental delay and a smaller fraction have endocrine abnormalities including diabetes meliitus and hypogonadism [473]. Despite preserved strength, patients are usually wheelchair-bound early in the second decade of life due to progressive ataxia.

Children with AT have several humoral and cell-mediated immune defects, including low serum IgA, IgE, and IgG, increased serum IgM as well as T- and B-cell lymphopenias with relative paucity of CD4+ cells [474]

Subsequent systemic manifestations include recurrent sinopulmonary infections and chronic bronchiectasis. Patients that survive into late adolescence are at increased risk of developing malignancies, most commonly leukemias and lymphomas (accounting for 85 % of malignancies), due to increased frequency of spontaneous chromosomal abnormalities in AT patients compared to general population [475]. Ovarian cancer, breast cancer, gastric cancer, melanoma, leiomyomas, and sarcomas, have also been observed.

Survival has improved with many individuals living past 25 years (some reported survival >50 years). Respiratory failure secondary to chronic lung disease +/− superimposed infection is the most common cause of failing health and death.

Ophthalmic Manifestations

Patients present in early childhood with progressive cerebellar ataxia and later develop conjunctival telangiectases. Telangiectases typically develop between 3 and 5 years of

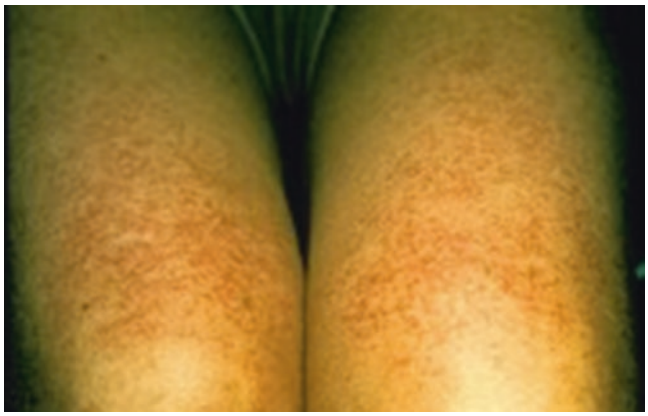

Fig. 16.31 Cutaneous telangiectasia in sun exposed areas (Courtesy Dr Frank Judisch collection U of Iowa)

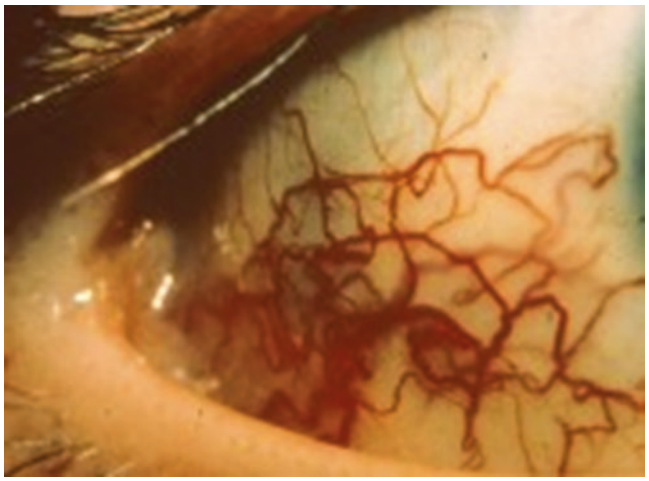

Fig. 16.32 Conjunctival telangiectasia (Courtesy Dr Frank Judisch collection U of Iowa)

age. The earlier ataxia can be misdiagnosed as ataxic cerebral palsy before the appearance of oculocutaneous telangiectases [469]. A characteristic oculomotor apraxia may occur more frequently than previously expected and often precedes the development of telangiectases [476].

The conjunctival telangiectasia is characteristically described as a dilated and corkscrew shaped conjunctival vessel in the interpalpebral fissure (Fig. 16.32). These vessels may extend into the fonices. The oculocutaneous telangiectasias may also be found on the nose, ears, palate and malar region. In addition to ocular motor apraxia, these patients may demonstrate hypometric saccades, deficient accommodation, strabismus and nystagmus [477].

Diagnosis

The clinical diagnosis of AT can be problematic before the appearance of telangiectases. The presence of early-onset ataxia with oculocutaneous telangiectases, however, supports the diagnosis of AT. The presence of oculomotor apraxia is a useful aid to early clinical diagnosis. The diagnosis can be reliably made by preschool age in patients with telangiectasia and oculomotor apraxia [478].

The differential diagnosis includes the ataxia-oculomotor apraxia (AOA) syndromes, AT like disease (ATLD), and Nijmaegen breakage syndrome (NBS). AOA Type 1&2 are due to deficiencies in aprataxin and senataxin, respectively. ATLD is caused by mutations in the *MRE11* gene, and manifests with milder ataxia. Nijmaegen breakage syndrome stems from an *NBS1* mutation, and consists of microcephaly and immunodeficiency. There is mention of an AT Fresno variant, with documentation of an ATM mutation, but with combined features of NBS (namely microcephaly and intellectual disability) and AT [479].

Serum testing includes elevated alpha-fetoprotein levels or decreased ATM protein on immunoblotting [471]. Approximately 95 % of people with AT have elevated serum alpha-fetoprotein levels after the age of two (increased rate of false positive results in children <2 years), and measured levels of AFP appear to increase slowly over time [480]. Immunoblotting is the more sensitive and specific test, with absent protein in 90 %, although trace protein may be seen in up to 10 %, which leads to ambiguity in interpretation.

Alternatively, DNA-based testing is available (see genetics section), with up to 97 % sensitivity when both sequencing and duplication/deletion analysis is performed.

Management

Patients with AT need special consideration for reading and school function since they demonstrate high-frequency of decreased accommodation ability and strabismus (38 %) which is compounded by the ataxia, hypermetric saccades and oculomotor apraxia findings [477]

The abnormal vessel formation is associated with ultraviolet damage and can be minimized by use of ultraviolet filter lenses [477]. Strict sun protection can limit cutaneous manifestations.

Early antibiotic treatment and pulmonary therapy for sinopulmonary infections is important. IVIG replacement therapy may be considered for those with frequent or severe infections, or low IgG levels [481]. Physical therapy for contractures can be helpful. Aggressive cancer screening is necessary given increased risk. Treatment of malignancies should be limited to standard-dose chemotherapeutic regimens without radiation or radiomimetic chemotherapeutic agents such as bleomycin whenever possible [482]

There has been a single small study that reports improvement of movement disorder symptoms (including ataxia, parkinsonism, chorea, myclonus) with treatment of amantadine, although this has not been replicated. Approximately

three quarters of subjects were classified as responders with at least a 20 % improvement (mean 30 %) on objective scale measures of the respective movement disorders [483].

Since patients with AT and their cultured cells are unusually sensitive to x-ray, patients undergoing treatment for malignancy should have the radiation dosage reduced by approximately 30 % and depending on the chemotherapeutic agents considered, reduced dosing regimens may be necessary [470, 484]. Treatment of malignancy with conventional dosages of radiation can be fatal to AT patients [470, 484]. There is no effective treatment currently available for halting the progression of AT.

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Ocular Manifestations of Psychiatric Diseases

17

James E. Elder and Andrew Court

Introduction

The ophthalmic manifestations of psychiatric disorders of childhood are varied, ranging from transient visual disturbance to the dire consequences of auto-enucleation. Advances in neuroscience have resulted in changing concepts of the nature of psychiatric disease [1, 2]. The biologic understanding of psychiatric and neurologic disease at some levels makes the classification of diseases somewhat challenging. This is reflected in the topics covered in this chapter. This chapter will be confined to those disorders that are classically considered to be psychiatric such as conversion disorders, psychosis, depression and anxiety, whereas, complex neuro-biologic disorders such as autism are addressed in Chap. 15 (Ocular Manifestations of Neurologic Diseases) while learning difficulties are covered in this chapter. We appreciate this is a somewhat arbitrary division.

Somatic Symptom and Related Disorders

Nonorganic Visual Loss

Definition

Many terms have been used to describe the situation in which there is "no organic basis" for a patient's symptoms. In a survey of British neurologists and psychiatrists Mace and Trimble listed abnormal illness behaviour, conversion, functional, hypochondriasis, hysteria, malingering, neurotic, psychogenic, psychosomatic, somatoform and supratentorial as possible terms to describe this situation [3]. Differences in terminology reflect perceived differences in psychological etiology with varying degrees of patient insight.

We favour the use of the expression "nonorganic visual loss" as we believe it more accurately reflects the clinician's view on this often complex diagnosis. Its use implies the ophthalmologist is unable to identify an ocular or neural disorder that is causing the subject's visual symptoms. Potential weaknesses in this terminology include a denial of organic etiology associated with psychiatric disease (in contrast to pathology suggested by newer biological models) and of lessening the perceived clinical importance of such presentations [4]. A possible alternative term that may satisfy these various concerns is "non-ophthalmic visual loss". The authors are unaware of this expression being used and are reluctant to add yet another label to contribute to the multiplicity of terms currently in use. A more detailed discussion can be found elsewhere [5–7].

Nonorganic visual loss is defined as any visual symptom (most commonly blurring of vision and/or loss of peripheral visual field) that cannot be attributed to any ocular or neurologic disease. It is debated if this is a positive diagnosis or a diagnosis of exclusion. Those in favour of this being a positive diagnosis suggest that the demonstration of a nonorganic feature such as a tubular visual field or normal visual acuity with encouragement or a minimal refractive correction is positive proof that the symptoms are not the result of any organic disorder [4, 6–8]. Others maintain that it remains a diagnosis of exclusion and state that "A complete neuro-ophthalmologic examination of the afferent and efferent visual system is essential to eliminate the possibility of organic causes of visual loss" [9]. There are examples of overlap between organic and nonorganic disease and cases in which are initially labelled as nonorganic that subsequently develop organic disease [10, 11]. It has long been known that there are cases that have both features of organic and nonorganic disease [12, 13].

Nonorganic visual loss can be divided into two broad groups; conversion disorder and factitious disorder. Conversion disorder is the manifestation of a significant

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symptom that has no physiological explanation and the patient does not actively (or consciously) contribute to the manifestation of the presenting symptom(s). Factitious disorder entails active falsification of history, symptoms and on occasion physical signs to obtain medical attention in the absence of any other obvious external reward. This is different from malingering which by definition has falsification of history, symptoms and on occasions physical signs for secondary gain. Factitious disorder and malingering are discussed in more detail below (see Factitious Disorder, page 578). In much of the older literature conversion disorders are referred to as hysterical blindness or functional visual loss. Both conversion reactions and factitious disorders are part of the "Somatic symptom and related disorders" as defined in DSM 5 [14].

Conversion disorders are defined in DSM 5 as follows:

"Diagnostic Criteria

1. One or more symptoms of altered voluntary motor or sensory function.
2. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.
3. The symptom or deficit is not better explained by another medical or mental disorder.
4. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify symptom type:

- With weakness or paralysis
- With abnormal movement (e.g., tremor, dystonic movement, myoclonus, gait disorder)
- With swallowing symptoms
- With speech symptom (e.g., dysphonia, slurred speech)
- With attacks or seizures
- With anesthesia or sensory loss
- With special sensory symptom (e.g., visual, olfactory, or hearing disturbance)
- With mixed symptoms

Specify if:

- Acute episode: Symptoms present for less than 6 months.
- Persistent: Symptoms occurring for 6 months or more.

Specify if:

- With psychological stressor
- Without psychological stressor" [14]

Most cases of conversion disorder pertaining to pediatric nonorganic visual loss are short-lived disturbances and thus are classified as acute episodes of conversion disorder.

Nonorganic ophthalmic motor abnormalities are recognised and are discussed separately in the sections on Tics and Tourette syndrome below.

History

When reviewing ancient texts it is difficult to distinguish between descriptions of true organic disease, other psychiatric disorders and possible nonorganic disorders [5]. Such distinctions became more accurate with the development of a more modern understanding of disease etiology in the nineteen century. The French neurologists Pierre Briquet and Jean-Martin Charcot reported extensively on "hysterical illnesses" including nonorganic hemianopsia—predominately in adults [15]. These early reports mainly dealt with nonorganic field loss. There is an extensive military medical literature concerning nonorganic visual loss and related disorders starting in the nineteenth century [5].

Reports of nonorganic visual loss in children were rare before the 1940s [16]. In 1934 Moore reported that, "…. on three occasions I have seen hysterical blindness in children under the age of eight." but gave no further clinical information [17]. Eames in 1947 examined visual fields in 193 unselected school children in Boston [12]. In this study 9 % of children were found to have tubular fields and one child had a spiral field. This extremely high rate of field loss has not been found in subsequent studies and calls into question the possibility of inadvertent tester influence on the subjects. Such criticisms have also been made of Charcot's study of hysteria [15].

Yasuna in his 1951 paper refers to a single case report in the French literature published in 1947 [18]. In that report a 14 year old girl experienced the acute onset of nonorganic visual loss after seeing a movie about a blind girl. Yasuna reported on 19 individuals with "hysterical amblyopia" 10 of whom were 16 years of age or younger [18]. These children were predominately female, often had some degree of field constriction on testing and were described as having "poor emotional stability and frequently were of less than average intelligence. Many of the children in this group were doing poorly at school". In 1955 Schlaegel and Quilala reported finding tubular fields in 42 of 800 patients assessed at the Eye Clinic of the Indiana University Medical School [8]. Fourteen of these were between 7 and 19 years old. Fifteen of the 42 (36 %) patients with tubular fields were described as having organic ocular disease (including cataract, uveitis, macular plaque, glaucoma, keratitis, esotropia, drusen retinae, enucleation of fellow eye and corneal burn). These authors concluded that "Hysterical amblyopia may overlay organic disease, so that the diagnosis must not be made by exclusion but must be based on its characteristic diagnostic features" [8]. No comment is made in this report regarding the importance of examiner influence ("suggestibility"). The importance of this factor is acknowledged by many authors [16, 19, 20].

Epidemiology

It is commonly suggested that 1–5% of referrals to ophthalmologists are the result of nonorganic visual loss [8, 21]. A population study from Finland of the incidence of pediatric nonorganic visual loss reported that 40 of 2280 (1.75%) referred children had nonorganic visual loss [22]. These cases were identified from a school population of ~14,000 aged from 7 to 18 years old. This represents an incidence of 1.4/1000/year [22]. Yasuna in 1963 reported an incidence of 1.6 cases per annum of pediatric nonorganic visual loss in his practice over a 16 year period [23]. He noted that he made this diagnosis in approximately the same number of adults during this 16 period. Kinori et al. in 2011 reported seeing 12 children with nonorganic vision loss over an 11 year period in an Israeli hospital setting [24]. Lim et al. reported their experience with nonorganic visual loss in a tertiary neuro-ophthalmology service in Oaklahoma, USA in 2005. Over a 5 year interval they diagnosed 56 children with nonorganic visual loss [10]. Hirai et al. diagnosed nonorganic visual loss in 41 children in 2 years in Nagoya Japan in 1996–1998 [25]. At our center, we have seen 206 children with nonorganic visual loss over 24 years giving a rate of 8.6 cases per year in a purely pediatric ophthalmology practice in southeast Australia. This equates to ~7/1000 new cases during this time period. The wide variation in reported prevalence and incidence points to potential ascertainment and perhaps cultural bias.

Most studies report preponderance of females. Lim et al. analysed 13 studies and noted 59–92% of reported cases were female [10]. It has long been suggested that nonorganic visual loss is more common in the older pediatric age group [18]. Lim et al. noted that 52 of 138 (39%) patients in their series were in their second decade at the time of diagnosis [10]. The age range in that series was 7–76 years.

Systemic Manifestations

Nonorganic visual loss may be a relatively minor and isolated disorder with limited systemic (i.e. other psychiatric) manifestations [26]. Headache is frequently reported in association with nonorganic visual loss [23, 24, 26–29]. Psychiatric comorbidities with nonorganic visual loss are reported to be common. Taich et al. reported 19/71 (27%) children diagnoses with nonorganic visual loss had prior diagnosis of anxiety, depression and Attention Deficit/Hyperactivity Disorder (ADHD) [30]. For another four children it was considered highly likely they had a psychiatric diagnosis and in 22/71 (34%) significant stresses at home or school were identified [30]. Bain et al. report that 18/30 (60%) of children with a diagnosis of nonorganic visual loss "admitted concurrent social problems, either at home or in the school" [27] Examples cited were "impending exams, bullying, recent change of school and difficulties with school work". These authors also noted parental divorce or separation in 5/30 cases (17%) [27]. This is supported by the work of Lim et al. who describe 11/24 children reporting social stressors [10].

It is well recognised that nonorganic disorders generally may be seen in children subjected to abuse [31]. Nonorganic visual disorders have been described in cases of previously undisclosed child abuse [10, 28, 32]. Chapter 5 addresses this consideration further. Types of abuse reported have been physical [28, 32] or sexual [10, 28, 33]. The incidence of associated abuse in cases of nonorganic visual loss is not known with the highest incidence of 4/23 (17%) being reported by Catalano et al. [28].

Rarely a significant psychiatric disorder may be diagnosed in a child presenting with nonorganic visual loss. A case of childhood schizophrenia was eventually diagnosed in a child with persistent nonorganic visual loss [28].

Ophthalmic Manifestations

Weller and Wiedemann reviewed presenting symptoms of hysteria in ophthalmology and suggested dividing these into sensory and motor [20]. Enzenauer et al. detail an exhaustive list of possible presenting symptoms in all age groups in their monograph *Functional Ophthalmic Disorders* (see Table 17.1) [34]. The most common ophthalmic manifestation in the

Table 17.1 Symptoms reported in hysterical ophthalmic disorders

Visual acuity
Decreased, blurred, and/or fluctuating visual activity, monocular or binocular
Total or partial blindness/amaurosis, usually monocular
Amblyopia, photophobic amblyopia, one or both eyes
Looking past objects, jumbling of print, film over one eye, difficulty judging distances
Visual hallucinations, prolonged after images, muscae volitantes (flying floaters)
Polyopia: diplopia, triplopia, monocular, and binocular
Seeing out of proportion or in color: micropsia, macropsia, megalopsia, dysmegalopsia, micromegalopsia, erythopsia, xanthopsia
Visual fields
Tubular fields: concentric contraction
Inversion of the fields: smaller from central to peripheral
Color fields: contraction, interlacing, or reversal of normal order of color field
Fields: spiral, "gun barrel," contracting or expanding spiral, fatigue spiral, helicoids contractions
"Oscillating field" (test object disappears and reappears)
Star-shaped field
Interweave or interlacing of the various isopter lines
Scotomas: central, paracentral, ring
Hemianopsia: homonymous, transient, "missing half," bitemporal
Color and light disturbances
Dark adaptation abnormality, night blindness (nyctalopia), day blindness (hemeralopia)
Color vision abnormalities: achromatopsia, dyschromatopsia, purple chromatopsia, color blindness
Photopsia: flashes of light, colored balls, glittering surfaces before the eyes

(Modified from Enzenauer RW, Morris W.R., O'Donnell, T. Montrey J. Functional Ophthalmic Disorders. Switzerland: Springer; 2014 [5] with permission from Springer International Publishing, Switzerland)

Table 17.2 Symptoms at presentation of nonorganic visual loss

Series	Year	No children	Blurred/ reduced vision	Field loss	Other subjective visual disturbance	Polyopia/ diplopia	Other ophthalmic	Other symptoms
Yasuna [23]	1963	26	26 (100 %)	NR	NR	NR	NR	NR
Keltner et al. [29]	1985	25/84	74 (88 %)	10 (12 %)	6 (7 %)	15 (18 %)	NR	Headache 26 (31 %)
Catalano et al. [28]	1986	23	23 (100 %)	2 (9 %)	2 (9 %)	4 (19 %)	NR	Headache 11 (48 %)
Clarke et al. [26]	1996	70	54 (77 %)	NR	9 (13 %)	7 (10 %)	NR	NR
Bain et al. [27]	2000	30	28 (93 %)	5 (17 %)	3 (10 %)	5 (17 %)	NR	Headache 13 (43 %)
Kinori et al. [24]	2011	12	12 (100 %)	1 (8 %)	NR	3 (25 %)	3 (25 %) 2 ptosis, 1 blephaospasm	Headache 4 (33 %)
Totals		161[a]	143/161 (89 %)	8/65 (12 %)[b]	14/123 (11 %)[b]	19/135 (14 %)[b]	3/12 (25 %)[b]	28/65 (43 %)[b]

NR = not reported
[a]All totals exclude the series of Keltner et al. as it is not possible to separate pediatric and adult patients for analysis
[b]Excludes series from analysis if feature NR, hence totals < 161

Table 17.3 Visual acuity at presentation

Series	Year	No children	Blurred/reduced vision	VA < 6/60	VA 6/60–6/12	Comment
Yasuna [23]	1963	26	26 (100 %)	9/26 (35 %)	16/26 (62 %)	
Catalano et al. [28]	1986	23	23 (100 %)	NR	NR	7/23 (30 %) ≤6/30
Sletteberg [36]	1989	33/54 (≤20 years)	43/54 (80 %)	13/54 (24 %)	30/54 (56 %)	Mainly pediatric, unable to separate adult & pediatric data
Barris [35]	1992	15/45	9/15 (60 %)	3/15 (20 %)	6/15 (40 %)	"careful urging" during VA assessment
Bain et al. [27]	2000	30	28/30 (93 %)	3/30 (10 %)	16/30 (53 %)	
Kinori et al. [24]	2011	12	12/12 (100 %)	6/12 (50 %)	1/12 (8 %)	
Totals		139	98/106 (92 %)*	21/83 (25 %)^	39/83 (47 %)^	

NR not recorded
* Excludes Sletteberg et al. as unable to separate adults and children
^ Excludes Sletteberg at al (as unable to separate adults and children) and Catalano as "claimed" VA at presentation not recorded in all cases

pediatric age group is some degree of blurring or loss of vision [23, 24, 26–29]. This can vary from minor to severe and may affect near or distance visual function or both and be unilateral or bilateral. Less frequent presentations are subjective disturbance of visual experience (most commonly seeing colored spots or lines in visual field) [26–28], visual field defects [24, 27, 28], diplopia (or polyopia) [24, 26–28] and very rarely associated ophthalmic motor abnormalities such as ptosis [24]. Table 17.2 provides a summary of the ophthalmic presenting features from six retrospective pediatric reports.

The visual acuity measured at presentation can vary markedly. Approximately 25 % of children are reported to have acuity <6/60 and approximately 50 % in the range of 6/60–6/12 (see in Table 17.3). Most published series report bilateral blurring in the range of 74–96 % [23, 24, 26–28]. The report of Barris et al. is an outlier with regard to this reporting 5/9 (55 %) with unilateral symptoms and 4/9 (45 %) with bilateral symptoms of blurring [35]. This report is also unusual in the large number of children noted to have abnormal visual fields (14/15).

Most pediatric series report a low rate of visual field defects in the range of 8–17 % [24, 27, 28] with the series of Barris et al. being an exception reporting 93 % [35]. It is of interest that this report has an overall rate of visual field defect of 96 % in adults and children which is extremely high. This may represent a systematic bias in measurement of visual fields. Pattern of visual field loss reported in children include non-specific constriction, cloverleaf, spiral (the visual field becomes smaller as the same isopter is tested repeatedly with the same size target), tubular, monocular hemianopia and intersecting isopters [8, 22, 24, 27, 35–39]. Tubular visual fields will only be documented if fields are measured at two distances with a tangent screen: demonstrating a failure for the field to enlarge physiologically at an increased distance. The case of monocular hemianopia reported by Acaroğlu et al. is the only one to our knowledge reported in the recent pediatric literature and is well documented [38].

Diplopia or polyopia has been noted in 10–25 % of pediatric nonorganic visual presentations [24, 26–28]. These may

be monocular or binocular or both at different times with the same patient. Other subjective visual disturbances that have been reported by children are micropsia [28], "lines or spots in front of their eyes, illusory movement of the environment, pain on visual tasks or a decrease in colour vision" [26] and photopsia, photophobia and altered color vision [27] with incidence of 9–13 % [26–28].

As in adults there can be an overlap of organic and nonorganic disease in children [10, 24, 40]. A history of organic disease should not cause the clinician to dismiss the possibility of nonorganic disease and vice-versa.

Most reports suggest that the prognosis for spontaneous resolution of nonorganic visual loss in children is excellent [10, 24, 27, 28, 36, 41]. Some authors have shown better prognosis for children than adults. Sletteberg et al. reported 10/14 (71 %) patients <15 years of age had spontaneous resolution compared to only 3/15 (20 %) patients >15 years of age [36]. Lim et al. observed resolution of nonorganic visual loss in 85 % of children and 44 % of adults [10]. It has also been noted that significant psychiatric disorders requiring formal psychiatric intervention is more common in adults [10, 36].

The speed of resolution of symptoms in children is said to be rapid. Catalano et al. reported 34 % resolving within 24 h, 61 % within 2 months and 71 % within 3 months [28].

Recurrence of nonorganic visual loss after a period of resolution is well known to occur [24, 41]. Rada et al. reported recurrence during follow-up in 15 % of children [41] and Kinori et al. noted it in 25 % [24]. The severity and duration of recurrence of symptoms was not described though Kinori et al. reported multiple relapses in some children [24].

Diagnosis

There are two principle aims in the initial clinical assessment of a child with suspected nonorganic visual loss. The first is a thorough clinical examination to exclude obvious organic disease. The second is demonstration that visual function is better than claimed (or is indeed normal) or that the claimed visual symptoms are non-physiologic. This depends on the child being unaware that the responses given to examination tests are not consistent with the level of visual function initially claimed and a lack of knowledge of the normal physiology of the visual system. On occasion, clinical assessment will need to be supplemented by further investigation. Flexibility in assessment is also essential as it is not always apparent at first meeting the child and guardians that nonorganic visual loss is a diagnostic possibility. Different strategies are utilised depending on the laterality and severity of claimed vision loss.

Sir Stewart Duke-Elder emphasized the importance of clinical skill in his statement; *"One point is important: the examiner should know thoroughly the tests he proposes to carry out, for the most important feature in such testing is the rapid and sure manipulation; few succeed unless they are well prepared."* [42] It is vital that the examination procedure appear routine and that the child be unaware that the examiner is attempting to demonstrate improved visual function [43, 44]. Drews suggested that the tests utilised in assessment of nonorganic visual loss be practiced with routine patients to improve skill and create awareness of usual responses [43]. The importance of a neutral and nonjudgemental attitude has been emphasised by many authors [5, 43, 45, 46]. It is important that the ophthalmologist not demonstrate any irritation nor lose patience with a child during the course of assessment. An attitude of friendly encouragement is most likely to gain optimal cooperation.

Routine historical information should be acquired from the child and guardians. Often the most striking feature of the history is the child's apparent indifference to their symptoms. This *la belle indifference* is frequently noted and is more often seen in cases of so called "hysteria" than malingering. On occasions it is evident that parental anxiety with regard to the symptoms is greater than that of the child. This may especially be the case if there have been previously inconclusive assessments prior to the current consultation.

On specific questioning there may be inconsistencies related to visual activities. A child may describe poor visual function yet not experience any difficulty with reading or playing games on an electronic device. School work or performance may or may not be adversely affected.

It is possible that not all of the relevant history will be obtained initially. This particularly applies to the psychosocial aspects of the history that may not be fully explored until the possible nonorganic nature of the presentation is becoming apparent. There is often some benefit in interviewing the parents or guardians separately from the child to obtain this history. Such enquiry should be open-ended such as: "Are you aware of any problems at school?" or "Have there been any events or stresses at home?" Significant stressful events such as bullying, death of a relative or parental separation may then become evident that may not have seemed relevant earlier in the consultation. A careful family history for significant ophthalmic disease may help explain the source of a child's visual symptoms. Holden and Duvall-Young reported three children with a family history of retinitis pigmentosa and nonorganic symptoms closely resembling those of retinitis pigmentosa [47]. Skoog et al. reported similar observations in their series of patients seen at a Swedish diagnostic center for retinal degenerations and dystrophies [48].

Initial clinical examination is directed at the detection of organic pathology that would explain the presenting symptoms. Once excluded, the aim of clinical examination switches to the demonstration that visual function is better than claimed (and, if possible, that it is normal) or that claimed visual symptoms are non-physiologic. An example of the former would be demonstration of normal visual acuity with a "trick refraction" such as plano lenses which are presented with the suggestion that they are a true glasses prescription. An example of the second would be the demonstration of a spiral visual field on perimetry.

Many reports have emphasised the importance of initially observing the child move around the waiting and examination rooms [5]. This is relevant for the occasional child who is claiming bilaterally and significantly reduced visual acuity or field. The observation that such a child moves freely is suggestive that visual function is better than claimed but cannot be taken as positive proof that this is the case as some children with severe organic impairments can be remarkably adaptive, especially when the changes are chronic rather than acute. Acute discovery of a chronic organic symptom, previously not reported by the child, must be considered.

A comprehensive review of clinical examination methods for both children and adults with nonorganic visual loss is available in the monograph of Enzenauer et al. [5]. The following discussion is limited to the clinical tests that are useful in the assessment of children and are in common usage. Clinical tests to be considered are listed in Table 17.4.

Table 17.4 Clinical tests used in the examination of children to assist in diagnosis of nonorganic visual loss

Test	Indication	Response	Significance
Pupil response	Bilateral total blindness	Pupil response present	Excludes ocular cause of visual loss
	Unilateral total blindness	No relative afferent pupil defect	Visual function better than NPL
Optokinetic nystagmus	Bilateral or unilateral total blindness	OKN response seen	Confirms presence of vision
	Reduced vision[a]	OKN response to high frequency grating	Confirms vision better than claimed
Mirror test	Bilateral or unilateral total blindness	Eye movement elicited (unilateral with "bad" eye tested)	Confirms presence of vision
Threat/Startle card/Ridiculous face	Bilateral or unilateral total blindness	Noticeable response from subject (unilateral with "bad" eye tested)	Confirms presence of vision
Base out prism (4 or 6Δ for fusional response if bilateral total loss & 25Δ for refixation movement if unilateral total loss)	Bilateral total blindness	Fusion response 4–6 Δ prism	Confirms presence of vision
	Unilateral total blindness	Refixation movement with 25 Δ in front of "bad" eye	Confirms presence of vision
Preferential looking test (Teller Acuity Cards™ or similar)	Bilateral or unilateral total blindness	Fixation response observed	Confirms presence of vision
	Reduced vision	Fixation response observed to high frequency grating	Confirms vision better than claimed
Proprioceptive tests	Bilateral total blindness	Exaggerated difficulty	Highly suggestive of nonorganic defect
Down up refraction ("Doctor killing test")	Reduced vision	Improved visual acuity with encouragement & patience	Confirms vision better than claimed
Refractive trickery	Unilateral total loss or reduced vision	Improved visual acuity	Confirms vision better than claimed
Stereopsis	Unilateral total blindness	Any evidence of stereopsis	Confirms presence of vision
	Reduced vision	Higher level of stereopsis found	Confirms vision better than claimed
Red & green color filters with duochrome or red & green letters on white background or Worth 4-dots	Unilateral total blindness	See letters with "bad" eye	Confirms presence of vision
		See 4 dots with Worth test	
Ishihara tracing lines	Reduced vision	Unable to read numbers but can trace lines designed for innumerate younger children	Confirms vision better than claimed
Tangent screen perimetry	Reduced vision or visual field	Gross constriction	Inconsistent with observed mobility
		Spiral field Tubular fields	Non-physiologic
Goldman perimetry	Reduced vision or visual field	Gross constriction	Inconsistent with observed mobility
		Spiral field Crossing isopters Monocular hemianopia Reduced uniocular field of fixation with eye movement	Non-physiologic
Automated perimetry[b]	Reduced vision or visual field	Gross constriction	Inconsistent with observed mobility
		Monocular hemianopia Binocular testing with preceding instruction "good" or "bad" eye being tested	Non-physiologic constriction when patient believes bad eye is being tested

[a]In all cases reduced vision may be bilateral or unilateral

[b]Tangent or Goldman perimetry are generally superior methods for testing visual fields in children with suspect nonorganic defects

The order in which the various tests are used to distinguish organic and nonorganic disorders is largely determined by the severity and laterality of claimed visual loss. As visual field defects are infrequently symptomatic in children and visual field testing is inherently difficult at younger ages such testing is often performed later in the assessment to confirm non-physiologic nature of a patient's symptoms.

Eliciting the pupil response is a measure of the integrity of the afferent visual pathway. In cases of organic bilateral severe visual loss (no perception of light) anterior to the chiasm bilateral amaurotic pupil responses will be seen. Normal pupil responses indicate either post chiasmic disease or a nonorganic disorder.

The presence of optokinetic nystagmus (OKN) is indicative of some visual function. A large mirror positioned directly in front of the patient and then slowly tilted around either the horizontal or vertical axis will induce involuntary following eye movements in almost all sighted individuals thus providing proof of some level of vision. Unexpected visual stimuli such as a sudden threatening movement or ridiculous facial expression of the part of the examiner will often elicit a response from a child that can only be the result of a visual response. Although the presentation of printed profanity as a method of eliciting a startle response has been used in adults, discretion is perhaps warranted when considering this technique in a child. Placing a small base out prism in front of either eye may induce a fusion response that is also evidence of vision. Tests that are not perceived by the patient as tests of visual function such as preferential looking test may elicit a response [34]. Finally tests of proprioception, such as touching both index fingers tip to tip in front of the face, may be mistakenly believed to require visual input and thus be paradoxically poorly performed by an individual with nonorganic visual loss. In reality a child with newly acquired severe visual loss will be able to perform such test quite well.

The absence of a relative afferent pupil defect is very suggestive that vision is better than no perception of light. All other tests used above for a child claiming binocular total loss of vision can be used for a child claiming unilateral total loss of vision. The better seeing eye is occluded and the test then performed. In some cases when performing the base out prism test it may be better to use a stronger prism (25Δ) and observe to see if there is an induced refixation movement rather than looking for the small fusional movement induce by a 4–6Δ base out prism.

Refractive trickery is useful in cases of unilateral or bilateral reduced vision more than reported no perception of light. A detailed discussion of the history and attribution of tests used in refractive trickery is beyond the scope of this text. For readers requiring further information should consult *Functional Ophthalmic Disorders* by Enzenauer et al. [5]. The principle is to suggest to the child that the refractive correction, provided either in trial lenses or the phoropter, will improve the vision when in fact it should not, or to suggest to the child that they are using a better eye when in fact they are using the weaker eye. These techniques tend to be particularly useful when a child responds positively to a query about whether they are interested in obtaining glasses, particularly at times when wearing glasses is considered fashionable or another family member has received attention around the receipt of new glasses.

One technique of refractive trickery is to induce optical blur for both eyes and then, unbeknown to the child, gradually lessen this blur for one or both eyes while encouraging the child to read further down the vision chart. It is important that the changing of lenses is done smoothly. It is often helpful to obscure the child's view of the vision chart while such manoeuvres are performed. The examiner should encourage the child throughout this procedure and stress that the glasses being tested are very powerful and the vision test is becoming easier. This takes advantage of the child's suggestibility. In cases of unilateral blindness the better seeing eye is left blurred while blur for the reportedly worse eye is gradually reduced. Blur is most commonly with a hypermetropic over correction or cross cylinder (equal but opposite sign cylindrical lenses with axes at 90^0). The power of the blurring lens must be sufficient to achieve an expected acuity less than the reportedly worse eye. Thus, this test is best performed after cycloplegic refraction to allow for knowledge of the correct refraction of both eyes. The blur of cycloplegia may also be useful as it can cause some confusion for the child and the relief of this blur may induce the child to see better than earlier in the assessment process. It is important to observe the child, especially if using a phoropter, to note if there is alternate eye closure occurring. Such behaviour may be used in an older child to check which eye is being tested and is said to be utilised by adults who are malingering and attempting to foil the examiner's trickery [49].

Stereopsis is dependent of both eyes seeing and thus the finding of stereopsis implies both eyes can see. This test depends on the subject being ignorant of this physiologic fact. Verhoeff in 1942 showed that high grade stereopsis correlated with good and equal vision [50] and Levy and Glick correlated levels of visual acuity with measured stereopsis using the Titmus Stereo Test™ (Stereo Optical, Chicago, Illinois, USA) in 1974 [51]. In this study normal subjects were tested and monocular blur was used to induce reduced visual acuity in one eye and stereopsis was measured at different levels of reduced visual acuity. The correlation found by Levy and Glick are tabulated in Table 17.5. The stereo fly can also be useful in a child presenting with a complaint of bilateral blindness as it may induce a startle response indicative of vision, similar to those tests described above.

Table 17.5 Correlation between stereo acuity and visual acuity

Visual acuity	Stereopsis (seconds of arc)
20/20	40
20/25	43
20/30	52
20/40	61
20/50	78
20/70	94
20/100	124
20/200	160

(Adapted from Levy NS, Glick EB. Stereoscopic perception and Snellen visual acuity. American journal of ophthalmology. 1974;78(4): 722-4 [51] with permission from Elsevier)

Colored filters that dissociate the visual input to either eye are useful in detecting claimed total blindness in one eye. Herman Snellen is credited with being the first to suggest colored filters for this purpose [5]. With red and green filters in front of either eye the child is then asked to read the letters on a duochrome chart or read a word (such as FRIEND) in which alternate letters are green or red or view the Worth 4-dots. If the child reads the entire duochrome line or word or counts 4 lights they have vision in both eyes and if using a particular line on a Snellen or picture chart, one establishes the acuity in both eyes.

Down up refraction (sometimes referred to as "doctor killing refraction" or "toothpaste refraction") is measuring acuity starting from the bottom of the acuity chart with the smallest optotype and gradually asking the subject to read successively larger lines. The origin of this term is obscure but the meaning is readily apparent when one considers the time that may be required to do this test. This test required significant patience and encouragement on the part of the examiner. It is important to stress how easy each line is to read. Its success with children depends on their suggestibility.

Ishihara line tracing was described by Bourke and Gole [52] as ancillary test for nonorganic visual loss. These authors observed that some children with nonorganic visual loss claimed not to be able to read the numbers on an Ishihara test but were able to trace the winding lines on the plates designed for innumerate individuals. This response is clearly non-physiologic. These authors also noted that some children show inconsistency when reading the Ishihara plates through a red filter [52]. When viewing the Ishihara plate through a red filter all numbers are visible even if there is a color vision defect. Bourke and Gole described a 17 year old girl who claimed to be unable to see the numbers (other than the initial test plate) both without and with a red filter which is a non-physiologic response.

Visual field testing may be used to detect non-physiologic field loss in cases of claimed unilateral total blindness. Osako et al. demonstrated abnormalities in monocular static perimetry in children with nonorganic visual loss [53]. These authors were comparing normal children with children confirmed to have nonorganic visual loss. Smith and Baker suggested that standard static perimetry is unable to satisfactorily distinguish nonorganic and organic causes of field loss when the fields of a group of patients with known organic field loss were compared with a group of patients with nonorganic visual loss [54]. Martin modified a Humphrey Field Analyser™ (Carl Zeiss Meditec AG, Jena, Germany) so that static perimetry could be performed on both eyes simultaneously [55]. He was able to demonstrate significant differences if the patient was instructed that the "bad" eye was being test compared with when the "good" eye was being tested and that these differences were non-physiologic confirming the finding of nonorganic visual loss. Unless the method of Martin [55] is used, some caution should be taken when interpreting static perimetry in children with suspected nonorganic visual loss. Rather, confrontation technique (as described above for reported tunnel visual fields) or tangent screen, may be more useful in detecting nonorganic visual field loss.

Ali has described a simple and useful technique to distinguish organic and nonorganic constricted visual fields with the Goldman perimeter [56]. This technique compares the size of the constricted field measured with standard steady fixation and kinetic perimetry (target moving peripheral to central) with the field measured with the subject instructed to follow the light until it disappears from view while the target is moved from the central visual field in a peripheral direction. The field measured with eye movement is called the "uniocular field of fixation". Normal physiology would dictate that the uniocular field of fixation (with eye movement) is larger than the field measured with standard steady and central fixation. Ali clearly demonstrated that in individuals with organic causes for field constriction the uniocular field of fixation was larger as would be expected while in individuals with nonorganic field constriction the uniocular field of fixation remained the same size or indeed smaller [56]. We have found this simple perimetry technique useful in diagnosing nonorganic field defects.

Scott and Egan have drawn attention to the fact that the presence of a central scotoma is likely to have an organic cause, even if there are other features that suggest a nonorganic diagnosis [40].

Perimetry has a long history in the assessment of nonorganic visual loss [15]. Tangent screen testing of visual fields in cases of nonorganic visual loss was first used in the nineteenth century and has been used to document nonphysiologic or field defect such as spiralling isopters and tubular fields.

Further investigation. The decision to initiate further investigation can be difficult. In younger children with suspected nonorganic visual loss this decision may be further complicated by the need for general anesthesia to do so. Some authors have extensively used electrophysiology and neuroimaging in all patients with suspected nonorganic visual loss regardless of clinical findings [4, 35]. Some may feel compelled to do so out of medicolegal concerns. Others suggest further investigation only if there is uncertainty of diagnosis after clinical assessment [24, 27]. If uncertainty remains, another option may be to re-examine the child after a period of time without further intervention or testing and then only proceed with further investigation if the symptoms do not resolve spontaneously. It can be difficult for a child to maintain a purposeful falsehood in the absence of true chronic psychiatric disease. Electroretinogram, fundus autofluorescence, and optical coherence tomography may be a particularly useful tests to detect signs of retinal dystrophy or other subtle foveal pathology in cases where there is uncertainty [57–59].

Visual evoked responses (VER). The first reports of the use of VER in detecting nonorganic visual loss appeared in 1960s [60–62]. Potts and Nagaya reported on three (presumably) adult patients with "hysterical amblyopia" and demonstrated normal light adapted flash VER despite the claim of reduced vision [61]. Krill reported 23 patients (15 of whom were age 16 years and younger) with "hysterical amblyopia" based on the finding of reduced visual acuity and/or abnormal visual fields [62]. Krill noted abnormal dark adaptation with abnormally elevated final dark adaption thresholds in 13 of 23 subjects and an upward shift of the final dark adaptation threshold on prolonged testing in 19 of 23 despite normal ERG and VER [62]. It was suggested that this upward deflection of dark adaptation threshold on prolonged testing (called the "exhaustion phenomenon") may be unique to "hysterical amblyopia" [62]. Behrman reported a larger series of 35 patients 51 % of whom were under 16 years old [60]. Many of Behrman's patients presented with constricted visual fields and paradoxically normal electroretinograms with abnormal dark adaption curves [60]. In these patients she undertook dark adapted flash VER which was normal prompting her to suggest that "A normal dark-adapted VER, recorded despite a poor subjective dark-adaptation curve, is at present the best indication of hysterical amblyopia" [60].

Pattern VER has supplanted flash VER as the method of choice of recording VER in cases of suspected nonorganic vision loss [63]. Other authors have published reports cautioning against the reliability of both dark adaptation [64] and VER in the diagnosis of nonorganic vision loss [65, 66]. Both Bumgartner et al. and Morgan et al. demonstrated normal adults are consciously able to alter or suppress pattern VER [65, 66]. Saitoh et al. reported that pattern VER is supranormal in all age groups of subjects with "psychogenic visual disturbance" and were unable to offer an explanation for this observation but cautioned that it may be the result of some as yet unrecognised abnormality in the visual pathway [67]. These authors reported that in the case of malingers (all of whom were adults) the VER was subnormal [67]. They suggested that malingers shifted fixation to disrupt the testing process to create an invalid result. The high rates of normal pattern VER in children with nonorganic vision loss reported by some authors suggests that the value of this test may be greater in children [67–69]. This is presumably related to higher compliance with fixation during testing and a low incidence of malingering in children.

Modification in recording techniques has been reported to increase the reliability of VER in detecting nonorganic visual loss. In particular sinusoid patterns [70], step VER (using multiple recording channels) [71, 72], multifocal VER (using both multiple recording channels and multiple stimulation positions across the central visual field) [73] and pattern appearance VER [74] have been described as improvements. Wright et al. have demonstrated that chloral hydrate sedation has a minimal effect on pattern VER and may be a useful technique in uncooperative children [75].

Differential Diagnosis

The differential diagnosis of nonorganic visual loss includes those disorders that give rise to visual loss without an obvious ocular explanation. These include early cone or cone-rod dystrophies, Leber congenital amaurosis, achromatopsia (although nystagmus and photophobia usually present), early Stargaardt disease, congenital stationary night blindness (although high refractive error often present), amblyopia, paraneoplastic and autoimmune retinopathy (much more frequent in adults), retrobulbar optic nerve disease (without optic atrophy) and central defects from the chiasm posteriorly. Clinically many of these disorders will be readily distinguished with findings such as a relative afferent pupil defect or a true homonymous hemianopia in retrobulbar disorders.

Misdiagnosis of organic disease as nonorganic visual loss has rarely been reported in children and is worthy of consideration. Krill and Newell reported 2 of 59 patients (34 of whom were <18 years old) who developed organic disease after an initial diagnosis of nonorganic visual loss [19]. One developed "macular degeneration" and the second unilateral optic atrophy and "was thought to have early multiple sclerosis." The age of these patients was not stated in the report. Rada et al. reported three children who had no evidence of organic disease initially and these authors suggested that the organic disease may have been co-existent or incipient with the possibility that the true nature of the disease was "initially masked by emotional aspects" [41] Two of these patients are described in detail and both had macular pathology and one had a central scotoma at presentation. Scott and Egan reported a 14 year old boy who was diagnosed as having nonorganic

visual loss on the basis of Titmus test stereopsis of 40" of arc despite have best recorded visual acuities of 20/70 and 20/60 and an otherwise entirely normal examination [40]. This boy was subsequently found to have an abnormal multifocal electroretinogram and was diagnosed as having a cone dystrophy. More recently Lim et al. have reported two children aged 11 and 16 years who were found to have Stargardt disease and cone dystrophy respectively on investigation for persistent unexplained "nonorganic" visual loss [10]. The 11 year showed a central scotoma on automated perimetry and had mild temporal disc pallor at presentation both of which call into question the initial diagnosis of nonorganic disease. These authors also reported a 21 year old woman who presented with sequential bilateral visual loss with fluctuating vision who was treated as having "optic neuritis" with no other supporting features on extensive investigation. Subsequent testing revealed a diagnosis of Leber hereditary optic atrophy [10].

Management

The most common management strategy used with children with nonorganic visual loss is simple reassurance [26–28, 41, 76]. This advice is primarily based on the excellent spontaneous resolution rate found in most studies [10, 24, 27, 28, 36, 41]. It has been suggested that this management can be undertaken by "an interested and concerned ophthalmologist who provides both the parents and the child reassurance and the opportunity to discuss sources of conflict." [41] It is recommended that the child not be confronted with the nonorganic nature of the symptoms [26, 77], although there may be some advantage to having a discussion in front of the child indicating the "good news" that they are normal and their symptoms will resolve thus ensuring parent and child are "on the same page". It is considered important to leave the child with a diplomatic "way out" [78]. Several authors have advised against placebo therapy, even for short periods of time because of concern of reinforcing the concept of organic disease for both parents and child [21, 41].

Other physicians believe that a discussion of the diagnosis and management plan with the parents or guardians without the child present is recommended. In either plan, it is important that the parents have a clear understanding of diagnosis that is being suggested. Many parents are relieved by this news but some may be confused or even frustrated and angry with their child for causing distress and anxiety [26]. It is vital that the parents are made aware of the unconscious processes that give rise to this scenario. The parents are an important part of the process of reassuring the child and they might also be made aware of the warning signs of nonresolution of symptoms, development of other nonorganic somatic complaints, and the identification of potential stressors in the child's life that may not yet have come to light, particularly if such warning signs occur.

Psychiatric referral is not required for self-limiting presentations. In children that have persisting symptoms these are often mild and have a limited impact on daily function [36, 41]. Patients who have a prolonged clinical course, ongoing disability, multiple nonorganic somatic symptoms or the possibility of psychological comorbidity may benefit from psychiatric assessment. This assessment should include an assessment of comorbid anxiety or depressive conditions, possible underlying background psychological stress and family functioning. It may also require an assessment of possible secondary gains that the patient may be receiving from their symptoms [79]. In this situation the diagnosis may be a factitious disorder and this is discussed in more detail below.

Factitious Disorder (Previously Münchausen Syndrome)

Definition

Factitious disorder is the falsification of medical or psychological symptom or signs in oneself or others. The diagnosis of factitious disorder "requires demonstrating that the individual is taking surreptitious actions to misrepresent, simulate, or cause signs or symptoms of illness or injury in the absence of obvious external rewards." [14]. It is further subdivided into factious disorder by self or by others. Previously this was often referred to as Münchausen syndrome or Münchausen by proxy. Factitious disorder by others is discussed in Chap. 6 (Ocular Manifestations of Child Abuse). Factitious disorder is differentiated from malingering on the basis of the absence of any obvious reward beyond receiving "medical attention" in the case of factitious disorder and a clearly identifiable personal gain in malingering such as financial gain or avoidance of some duty [14]. Malingering is classified as an antisocial personality disorder [14]. By definition antisocial personality disorder is not diagnosed in individuals under 18 years old and is thus not considered to be a pediatric condition. This is consistent with the lack of reports of ocular malingering in the pediatric literature [18, 29, 67].

DSM-5 defines self–induced factitious disorder as follows:

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.
B. The individual presents himself or herself to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.

The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder [14].

History

The expression "Münchausen's Syndrome" was first used by British psychiatrist Richard Asher to describe the deliberate falsification of physical symptoms in oneself in 1951 [80]. Orly and Haines have written a history of the use of the term [81]. Hieronymus Carl Friedrich Freiherr von Münchhausen was a wealthy aristocrat who wrote a series of exaggerated tales that resulted in his name being linked to the disorder [81].

The first report of ophthalmic factitious disorder involving a child was written by Jay et al. in 1982 [82].

Epidemiology

Ophthalmic factitious disorder is extremely rare [18, 29, 67] and there are no publications reporting incidence or prevalence. This appears to be almost exclusively a female disorder with all published case reports of factitious ocular injuries in children being female [33, 82–86].

Systemic Manifestations

Patients with factitious disorder fabricate or exaggerate symptoms in order to receive medical care. Secondary gains may be related to attention, escape from other family or social situations, and other perceived benefits of the "sick role". The case reported by Voutilainen and Tuppurainen is particularly important as there was a long history of ophthalmic manifestations commencing at age 12 that were eventually determined to be the result of protracted sexual abuse by her father [33]. Almost any medical symptom may be reported. Common examples include seizures, black outs, gastrointestinal symptoms and asthma [87]. Patients may also create clinical signs (for example by bruising [81, 88] or fever [89]), manipulate their laboratory tests specimens [90, 91], falsifying medical records, ingesting or injecting substances (such as insulin to induce hypoglycemia [92]).

Ophthalmic Manifestations

In his major review of "unnatural" ocular injuries, Taylor commented that self-inflicted eye injury in childhood falls mainly into categories of dermatitis, keratoconjunctivitis, ocular self-mutilation and trichotillomania [93]. Trichotillomania is considered below (see page 592). He also emphasised the importance of underlying medical conditions as the primary cause rather than psychiatric disturbance in children.

Periocular self-induced dermatitis (*dermatitis artefacta*) has been reported in a 13 year old girl [85]. The eyebrows were involved as well as other areas on her face and body more generally. The exact nature of the eyebrow involvement was not described. These authors stress the observation that this often occurs in multiple sites in the one patient, often on anterior skin surface that are easily accessible [85]. Tong et al. describe a 10 year old girl who presented with the complaint of a bilateral lower eyelid "rash" that was subsequently found to be the result of her coloring the eyelid skin with a purple marker [94].

Keratoconjunctivitis is the most commonly reported self-factitious disorder reported in childhood with four reports [33, 82, 84, 86]. Jay et al. reported an 18 year old girl who had a history of unexplained recurrent corneal ulceration and conjunctival trauma going back to age 7 years that had resulted in corneal scarring. Psychiatric assessment was not undertaken and she was lost to follow-up [82]. The keratoconjunctivitis can be produced mechanically with fingers [82], chemical agents [33], chalk particles [84] and tissue paper [86]. All authors stress the recurrent nature of the injuries and the difficulty in making the diagnosis. This should be distinguished from the incidental and somewhat accidental singular episode of deposition of a foreign body on the ocular surface or conjunctival fornix by a child during play, usually in only one eye. These have been referred to as 'teddy bear granulomas" due to stuffing or fur of the bear being the material discovered [95–98].

Penetrating injury has not been described as a self-factitious injury in a child. In a case reported by Voutilainen and Tuppurainen ophthalmic symptoms were secondary to incest. Her symptoms commenced at 12 years of age with non organic visual loss, followed by factitious keratoconjunctivitis and finally self-induced scleral perforation with a safety pin at 20 years of age [33]. These and other authors have stressed that there can be overlap with other ophthalmic manifestations of psychiatric disease such as nonorganic vision loss [33, 82].

The visual outcome is primarily determined by the nature and severity of the induced injury. Permanent visual impairment is possible [33].

Diagnosis

The ophthalmic diagnosis requires a high index of suspicion [86, 93]. A history of other poorly explained ophthalmic symptoms may be important [33]. The injuries may be inconsistent with history or there may be no explanation given. Parents may be complicit in their interactions with their child and treating physicians [84]. As the noxious agent is introduced into the eye or onto the surrounding skin by the patient ease of access is important and it has been suggested that the inferior fornix is more often involved [86, 99]. In cases of *dermatitis artefacta* multiples site on the anterior surface of the body may be a clue to the diagnosis [85]. Delay in the diagnosis of factitious disorder may result in considerable expense to the health system [100] as well as irreparable harm to the patient.

An importance differential diagnosis for factitious corneal injury is congenital corneal hypesthesia and corneal sensation needs to be carefully tested all cases. Conditions that need to be considered in this respect are congenital corneal hypoesthesia, Lesch-Nyhan and Smith Magennis syndromes [83, 93, 101]. Self-inflicted corneal injury due congenital corneal hypesthesia usually presents at a much younger age [83, 93]. The four boys described by Trope et al. with congenital corneal anesthesia and corneal injury were all under 2.5 years of age at the time of presentation [83].

Management

The ophthalmic management is determined by the nature and severity of the induced eye disorder.

Factitious disorders are usually resistant to psychiatric treatment as patients deny responsibility for their actions and often change medical care teams when confronted [102]. These conditions often overlap with personality disorder [102]. Factitious disorder places a significant cost burden on medical systems [102, 103] and detection may depend on chance recognition of the subject by a previous treating health practitioner [103].

Tics

Definition

Tics are defined as "repeated, individually recognizable, intermittent movements or movement fragments that are almost always briefly suppressible and are usually associated with awareness of an urge to perform the movement." [104] The DSM-5 classifies Tic Disorders as a subcategory of Neurodevelopmental Disorders [14]. Neurologically tics are part of the spectrum of hyperkinetic movements can be considered as "unwanted or excess movements" and include in addition to tics; dystonia, chorea, athetosis, myoclonus, tremor and stereotypies [104]. There are periods of normal movement between episodes of abnormal movement.

Tics are further subdivided into simple, complex and phonic [104]. Complex motor tics are more complex or sequential movements involving multiple muscle groups. In the case of complex motor tics there can be significant overlap with obsessive-compulsive disorder [104] but this does not seem to be seen with ocular tics even if chronic [105]. Tourette syndrome forms a major subset of motor tics and demonstrates more variability and is significantly more disabling [106].

The duration of the symptoms is of some importance in distinguishing "transient" tics from more chronic tics and conditions such as Tourette's syndrome [107]. Recently there has been discussion as to what constitutes a "transient tic disorder" [108]. It would appear that there is considerable overlap between transient tics and conditions such as Tourette syndrome with reports of individuals within the one kinship with transient tics and Tourette syndrome in different individuals [109, 110].

In DSM-5 transient tic disorder has been renamed "provisional tic disorder" to allow for fact that at the time of diagnosis it is uncertain if the disorder will persist for <12 months which is the only distinguishing characteristic currently between transient and chronic disorder [108]. The criteria for diagnosis provisional tic disorder are as follows:

A. Single or multiple motor tics and/or vocal tics (a tic is a sudden, rapid, recurrent, non-rhythmic motor movement or vocalization)
B. The tics have been present for less than 1 year since first tic onset
C. The onset is before age 18 years
D. The disturbance is not due to the direct physiological effects of a substance (e.g., cocaine) or a general medical condition (e.g., stroke, Huntington's disease, or postviral encephalitis)
E. Criteria have never been met for Tourette's disorder or chronic motor or vocal tic disorder [14, 108]

History

Since Tourette's first description of the syndrome that bears his name in 1885 [111] there have been numerous publications regarding tics and associated conditions. Eye blinking as a transient tic in childhood has long been recognised in the general medical literature with Corbett giving a brief summary and reference to earlier descriptions in 1971 [107]. The first ophthalmic reference to eye blinking as an innocent and transient phenomenon in the ophthalmic literature is by Vrabec et al. in 1989 [112].

Epidemiology

The prevalence of tics varies with the population studied and the stringency of criteria used to define the condition [113]. Estimates range from 1 to 29 % of children [113–117]. A recent meta-analysis of 22 studies of tic disorders in general populations revealed an incidence of 3 % (confidence interval 1.6–5.6) [117]. Tics are more common in boys [104, 117, 118] and in children in special education settings [116, 117]. Eye blinking tics usually present in the first decade of life [105, 110, 112, 118]. There is evidence that tics are more common in childhood with a declining prevalence in adults [117].

Systemic Manifestations

Nonocular tics are probably the most common associated nonocular manifestation. Bisker et al. [105] and Jung et al. [110] both reported over 20 % of patients having nonocular and/or vocal tics in association with their ocular tics. The majority of non-ocular tics involve the face, head, neck and upper extremities. Jung et al. showed a significant association between the duration of the tic and somatic complaints and attention problems [110]. A weak association with ADHD, development delay and autism have been reported [105, 110, 118]. Overall however, tic disorders often occurs in children who are otherwise developing normally with no significant comorbidity [119].

Initial reports stressed the observation that ophthalmic tics (eye blinking and eyelid pulling) were isolated motor tics [112, 120]. Subsequent reports have described a signifi-

cant proportion of child having other tics. Bisker et al. reported 16 % having nonocular tics, 9 % having vocal tics and 5 % having both nonocular and vocal tics in addition to the ocular tic [105]. Three of seventeen children with excessive blinking reported by Vrabec et al. subsequently developed other facial tics (nose wrinkling, nose rubbing and ear pulling) [112]. Obsessive-compulsive disorder does not seem to be associated with chronic ocular tic disorder [105].

Ophthalmic Manifestations

The most common ophthalmic tic in childhood is excessive eye blinking [105, 110, 112, 118]. Vrabec et al. described 17 children with isolated excessive blinking with no excessive orbicularis contraction nor evidence of other ocular disease [112]. Eye rolling and widening of the palpebral aperture ("eye widening") was as common as excessive blinking in the series reported by Bisker et al. [105]. Eyelid pulling was described in five children by Catalano et al. [120]. Shawkat et al. reported an 8 year old girl with intermittent opsiclonus-like eye movements that persisted for 5 months [121]. The frequency of these movements was a less than usually seen with opsiclonus and they were associated with eyebrow raising, facial grimacing, limb movement and aching of her back consistent with non-ocular tics [121].

Ptosis has rarely been described, either as an isolated observation [122] or in association with blinking [118]. The case of nonorganic ptosis reported by Mohamed and Patil is of interest as the ptosis was unilateral and isolated apart from some slight ipsilateral eyebrow depression [122]. In many respects this does not fit the definition of a tic in that it is hypokinetic rather than hyperkinetic! It has more in common with hysterical paralysis [123]. This child had a history of previous nonorganic abdominal pain and possible chronic fatigue syndrome as well as protracted pain after a minor foot injury.

Early reports stressed the benign nature and favourable outcome for ocular tics [112, 118, 120]. In general the tics were classified as transient. Longer term follow-up has shown that this perhaps not the case [105]. Bisker et al. reassessed 32 of 43 children with ocular tics after an average of 6.1 years [105]. At follow-up 14 (44 %) were noted to have persistence of ocular tic, 3 (9 %) had developed nonocular tics, 5 (16 %) had new vocal tics and 4 (13 %) had both new nonocular and vocal tics. One (3 %) child had been diagnosed with Tourette syndrome and 3 (9 %) with ADHD [105]. These results suggest that ocular tics may not be as benign as first reported and supports the change in terminology from transient to provisional tic disorder [108]. Recurrent episodes of excessive blinking have been reported [112].

Most of the ophthalmic reports relating to excessive blinking and eye lid pulling have not used strict diagnostic criteria as described above [112, 118, 120, 121]. More recent studies have used defined criteria, either specifically defined and consistent with the definitions of tic given above [105] or ICD-10 [110].

Diagnosis

Diagnosis of tics is usually made on clinical assessment. Questionnaires may be useful preliminary screening tools to identify individuals at risk of having Tourette syndrome [117]. Apter et al. developed a four item self-report questionnaire regarding the lifetime incidence of tics [124] and this has been widely used by other researchers [117].

Differential Diagnosis

The study of Coats et al. is useful as real life description of 99 children prospectively presenting to an ophthalmologist with the main complaint of excessive blinking [118]. The fact that the study was undertaken in a tertiary referral center may explain the range of significant pathology diagnosed in some children. Isolated excessive blinking was reported as the chief complaint in 70 % with multiple associated complaints including discomfort, blurred vision, conjunctival injection, other abnormal movements, photophobia, etc. [118]. Ninety percent were bilateral and definitive diagnosis was made in 98 % (see Table 17.6). Thirty-five percent were considered to have a tic syndrome with 21 % being isolated motor tics, 10 % isolated motor tic with detected psychologic stressor and 2 % had a diagnosis of Tourette syndrome. Twenty-two percent were noted to have co-existing central nervous system disease that was thought to be related in 6 % [118]. The findings of this report emphases the need for careful and thorough ophthalmic assessment in reaching a diagnosis when a child presents with excessive blinking. Rarely other organic disease such as Lesch-Nyhan syndrome can also manifest tics or blepharospasm as a feature [125]. Perhaps the most commonly overlooked cause of excessive blinking is blepharitis.

Management

Often ophthalmic management of isolated tics such as excessive blinking is simple reassurance [112, 118]. Formal psychiatric intervention is seldom required for these children. A small proportion of children presenting with isolated tics subsequently have formal psychiatric diagnoses made such as Tourette syndrome and ADHD [105]. Patients with chronic or complex tics also require more consideration of psychiatric consultation.

Tourette Syndrome

Definition

Tourette syndrome is a complex neurologic disorder of childhood-onset tics (motor and vocal) with features of ADHD, obsessive-compulsive disorder and other behavioural problems including poor impulse control, inability to control anger and possible self-injurious behaviour [126].

Table 17.6 Final Diagnosis in 99 children presenting with excessive eye blinking

Diagnosis	Bilateral blinking—n ≈ %	Unilateral blinking—n ≈ %
Habit tic[a]	21	2
Uncorrected refractive error	14	–
Conjunctivitis (allergic 12, other 2)	14	–
Psychogenic[a]	10	–
Intermittent exotropia	10	1
Keratitis (foreign body 3, rosacea 1, microbial 1)	5	1
Dry eyes	5	–
CNS disease (brain tumour 2, ADEM 1, epilepsy 1)[b]	4	–
Lid abnormalities (blepharitis 2, trichiasis 1)	3	–
Marcus-Gunn jaw winking	–	2
Orbicularis myokymia	–	2
Tourette syndrome[c]	1	1
Uveitis	–	1
Unclassified[d]	2	–
Total	89	10

(Modified from Coats DK, Paysse EA, Kim DS. Excessive blinking in childhood: a prospective evaluation of 99 children. Ophthalmology. 2001;108(9):1556-61 [118] with permission from Elsevier)
[a]Differentiated on the basis of psychogenic having identifiable psychological stresses
[b]All diagnosed prior to presenting for ophthalmic assessment
[c]Not clear if were pre-existing or new diagnosis after ophthalmic examination
[d]One had Duchenne muscular dystrophy

Tourette syndrome is defined as follows in DSM-5:

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis) [14, 108].

The pathogenesis of Tourette syndrome remains uncertain [127]. The available evidence supports "the notion that it is that Tourette's syndrome is an inherited, developmental disorder of synaptic neurotransmission resulting in the disinhibition of the cortico–striatal–thalamic–cortical circuitry." [126] Tourette in his original description suggested that it was a familial condition [111] but to date no specific genetic cause has been identified [127].

History

First described in 1885 by French neurologist Georges Gilles de la Tourette [111], this condition was for the next 80 years considered to be a rare psychological disorder [128]. From the 1960s onward reports of treatment with neuroleptic medications emerged and the current concept of a developmental disorder of synaptic neurotransmission emerged [126]. There were relatively few reports relating to Tourette syndrome in the ophthalmic literature until the 1980s as it was regarded as a purely psychiatric disorder despite the obvious ocular involvement. Amongst the first reports in the ophthalmic literature were those of Enoch et al. relating to visual field defects in individuals with Tourette syndrome [129].

Epidemiology

The prevalence of Tourette syndrome in children has been estimated to be 0.77 % compared with 0.05 % in adults in a recent meta-analysis [117]. In a large Danish study Tourette syndrome was found to have a cumulative incidence of 6.6/10,000 by age 13 years [130]. Tourette syndrome is more common in boys than girls with a ratio of approximately 4:1 [117]. Tourette syndrome is manifest by 11 years old in 96 % of cases with most having onset between 3 and 8 years [126].

Systemic Manifestations

The nonocular tics include other motor tics and vocal tics. These may range from relatively simple to complex tics. Complex tics are often "camouflaged" behind a seemingly intentional movement such as brushing the hair away from the face with an arm, and are only distinguished as tics by their repetitive nature. Motor tics may be clonic (rapid) or tonic (sustained). Rarely, serious injuries can result from the motor tics such as spinal cord injury [131].

Phonic tics may be simple with sniffing, throat clearing, grunting, squeaking, screaming, coughing, barking, blowing and sucking noises [126]. More complex phonic tics result in recognisable speech with sufferers shouting obscenities, profanities, repetition of other people's speech or their own. Some affected individuals can partially suppress less socially acceptable utterances. These tics may have premonitory sensations [126].

Other associated features include ADHD, obsessive-compulsive disorder and other behavioural problems including poor impulse control, inability to control anger and sometimes self-injurious behaviour [126].

The natural history of Tourette syndrome is of eventual lessening of the severity of symptoms in many affected individuals [126, 132]. The reported prevalence is certainly less in adults than children [117]. There is evidence that adults with Tourette syndrome often underestimate the ongoing presence and severity of their tics [132]. As many as 90 % of affected adults still have tics [132].

Ophthalmic Manifestations

Tics involving eye movement or eyelid/eye brow movement are very frequently observed in Tourette syndrome [132–136]. Eye movement tics may take the form of eye rolling deviations in any direction [134–136] or staring [136]. Less frequently the ocular deviation may be more prolonged and resemble an oculogyric crisis and this is referred to as a "dystonic tic" [136]. Blepharospasm (clonic tic) is the most common eyelid tic [133–136]. Widening of the palpebral fissure secondary to levator overaction can also be seen [133, 136]. Eyelid and eyebrow tics are often associated with both frontalis overaction and lower facial muscle tics [133]. Tulen et al. reported that patients with Tourette have higher blink rates than normal controls when not manifesting their tics [137]. These authors also noted that tics were suppressed to some extent during conversation. Martino et al. noted that of the 212 patients with Tourette syndrome they studied, 78 % had eye movement tics and 93 % had eyelid and/or eyebrow tics reinforcing the fact that ocular tics are central to the diagnosis of Tourette syndrome [136].

Reports regarding visual field defects in Tourette syndrome are conflicting. Enoch et al. reported a series of patients with a variety of visual field defects obtained with Goldman kinetic perimetry [129]. These defects included arcuate scotoma, steps, baring of the blind spot and enlargement of the blind spot. The field defects were usually asymmetric. Two of the patients described by these authors had keratoconus which has not been described elsewhere in individuals with Tourette syndrome [129]. Tatlipinar et al. found no visual field defects with Goldman perimetry in their series of patients with Tourette syndrome [135].

Coats et al. in their report on excessive blinking in 99 children only found 2 cases of Tourette syndrome which suggests that patients with Tourette syndrome seldom present to pediatric ophthalmologists [118].

Eye movement recordings may help reveal some of the underlying neurobiology of Tourette syndrome. A 13 year old boy with Tourette syndrome demonstrated saccadic intrusions during smooth pursuit and optokinetic nystagmus with dysmetric reflexive and voluntary saccades and a complete inability to perform antisaccades [138]. This was hypothesized to be due to abnormalities in the frontal lobes and basal ganglia. Patients with Tourette syndrome have difficulty with delayed response saccadic tasks which are tasks in which a subject has to memorize a saccadic task and perform it after a specified delay [139]. It has been suggested that this may reflect their "difficulty in maintaining internally planned behaviours without acting on them" consistent with the inability to control tics [139].

Ocular trauma secondary to motor tics has been reported in patients with Tourette syndrome [140, 141]. It is rare and only reported in adults. Gaillard and Wolfensberger reported an adult that sustained lens subluxation and retinal detachment after striking his own eye [141].

Diagnosis

The diagnosis of Tourette syndrome is made on the basis of history and clinical assessment [126]. Video recordings can be useful for comparing the nature and severity of the clinical features over time [132]. It is important to recognize, as discussed above, that only a minority of children with ocular tic, will have Tourette syndrome.

Management

The ophthalmic management of Tourette syndrome is limited. There are reports of the use of botulinum toxin injection for ocular tics [142] and phonic tics [143] in children with Tourette syndrome. Botulinum toxin improved both the motor component of the ocular tic and the associated premonitory sensation [142].

The general management of Tourette syndrome involves addressing the tics and the associated behaviour disorders, in particular obsessive-compulsive disorder and ADHD [126, 144]. It is important to focus on educational and supportive interventions initially, with psychoactive medications being used when symptoms are chronic and severe. Kurlan gives a useful overview of management strategies [144]. Cognitive behavioural therapy has been used to help control tics and is termed "habit reversal" [144] Antipsychotic medications have been used to suppress tics but have frequent side effects while alpha-agonists are less effective but better tolerated [144]. Botulinum toxin has used for blepharospasm [144]. The place of more invasive therapies such as deep brain stimulation is being researched [144].

Attention Deficit/Hyperactivity Disorder (ADHD)

Definition

The DSM-5 defines ADHD as follows.

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):
   1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
      b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
      c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
      d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
      e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
      f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
      g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
      h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
      i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
   2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      a. Often fidgets with or taps hands or feet or squirms in seat.
      b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
      c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
      d. Often unable to play or engage in leisure activities quietly.
      e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
      f. Often talks excessively.
      g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
      h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
      i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal) [14].

There is no one cause for attention deficit/hyperactivity disorder and it appears to be the result of multiple genetic and environmental factors. This has been reviewed by Thapar et al. [145].

History

Abnormal behaviour in children consistent with what is now termed ADHD was first described by Sir George Still in 1902 and he regarded it as "an abnormal defect of moral control".

Excerpts from his original lectures on the subject have recently been republished [146]. Publications pertaining to ADHD and vision are much more recent with the article of Farrar et al. being amongst the earliest. [147]. They reported on the visual symptoms in children with ADHD. Attention was drawn to the possible association of ADHD and convergence insufficiency by two publications in 2005 [148, 149].

Epidemiology

It is estimated that the prevalence of ADHD is estimated to be 2–5 % [145, 150]. It has been suggested that variation in reporting rates from differing regions of the world represent methodological differences rather that true regional differences [150].

Systemic Manifestations

The principal features of ADHD are inattention, hyperactivity and impulsiveness in some combination that impair basic everyday function [151]. It is often pervasive in a child's life, interfering with establishing friendships, limiting academic progress and in later life can result in social and financial burdens [145, 151, 152]. The manifestations are all seen to some degree in normal child development and thus to make the diagnosis they need to be severe and out of proportion to normal age expectations [151]. There are no definitive biomarkers [145].

There is evidence that the effects of ADHD continue to have an impact in adult life [151, 152].

Ophthalmic Manifestations

The relationship between ocular problems and ADHD is far from clear. Increased rates of refractive error, amblyopia, heterophoria and subnormal stereovision, reduced visual acuity, abnormal convergence, visuoperceptual problems, smaller optic discs and decreased retinal vascular tortuosity have all been reported [149, 153–156]. Conversely other investigators have failed to show an increase in convergence insufficiency or heterotropia and no difference in visual acuity, binocular function or accommodation from normal [154, 157]. One group has shown that systemic pharmacological treatment makes no difference in the ocular manifestations [153] while a second has shown better visual acuity and visual field results with systemic treatment [158].

It is quite likely that much of this variation is related to the heterogeneity of the potential population of children studied. There is overlap in symptoms that can be ascribed to ADHD and to visual impairment [155, 159]. Examples would be difficulty with near work, poor concentration, poor completion of work, all of which could be ascribed to impaired concentration as the result of ADHD or be secondary to visual impairment [155]. It has been shown in one study that children on pharmacological treatment for ADHD demonstrated more visual symptoms than normal controls [147]. In another report children with symptomatic accommodative dysfunction or convergence insufficiency had higher rates of behaviours associated with ADHD and learning difficulties than controls [148]. Children with severe visual impairment also appear to manifest higher rates of ADHD than controls [159].

Whether the reported ocular manifestations of ADHD are truly associated remains controversial. They may share common root causes or may be comorbidities or it may be coincidence. As David Granet recently said of ADHD and ocular problems; "This isn't just "Which came first—the chicken or the egg?" This is, "Does the chicken come from the egg?"" [155].

There is no available information on the long term outcome of ocular problems in children with attention deficit/hyperactivity disorder.

Diagnosis

The diagnosis of ADHD is based on clinical assessment with reference to the diagnostic criteria outlined above [160]. It is importance to exclude depression, anxiety, sleep, mood, substance use and specific learning disorders when considering the diagnosis of ADHD as these may mimic some of the features of ADHD [160].

Some authorities recommend that all children with attention deficit/hyperactivity disorder should as a routine have a complete ocular examination [155]. Diagnosis of the ocular features may be impaired by the very nature of the underlying disorder: inattention, hyperactivity and impulsiveness. It is important that an ophthalmologist be aware of the potential ocular manifestations and the diagnosis of ADHD when attempting to elicit evidence that supports the diagnosis of an ocular problem. Children may be unusually frightened or adverse to examination stimuli. Speed of examination and multiple distracting stimuli (e.g. projected movies, toys) become critical as the child may be easily distracted. Positive reinforcement even in the face of incorrect responses will help overcome the tendency of some children with ADHD to be unusually adverse to criticsm.

Management

Both pharmacologic and behavioral interventions are used in the management of ADHD [160–166], Pharmacologic treatment may be with stimulants (methylphenidate and amphetamines) or non-stimulants (atomoxetine, guanfacine and clonidine) [160]. Available evidence suggests that stimultants are more effective than non-stimulants [166]. The American Academy of Pediatrics guideline for the management of ADHD recommends that pharmacologic intervention should be the first line of treatment in most cases [166]. Behavioral interventions include family therapy (behavioural parent training), behavioral classroom management and behavioral peer interventions [161].

There has been considerable debate about the role of treatments for ADHD and there are marked variations in the utilization of treatments in different geographic regions [167].

Ocular abnormalities in a child with ADHD require no specific management strategy other than what would usually be recommended for the same issue in a child without ADHD. Parents should be made aware of particular challenges that may occur if glasses, occlusion therapy for amblyopia or ocular medications are required. Developing strategies based on positive reinforcement, gradual extension of time tolerance (e.g. glasses wear or patching) and anticipating possible failure in a compassionate way, can be very useful.

Specific Learning Disorder

Definition

Specific learning disorders can be considered to be persistent difficulty learning key academic skills that lag significantly behind age expectations and are not explained by other cognitive impairment. These difficulties may be include "reading of single words accurately and fluently, reading comprehension, written expression and spelling, arithmetic calculation, and mathematical reasoning (solving mathematical problems)." [14] Specific learning disorders are considered to be biologic in origin and result from the "interaction of genetic, epigenetic, and environmental factors, which affect the brain's ability to perceive or process verbal or nonverbal information efficiently and accurately." [14].

For the purposes of simplicity the discussion of specific learning disorder in this chapter will be limited to that of dyslexia. Reading difficulties can be divided into a primary form (dyslexia) and secondary forms "caused by visual or hearing disorders, intellectual disability, experiential and/or instructional deficits." [168] Lyon et al. have defined dyslexia as "… a receptive language-based learning disability that is characterized by difficulties with decoding, fluent word recognition, and/or reading-comprehension skills. These difficulties typically result from a deficit in the phonologic component of language that makes it difficult to use the alphabetic code to decode the written word. Secondary consequences may include reduced reading experience that can impede growth of vocabulary, written expression, and background knowledge." [169] Reversal or letter and/or words and mirror writing are normal variants and do not make up part of the definition of dyslexia [168].

The literature of reading and dyslexia is voluminous and this chapter draws heavily on two sources: *Proust and the Squid—The Story and the Science of the Reading Brain* by Maryanne Wolf [170] and *Learning disabilities, dyslexia, and vision* the Joint Technical Report of the American Academy of Pediatrics [168].

Specific learning disorder is defined as follows in DSM-5:

A. Difficulties learning and using academic skills, as indicated by the presence of at least one of the following symptoms that have persisted for at least 6 months, despite the provision of interventions that target those difficulties:
   1. Inaccurate or slow and effortful word reading (e.g., reads single words aloud incorrectly or slowly and hesitantly, frequently guesses words, has difficulty sounding out words).
   2. Difficulty understanding the meaning of what is read (e.g., may read text accurately but not understand the sequence, relationships, inferences, or deeper meanings of what is read).
   3. Difficulties with spelling (e.g., may add, omit, or substitute vowels or consonants).
   4. Difficulties with written expression (e.g., makes multiple grammatical or punctuation errors within sentences; employs poor paragraph organization; written expression of ideas lacks clarity).
   5. Difficulties mastering number sense, number facts, or calculation (e.g., has poor understanding of numbers, their magnitude, and relationships; counts on fingers to add single-digit numbers instead of recalling the math fact as peers do; gets lost in the midst of arithmetic computation and may switch procedures).
   6. Difficulties with mathematical reasoning (e.g., has severe difficulty applying mathematical concepts, facts, or procedures to solve quantitative problems).

B. The affected academic skills are substantially and quantifiably below those expected for the individual's chronological age, and cause significant interference with academic or occupational performance, or with activities of daily living, as confirmed by individually administered standardized achievement measures and comprehensive clinical assessment. For individuals age 17 years and older, a documented history of impairing learning difficulties may be substituted for the standardized assessment.

C. The learning difficulties begin during school-age years but may not become fully manifest until the demands for those affected academic skills exceed the individual's limited capacities (e.g., as in timed tests, reading or writing lengthy complex reports for a tight deadline, excessively heavy academic loads).

D. The learning difficulties are not better accounted for by intellectual disabilities, uncorrected visual or auditory acuity, other mental or neurological disorders, psychosocial adversity, lack of proficiency in the language of academic instruction, or inadequate educational instruction [14].

History

Dyslexia is at least an old as written language. The modern study of dyslexia started in the late nineteenth century with the recognition of neurologic causes of "word blindness" (alexia). The word "dyslexia" was first used by Rudolf Berlin, a German ophthalmologist [168]. He described a young boy of apparently normal intellect who had great difficulty with reading and writing and would almost certainly be classified as being dyslexic with current definitions.

Epidemiology

Depending on the definition used between 5 and 20% of school aged children in the USA [168] are affected with slightly more than 50% being male [171]. Teachers tend to identify dyslexia more commonly in boys than girls and this is probably related to behaviour rather than representing a true difference [171]. Reading ability is thought to be normally distributed with dyslexia representing the lower end of a bell curve [172]. Dyslexia is observed in virtually all cultures and languages [170].

Systemic Manifestations

Learning difficulties are diverse and behaviorally are manifest as problems with processing information or generating an output [168]. Linguistic and mathematical skills are the major areas involved. The commonly accepted term for difficulty with reading is dyslexia. Linguistic learning difficulties may also involve difficulties with spelling and written expression.

Although the etiology of dyslexia is uncertain, it is believed to have both genetic and neural processing deficits [168]. Dyslexia has its origins in the complex neurobiological events that underlie language acquisition and processing as it pertains to reading and writing [168, 170, 173, 174].

Maryanne Wolf suggests "We were never born to read" and "Reading can be learned only because of the brain's plastic design, and when reading takes place, that individual brain is changed forever, both physiologically and intellectually." [170] Understanding of the neurobiology of reading and dyslexia is far from complete. The study of dyslexia is complicated by three factors according to Wolf: "the complex requirement of the reading brain; the fact that so many disciplines have been involved in its study; and the perplexing juxtaposition of singular strengths and devastating weakness in individuals with dyslexia." [170].

The phonological model is the most widely accepted. Reading is a decoding skill while spelling and writing are encoding skills. In alphabet based languages there is a sequence that allows reading to proceed: symbol (letter or grapheme) → sound (phonemes) → words and meanings (semantics) [168, 170, 173]. The link between visual input and hearing can be demonstrated as you read this page and hear your voice in your head while reading. This phenomenon cannot be suppressed.

There are differences in the manifestations of dyslexia in various languages [170]. This is influenced by the emphasis placed on particular characteristics within the language under consideration; German emphasises fluency, Chinese visual spatial skills (to recognise the myriad characters) and English phonological skills. Given these differences languages will use differing neural substrates to develop their "reading circuit" in the brain [170]. For languages that depend more on phonological skills for reading acquisition, such as notoriously irregular languages such as English and French, phoneme awareness and decoding are good predictors of dyslexia. For more predicatable and phonologically regular languages, like German, processing speed and comprehension are more clearly the markers of dyslexia [170].

Reading skills are influenced by very early language experience with preschool children typically learning 2–4 new word every day. Early reading experience (i.e. being read to) appears to have positive effects on later reading [170, 175]. These early experiences help form an understanding of the basic "rules" of a language before the more formal task of learning to read commences. There is good evidence that brain regions used in the reading process change as a child reading skills improve and mature [170]. In immature readers reading appears to be bihemispheric and involves significant areas in the occipital, parietal, temporal and frontal lobes while in fluent, skilled readers the left hemisphere is predominately involved with mainly occipital and frontal activity with significant bypassing of the parietal and temporal lobes [170]. This has given rise to concepts such as the "reading circuit" in the brain.

Systemic Manifestations

Dyslexia can have accompanying behavioural and psychiatric abnormalities that are consequences of the dyslexia and do not share common etiologies. Willcutt and Pennington have shown that children with dyslexia more commonly manifest evidence of ADHD, oppositional disorder, conduct disorder, anxiety and depression [176]. Boys are more likely to externalize behavioral responses, whichmay be evident as aggressive behaviour, while girls internalize psychopathology and this is more likely to manifest as depression [176].

Dyslexia is not a developmental lag and there is good evidence that dyslexia persists into adolescence [177] and adulthood [168, 178, 179]. Shaywitz et al. have shown in young adults that there are persisting functional abnormalities in both compensated (accurate but not fluent readers) and persistent (not accurate or fluent readers) [178].

Ophthalmic Manifestations

There are no recognised ocular manifestations that are characteristic or specific to dyslexia despite an enormous literature that obfuscates the issue [168]. There are ocular co-morbidities that may compound the problems of dyslexia such as

reduced visual acuity, refractive error and defects in accommodation and convergence [168]. The contribution of these defects is usually minor and is not related to the etiology of the dyslexia. It has been suggested that ocular motility disorders are more common in individuals with dyslexia, especially saccadic tracking disorders. It is more likely that eye movement variations are secondary to the difficulties with reading rather than primary [168]. The evidence for primary abnormalities in saccadic control in dyslexia is inconclusive [180].

In a large population study almost no differences were found in the rate of ophthalmic abnormalities between those children with "severe reading impairment" (defined as two standard deviations below the mean with a standardized reading assessment tool) and those without severe reading impairment [181]. No association was found between severe reading impairment and strabismus, motor fusion, sensory fusion at a distance, refractive error, amblyopia, convergence, accommodation, or contrast sensitivity. Abnormalities in sensory fusion at near were modestly more common in children with severe reading impairment compared with their peers (1 in 6 vs 1 in 10, P = .08), as were children with stereoacuity worse than 60 s/arc (1 in 6 vs 1 in 10, P = .001) [181]. The significance of these minor differences in a small group of children with severe reading impairment were unclear. Most children with severe reading impairment had entirely normal eye examinations.

A number of theories and therapies have been proposed that suggest that dyslexia has it's origins in visual abnormalities and that specific intervention has a very positive effect. These alleged therapies include colored lenses and overlays (Irlen lenses), behavioural optometry, training glasses, yoked prisms, low hyperopic glasses or bifocals and vision therapy [168]. The evidence base that underpins each of these theories and therapies has been systematically evaluated has been found severely lacking [168, 173, 182, 183].

Diagnosis

The diagnosis of dyslexia should not be made by ophthalmologists in isolation. Indeed, the ophthalmic examination is usually normal. Ideal is a coordinated collaboration of a multidisciplinary team that may consist of educators, educational remediation specialists, special services, psychologists, and physicians [168]. The diagnosis requires a detailed understanding of reading assessment and phonological processing [168, 173].

Management

Ophthalmologists should identify and treat any significant visual defect according to standard principles of treatment [168]. This may entail prescription of glasses for significant hypermetropia or other refractive error, treating significant convergence insufficiency and treatment to improve ocular alignment in cases of large phorias with asthenopic symptoms (this is rare) [173]. It is important to refer children with suspected dyslexia for appropriate educational assessment if this has not already been undertaken. Ophthalmologists have an important role in providing accurate information regarding controversial treatment modalities [168, 184].

There is good evidence that educational responses to dyslexia appropriately implemented make a difference [168, 175, 185, 186]. In a recent meta-analysis of interventions for struggling readers the authors stated, "…all struggling readers benefit from intervention regardless of their diagnosed learning disability status." [186].

Anorexia Nervosa

Definition

Anorexia nervosa is a major subtype of eating disorder that is common in children and adolescents [187]. The diagnostic criteria used in DSM-5 are as follows.

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight [14].

History

Case reports of "nervous consumption" in adolescents were first described by Morton in 1689. Further case reports have followed over the centuries and in 1911 Janet described anorexia nervosa as a "psychological illness". There have been many proposed theoretical models of understanding the illness since then and there continues to be no single agreed upon or proven etiology [188].

Ophthalmic features have been recognised for many years with formal reports first appearing in the 1950s [189]. Initial reports related to adults with anorexia and cataract [189, 190]. In 1980 Abraham et al. reported a small cross-sectional study looking for evidence of vitamin A deficiency in adolescents and adults with anorexia nervosa [191]. They reported little evidence to support such an association.

Epidemiology

The incidence of is 2.5–5/100,000 in children. The disorder is more common in girls [192, 193]. The ratio of female to male is 6:1 [193]. The incidence of eating disorders, including anorexia nervosa, is increasing in boys [194]. The life

time prevalence is between 0.5 and 2% [195]. and onset peaks between 13 and 18 years of age [196]. Anorexia nervosa has a mortality rate of between 5 and 6% [197]. The mortality of anorexia nervosa is significantly higher than other psychiatric disorders [198] with one-fifth of deaths the result of suicide [199].

Systemic Manifestations

Systemic manifestations of anorexia nervosa are mainly the consequence of severe malnutrition and all organ systems may be affected. Severe malnutrition will result in wasting of subcutaneous fat and muscle with increased bony prominences and protruding ribs [199]. Physical findings may include dry skin, lanugo, acrocyanosis, alopecia, low body temperature, dehydration and retarded growth with delayed puberty [199]. Common complications include a sensitivity to cold, amenorrhoea, gastrointestinal symptoms (such as constipation), bradycardia, osteopenia and increase in size of cerebral ventricles (pseudo atrophy) [199, 200]. A history of dieting and excessive exercise regimens are often indicators of anorexia nervosa [199].

Ophthalmic Manifestations

Most of the reports of ocular manifestations in patients with anorexia nervosa relate to adults but the results of many of these reports may well apply to children and will therefore be briefly summarized [189, 190, 201–211].

Anorexia nervosa results in significant nutritional abnormalities and it has been logically thought that vitamin A deficiency and associated eye problems may occur. There is in fact little evidence to support this. Abraham et al. demonstrated in a cross-sectional study of subjects with anorexia nervosa normal visual acuity and only minor ocular surfaces changes with minimal evidence for hypovitaminosis A [191]. Three of the 13 subjects were less than 18 years old. Gilbert et al. performed conjunctiva impression cytology to determine the nature of ocular surface abnormalities in individuals with anorexia nervosa and found moderate to severe squamous metaplasia in 5/7 but little else to support hypovitaminosis A [202]. They demonstrated reduced tear production with Schirmer testing and reduced blink in one patient. Only one of their subjects was less than 18 years old [202]. Berthout et al. have reported a single case of xerophthalmia with corneal ulceration, reduced field and abnormal electroretinogram in a patient with anorexia nervosa. The ocular surface changes responded favourably to supplementation with vitamin A but the visual field did not improve [206]. Gaudianai et al. reported five adults with severe weight loss due to anorexia nervosa with symptomatic dry eyes and lagophthalmos [212]. It was suggested that orbital fat atrophy with poor apposition of the eyelids to the eye and lagophthamos was responsible for the dry eyes.

Distorted body image has some role in the genesis of anorexia nervosa [187]. Quigley and Doane rightly asked the question if the presence of vision was needed before an individual could develop anorexia nervosa [213]. There are at least four reported cases of blind children or adolescents [213–215] and one blind adult developing anorexia nervosa [201]. In three of the blind children with anorexia nervosa the visual loss was congenital. It would appear that vision is not always necessary to develop a distorted body image.

There are at least two reports of adults with anorexia nervosa developing cataracts [189, 190] but none in children. There are publications suggesting anorexia nervosa is a cause of eyelash trichomegaly [216, 217]. A recent review of the literature has refuted this claim [218].

Retinal abnormalities have been reported twice [203, 209]. Shibuya and Hayasaka reported the case of a 21 year old woman who developed an non-ischemic central retinal vein occlusion that responded favourably to treatment [203]. Moschos et al. studied optical coherence tomography and multifocal electroretinograms in individuals with anorexia nervosa as compared to normal controls [209]. Individuals with anorexia nervosa showed reduced foveal thickness and reduced central amplitudes of multifocal electroretinograms. Vitamin A levels were noted to be normal and it is postulated there may be other nutritional disturbances that give rise to these changes [209].

Observations of eye movements and blinking in anorexia nervosa have been reported [204, 205, 208, 211, 219]. Anorexic adolescents less often look at the eyes of interviewers and do so for shorter durations than control subjects. Mutual eye gazing between anorexics and the interviewers is less frequent [219]. Eye tracking has been used to study gaze at food pictures [208]. These authors showed that anorexics initially used normal gaze when looking at food pictures and then switched to gaze avoidance movements. This gaze avoidance it thought to be cognitive. It is of interest that fasted control subjects showed the greatest attention to the food pictures [208]. Adults with anorexia nervosa have been noted to have squarewave jerks during smooth pursuit movements in two studies [204, 207]. Phillipou et al. demonstrated that squarewave jerks varied with level of anxiety and could be used to differentiate anorexics from controls [207]. They suggested that increased squarewave jerks may be a biomarker for anorexia nervosa and that this may indicate a role for GABA.

Alterations in blink rate have been observed [202, 205, 211]. Barbato et al. found an increased blink rate in anorexics compared to healthy controls which they interpreted as indicating increased dopaminergic activity [205]. Clinical observation in one patient revealed reduced blink rate thought to be due to "systemic motor retardation" [202]. Bellodi used electromyography to measure startle responses to loud noises in anorexics and normal controls [211]. Anorexics had lower magnitude startle responses than normal controls.

Diagnosis

Anorexia nervosa is a clinical diagnosis based on evidence of significant weight loss, the exclusion of organic causes for this weight loss and the assessment of typical cognitions and/or behaviours [14].

Routine clinical assessment of symptomatic patients will enable most significant ophthalmic diagnoses to be made. Vitamin A deficiency is rare in anorexia nervosa despite nutritional status but needs to be considered in cases of ocular surface disease. Retinal dysfunction is rare but may result in field loss.

Management

Ophthalmic management is mainly supportive with specific measures being required for conditions such as vitamin A deficiency, cataract and retinal vein occlusion. These manifestations are fortunately rare. Anorexia nervosa remains a disease with significant morbidity and mortality [187]. Fortunately ophthalmic manifestations are infrequent and will usually respond to appropriate interventions.

Anxiety and Depression

Childhood anxiety and depression are not discussed in detail as more often anxiety and/or depression are the psychiatric manifestations of significant ocular disease and not visa-versa. There is an extensive literature emphasising the importance of anxiety and depression in children with visual impairment and other ophthalmic disorders [220–230].

Brief mention will be made of eye movement studies in anxiety and depression of childhood. This has been reviewed by Rommelse et al. [180]. It is noted that adolescents with anxiety or depression perform differently than normal controls with anti-saccadic eye movement tasks. There is also an extensive literature relating rapid eye movement during sleep to depression [231, 232] but this is not an area of primary concern for ophthalmologists.

Psychosis

Definition

Childhood schizophrenia will be used as the archetypal psychosis of childhood. A more rigorous discussion of childhood psychosis is beyond the scope of this chapter.

The DSM-5 diagnostic criteria for schizophrenia are as follows.

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2) or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated) [14].

History

Current concepts of childhood schizophrenia are very different to those present for most of the twentieth century. Until the 1970s the term childhood schizophrenia was used to describe many children who would now be diagnosed with autism. Separate categories for childhood schizophrenia were removed in DSM II and ICD-9 with the same diagnostic criteria for schizophrenia being applied across all ages [233].

Epidemiology

Although extremely rare in children less than 10 years old, the incidence of schizophrenia rises during adolescence reaching its peak in early adulthood. Swedish data suggests the prevalence for all psychoses is 0.9 in 10,000 at 13 years old and 17.6 in 10,000 at 18 years old [234].

Systemic Manifestations

Childhood and adolescent-onset schizophrenia are usually associated with significant premorbid impairments in functioning and developmental delays. Illness is classically heralded with a prodromal period of social and academic decline followed by the onset of frank psychotic symptoms. Manifestations may include paranoid delusions, hallucinatory experiences and thought disorder. Early onset schizophrenia characteristically runs a chronic and deteriorating course leading to severe debility in adult life [235].

Ophthalmic Manifestations

Self-injurious Behaviour

Ocular self-injurious behaviour ranges from minor "injury" as seen with trichotillomania to the dire consequences of attempted or completed auto-enucleation. Serious self-injury to the eye is a rare event. Trichotillomania is generally considered to be a disorder of impulse control and will be considered separately. Self –injurious behavior as part of factitious disorder by self is also considered separately.

Self-enucleation is a rare manifestation of psychotic illness [236, 237]. It is mainly reported in young adult males and may have its origin in religious delusions [236–238]. The enucleation have been performed with a finger or a variety of implements that were readily available to the patients [236]. The visual effects are uniformly devastating and may result in bilateral visual loss if the chiasm is damaged or both eyes are enucleated [236]. There are two reports of psychotic 18 years olds removing their eye [238, 239]. The case of Rosen and Hoffman was delusional as the result of LSD and had been sexually assaulted. He stated that, "the devil possessed me …… plucked out my right eye" [238] Goldenberg and Sata reported an 18 year old male who amputated his right hand with a saw and removed his right eye with a screwdriver as the result of religious delusion [239]. This was his first manifestation of psychiatric illness. Kinnas and Brady [240] reported a case of a child with Down syndrome removing an eye. Self-injurious behaviour is a risk factor for suicide in individuals with schizophrenia and this must be remembered by all ophthalmologists who care for patients with severe self-induced injuries [241].

Eye Movement Abnormalities in Childhood Psychosis

It is thought by many researchers that "minor physical anomalies" may give a clue to the etiology of the neuro-genetic origins of schizophrenia [242]. Abnormalities in eye movement control have been extensively investigated in children and adolescents with schizophrenia and their relatives [180, 243]. Most commonly abnormalities in pursuit control have been described [244–251]. These can be abnormalities of reduced gain, saccadic intrusions, catch-up saccades and leading saccades. There is evidence that these pursuit abnormalities are more common in first degree relatives [245, 248–250]. Given the suspected complexity of the genetic causes of schizophrenia it is possible these associations may be non-specific [249]. Simple saccadic tasks do not appear to differentiate first degree relatives of childhood schizophrenics and normal controls [252]. Anti-saccadic tasks demonstrate differences between schizophrenics of all ages from their first degree relatives and normal controls [253].

Toyota et al. showed a significant association between constant exotropia and schizophrenia in an adult Japanese group of schizophrenics [254]. They also demonstrated an association with mutations in *PHOX2B* (alternative term PMX2B, OMIM 603851,4p13) which is known to be important in the development of gastrointestinal neurons [255] and is a paralogue of the *ARIX* (OMIM 602753, 11q13.4) which when mutated results in congenital fibrosis of the extraocular muscles type 2 [256]. Schiffman et al. have suggested there is an association between abnormalities of ocular alignment in early adolescence and later schizophrenia [257]. They consdiered a number of binocular abnormalities of motor and sensory function to create an "eye exam" scale and demonstrated a significant correlation with the subsequent diagnosis of schizophrenia approximately 20 years later [257]. Although this reached statistical significance no data was presented as to sensitivity and specificity.

Other Visual Tasks

Other visual functions have been shown to vary in individuals at risk of developing or with a diagnosis of schizophrenia. Schubert et al. have suggested that abnormal visual acuity tested at 4 years old in children of women with psychosis has an association with a likelihood of the child developing schizophrenia-spectrum disorder [258]. This finding and that of Schiffman et al. above need to be tested by others. If replicated it would suggest that there may be simple clinical tests that assigns risk for subsequent schizophrenia.

Abnormalities have been demonstrated in visual contrast detection tasks in schizophrenics [259]. Others have shown abnormalities in ability to orientate Vernier differences in young schizophrenics if a masking grating is presented soon after the Vernier stimulus [260]. These observations may reflect subtle variations in complex spatio-temporal processing in individuals with schizophrenia [260].

Visual Hallucinations

Visual hallucinations (along with auditory hallucinations) are very common in childhood onset schizophrenia: 80 and 95 % of cases respectively in one cases series [261]. Visual hallucinations have been described in children with psychosis as the presentation for homocystinuria [262, 263].

Diagnosis

The diagnosis of schizophrenia is clinical with no specific diagnostic test available. Differential diagnoses include affective psychoses, atypical psychoses and organic conditions.

Organic conditions that may present with psychotic symptoms include temporal and frontal lobe seizures, drug induced psychoses, rare neurodegenerative conditions and metabolic conditions such as homocytinuria.

The diagnosis of self-induced ocular trauma is generally not difficult as it is usually freely admitted and not concealed as it is with factitious disorders. As with any ocular trauma a careful and thorough assessment of the eye and adnexa is required. It is important to keep in mild related injuries such as intracranial injury if a sharp object has been utilised to cause the trauma. Detailed eye movement recordings are not part of the routine assessment of patients with psychiatric disorders.

Management

Ophthalmic management will be determined by the nature of the self-induced injury. In more severe injuries much of the management may be directed to improving cosmesis after the acute phase of injury management has passed. Long term psychiatric intervention is critical to prevent recurrence.

Visual outcome is determined in most cases by the original injury with more severe injuries having a poor visual prognosis.

Trichotillomania

Definition

Trichotillomania is abnormal removal of body hair from any site and is defined in DSM-5 as follows.

A. Recurrent pulling out of one's hair, resulting in hair loss.
B. Repeated attempts to decrease or stop hair pulling.
C. The hair pulling causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The hair pulling or hair loss is not attributable to another medical condition (e.g., a dermatological condition).
E. The hair pulling is not better explained by the symptoms of another mental disorder (e.g., attempts to improve a perceived defect or flaw in appearance in body dysmorphic disorder) [14].

History

The term trichotillomania was proposed by French dermatologist François Henri Hallopeau in 1889 [264]. He described the case of a young male who compulsively pulled hair from all over his body. Most reports since then have been in the pediatric, dermatology or psychiatric literature [265]. Ophthalmic reports of trichotillomania started appearing in the 1970s. Schenk reported the case of a 14 year old boy with trichotillomania of the eyelashes that was attributed to difficulties both with his brother and school work [266]. Initial ophthalmic reports did not comment on or recognize the significant psychological associations of trichotillomania [266, 267].

Epidemiology

The prevalence of trichotillomania is estimated to be 1–5 % of the general population though some surveys suggest that hair pulling may affect as much as 20 % of the population [268]. Most series report a female preponderance and onset in childhood [268–272]. The age of onset does not appear to be an important indicator of later psychological difficulties [273].

Systemic Manifestations

Scalp hair loss is the most common systemic manifestation and is reported in approximately 80 % of cases in larger series [269, 270, 272]. The major psychiatric co-morbidities are anxiety, obsessive-compulsive disorders and depression [268, 270, 272, 274, 275]. Substance abuse is occasionally associated [272].

Ophthalmic Manifestations

The ophthalmic features are eye lash and/or eyebrow loss. The typical features of eyelash loss are variable loss, with lashes of differing lengths that appear truncated, non-uniform and may be mal-aligned, tortuous or tufted [271, 276, 277]. The broken stubs of the lashes can be seen by slit lamp emanating from the lid margin follicles. There is generally no evidence of other lid margin or periocular skin disease [271, 277, 278]. The remainder of the ocular assessment is characteristically normal. Family members may observe and report the behaviour.

Diagnosis

Diagnosis is made on the basis of typical examination findings outlined above. The major differential diagnosis is alopecia areata [271, 277, 279]. The eyelashes in this disorder are variable absent, with no truncated hairs and the typical exclamation mark hairs which have a narrow base and broader tip are often seen [276, 277, 279]. There is often a family history of autoimmune disorder in cases of alopecia areata [279]. Infrequenly, skin biopsy may be required to differentiate the two disorders [279].

Management

Psychotherapy, drug treatments and behavioural therapies have been utilised with varying success [268, 270, 271, 280, 281]. In some children, especially those without other serious psychiatric disease, the disorder will resolve spontaneously.

Most reports stress the chronicity of this disorder with adults often reporting childhood onset [268, 270].

Personality Disorders

Definition

The general features of personality disorders are defined by DSM-5 as follows.

A. An enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture. This pattern is manifested in two (or more) of the following areas:
   1. Cognition (i.e., ways of perceiving and interpreting self, other people, and events).
   2. Affectivity (i.e., the range, intensity, lability, and appropriateness of emotional response).
   3. Interpersonal functioning.
   4. Impulse control.

B. The enduring pattern is inflexible and pervasive across a broad range of personal and social situations.

C. The enduring pattern leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The pattern is stable and of long duration, and its onset can be traced back at least to adolescence or early adulthood.

E. The enduring pattern is not better explained as a manifestation or consequence of another mental disorder.

F. The enduring pattern is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., head trauma) [14].

Although features of personality disorders may be present in adolescence the diagnosis of personality disorder is rarely made in children or adolescents. Antisocial personality disorder, which includes malingering, is by definition only made in individuals older than 18 years [14].

Ophthalmic Manifestations

These will not be discussed in detail in this chapter as there is limited literature about ocular manifestations in personality disorders. There is evidence that fearlessness or fear blindness in some personality disorders is linked to abnormal face gazing and eye contact [282–285]. This may be related to amygdala dysfunction [283].

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Ocular Manifestations of Pediatric Pulmonary Diseases

18

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Introduction

This chapter will familiarize the reader with the ophthalmologic manifestations of pediatric pulmonary conditions. Infectious, genetic, hematologic, metabolic, musculoskeletal, and rheumatologic diseases involving this organ system are discussed in other chapters of this book.

The diseases discussed are cystic fibrosis and eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome). Sarcoidosis is discussed in the rheumatology chapter; however, the pulmonary manifestations of sarcoidosis are discussed here. While asthma is not fully discussed in this chapter, the reader is reminded of the potential side effects of long-term corticosteroid use, including inhaled corticosteroids. Finally, pleuropulmonary blastoma, a rare and aggressive pulmonary malignancy in children that has been associated with ciliary body medulloepithelioma due to a familial cancer susceptibility syndrome, is discussed.

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Asthma

The ocular manifestations of asthma are primarily related to the use of systemic corticosteroids for treatment and control of the disease. Its association with atopic disease is discussed in the Allergy and Immunology chapter. Despite the well-known association between systemic corticosteroids and posterior subcapsular cataract (PSC) development [1–4], the occurrence of PSC cataracts with long-term inhaled corticosteroid treatment in children is rare, and studies have not found an increased risk of clinically significant PSC cataracts, even with intermittent brief courses of oral prednisone [3, 5–9]. Earlier studies on children and adolescents with severe asthma on daily oral corticosteroids did seem to demonstrate an increased risk of PSC cataract formation in childhood, though results varied and appeared to be dose- and/or duration-dependent [10–12]. When visual acuity was reported, the PSC cataracts found in the few inhaled corticosteroid studies and the oral corticosteroid studies were generally not visually significant at the time of the subjects' slit lamp examinations [3, 8, 11, 13]. In addition, reversibility of early corticosteroid-induced PSC cataracts has been reported in children with asthma and nephrotic syndrome [11, 14]. However, after many years of inhaled corticosteroid use into adulthood, the duration-related and possibly age-related risk for PSC cataract development may be increased and become visually significant [9, 15], so that periodic screening and education are sensible.

Other effects of corticosteroid treatment in children with asthma have been studied and reported. The effect of inhaled corticosteroids on intraocular pressure has not been shown to be a concern in the pediatric population [9, 13, 16–18]. Periorificial dermatitis, an acneiform eruption of unknown origin that usually occurs in the perioral region but can also involve the periocular areas, has been reported to occur with inhaled steroids, especially when delivered with a device equipped with face mask, in children with asthma [19–21].

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Periorificial dermatitis is known to occur with topical corticosteroids; thus, there is likely a direct local effect of the inhaled corticosteroid on the facial skin [19, 21].

Patients who develop complications of corticosteroid treatment of asthma should be co-managed with the primary care physician or pediatric sub-specialist managing the corticosteroid treatment. Surgical intervention may not be necessary if a corticosteroid-induced PSC cataract is not visually significant.

Severe cases of periorificial dermatitis may be treated with topical metronidazole and/or erythromycin [20, 21].

Cystic Fibrosis

Definition

Cystic fibrosis (CF) is a lethal monogenetic autosomal recessive genetic disease affecting the sinopulmonary and gastrointestinal systems, specifically chronic airway infection with obstructive lung disease, chronic sinusitis, recurrent pancreatitis, thickened intestinal secretions, and malabsorption due to pancreatic insufficiency.

History

CF was first defined as a distinct disorder in 1938 by Dorothy H. Andersen, a pathologist in New York, who reported a series of children presumed to have died from celiac disease but were found to have changes in the pancreas and lungs on autopsy [22–24]. She went on to develop diagnostic tests for cystic fibrosis, including an assay of pancreatic enzymes and the sweat test [23]. She and Richard G. Hodges also proposed in 1946 that the disease may be caused by a recessive mutation [25]. The first study of ocular findings in patients with CF was published in 1960 by Bruce and colleagues, who described retinal hemorrhages, venous dilatation and tortuosity, and optic nerve head edema [26]. The locus of the CF gene on chromosome 7 was reported in 1985 [27], followed by identification of the CF gene named cystic fibrosis transmembrane conductance regulator (CFTR), in 1989 [28–30].

Epidemiology

Cystic fibrosis is one of the most common lethal genetic diseases in populations of northern European descent, affecting approximately 1 in 3000–3400 live births [31], and an estimated 3.3 % of Caucasians in the United States are carriers of the CF gene [32, 33]. There is also a fairly high incidence among Hispanics at 1 in 9500. CF is rare in native Africans and Asians, estimated to occur in less than 1 in 50,000, but higher incidences are observed in American populations of these ethnic groups (1 in 15,300 and 1 in 32,100, respectively), suggesting Caucasian admixture [33]. Surveys of Native-American populations also indicate high incidences: 1 in 3970 in the Pueblo people, and 1 in 1580 in the Zuni. There is a slightly higher proportion (52–54 %) of male patients [32, 34]. The majority of patients are diagnosed during the first year of life [32]. Survival rates of cystic fibrosis patients in the United States have improved significantly, but most of the improvement has been limited to patients 2–15 years of age [35]. Female survival is consistently poorer than male survival [32, 35].

Systemic Manifestations

CF affects multiple organ systems including the pulmonary, gastrointestinal, endocrine and reproductive systems [36]. Pulmonary symptoms include chronic cough with sputum production, hemoptysis, pneumonia, obstructive lung disease, and bronchiectasis. Sinus disease is characterized by chronic sinusitis and polyposis. Patients with CF have chronic sinopulmonary infections with pathogenic organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Chronic lung disease and inflammation are associated with clubbing of the fingers and toes. Nutritional symptoms include failure to thrive and malabsorption of fat and fat-soluble vitamins. Gastrointestinal symptoms can be present in the neonatal period including meconium ileus, protracted jaundice, abdominal or scrotal calcifications, and intestinal atresia. Older children have chronic diarrhea, steatorrhea, abdominal distention, chronic constipation, and cholestasis. Reproductive symptoms and signs include delayed puberty and azoospermia secondary to congenital bilateral absence of the vas deferens. CF complications include allergic bronchopulmonary aspergillosis, distal intestinal obstruction syndrome, rectal prolapse, liver disease, recurrent or chronic pancreatitis, and diabetes.

While general anesthesia was previously reported in the 1960s and mid-1980s to be a risk factor for increased mortality and decline in the lung function of patients with CF, the safety of modern anesthesia techniques has improved the outcome for those patients with mild to moderate lung disease. This was reported in a series of 19 patients who underwent general anesthesia for peripherally inserted central catheter (PICC) placement for antibiotics to treat a pulmonary exacerbation [37]. There was no significant deterioration in lung function or clinical status within the first 24–48 h after anesthesia. Nevertheless, patients with CF undergoing general anesthesia should be monitored closely postoperatively for worsening of lung function and clinical status.

Ophthalmic Manifestations

Ophthalmic findings in CF are predominantly a secondary result of other organ system involvement [38]. Retinal findings correlate with the severity and rapidity of pulmonary insufficiency, with hypercapnia and chronic ischemia being significant factors [24]. Bruce described retinal venous dilatation and tortuosity, intraretinal hemorrhages, macular cyst and hole formation and optic nerve head edema in a cohort of patients aged 11 months to 16.5 years of age in moderate to severe stages of CF. He speculated that the changes may have been due to chronic hypoxia and hypercapnia, with similar changes previously described in adults with chronic pulmonary insufficiency [26]. These fundus findings of chronic pulmonary insufficiency have been described in children as well, with most of the changes being reversible with improvement of respiratory status [24, 39, 40]. Whether or not these patients had diabetes was not noted. However, all the patients had received large doses of chloramphenicol, which is known to cause toxic optic neuropathy [41–43]. This will be discussed below.

Regarding the retinal findings, there is likely retinal vascular incompetence, which may be associated with diabetes in patients with CF. CF patients with diabetes were found to have a breakdown of the blood-retina barrier by vitreous fluorophotometry similar to age- and sex-matched insulin-dependent diabetic patients without CF. The mean vitreous fluorescein concentration was significantly lower in CF patients without diabetes [44]. Overall, the vascular changes seen in the retina as well as the conjunctiva may be a result of the patient's CF status and/or the concurrence of diabetes [45]. Congestion of conjunctival venules with erythrocyte aggregation was found to be significantly more common in patients with CF between 15 and 26 years of age compared to healthy control patients [45]. These changes were not related to the coexistence of diabetes [45]. There was, however, an increased prevalence of conjunctival microaneurysms in CF patients with glucose intolerance [45]. Retinal vascular changes were primarily seen in patients with severe CF, especially those with impaired glucose tolerance, but without abnormalities on fluorescein angiography [45, 46]. There was no correlation between the conjunctival and retinal vascular changes [45]. Intraretinal hemorrhages have also been described in young adult patients with CF in association with other factors including Valsalva retinopathy and travel to high altitude [47, 48].

Ocular surface abnormalities are common among patients with CF, though typically asymptomatic. Mild to moderate corneal staining with fluorescein is seen in more than half of children with CF [38, 49]. There is an increased incidence of blepharitis, as well as decreased Schirmer and tear break-up time (TBUT) testing and tear lysozyme [38, 50–52]. Other factors involving the tear film and the conjunctival epithelium may also play a role in ocular surface disease. In addition to conjunctival vascular changes, evaluation of conjunctival epithelial cells in patients with CF by flow cytometry and impression cytology has revealed overexpression of cell surface molecules involved in inflammatory and immune responses and apoptosis, including HLA-DR, intercellular adhesion molecule-1 (ICAM-1) and Fas, as well as reduced goblet cell numbers and presence of squamous metaplasia [50, 53–57]. The latter two findings may be a sign of mild vitamin A deficiency. An increase in HLA-DR expression was also positively correlated with abnormal Schirmer and TBUT testing [50]. Interestingly, the CFTR protein, which is a chloride channel, has been found on the apical domain of bulbar and palpebral conjunctival epithelial cells and may play a role in dry eye syndrome [58]. The tears of patients with CF have also been found to have increased levels of chemokines and cytokines regulating inflammation [59–61] and abnormal electrolyte levels, specifically sodium and calcium [49]. Abnormal tear mucus ferning has also been described in children with CF due to the abnormal electrolyte concentration, which also contributes to the increased hyperviscosity of mucus in CF [62]. Aqueous, mucin or lipid tear component abnormalities may explain the corneal epithelial abnormalities found in CF [38, 52].

Conjunctival and corneal xerosis, one of the ocular consequences of vitamin A deficiency (xerophthalmia) [57], has been infrequently reported in children with CF, though sometimes as a presenting sign of CF [63–66]. Vitamin A is essential for differentiation of rapidly dividing epithelial cells [57, 67]. The presence of xerosis is suggestive of present or prior vitamin A deficiency [68]. On presentation, there is corneal and conjunctival keratinization due to squamous metaplasia with thickened, granular, non-wettable conjunctiva, and patients may have severe photophobia [63, 66, 69–71]. Bitot's spots may also be seen [71], more commonly on temporal conjunctiva and, when present nasally, are associated with more advanced or active vitamin A deficiency [72]. The presence of Bitot's spots may also be associated with nyctalopia [71]. Advanced corneal xerosis can lead to ulceration, descemetocele formation [64] and even corneal perforation with lens extrusion and *Pseudomonas aeruginosa* endophthalmitis [65]. Endogenous *Pseudomonas* endophthalmitis has been reported in young adults, usually following lung transplantation when immunosuppressed [73–75], but endophthalmitis may also occur due to severe corneal thinning and perforation in severe corneal xerosis in patients with CF colonized with *Pseudomonas*. The role of vitamin A in immune function may also contribute to this risk [57].

Vitamin A deficiency continues to occur in patients with CF, though much less frequently [76], regardless of pancreatic function or pancreatic enzyme and vitamin supplementation [67, 70, 77, 78], but the deficiency and its effects, including xerosis, can be asymptomatic or subclinical [67].

This persistent deficiency could be an indication of a need for additional vitamin A supplementation, poor compliance, or possibly zinc deficiency, which has also been reported to occur in CF [66, 70, 77, 79]. Liver function may also play a role [80]. However, vitamin A toxicity due to excessive supplementation is also of concern and appropriate dosing may need to be monitored with serum retinol levels [76, 81]. A serum retinol level below 20–30 microgram/dL is considered to demonstrate vitamin A deficiency, while a level below 10 microgram/dL is indicative of severe deficiency [57, 81]. Levels below these cutoffs significantly increase the risk of xerophthalmia [57]. The upper limit is 72 microgram/dL [81].

When examining the anterior segment of a patient with CF, the lens may show cataractous changes, especially if the patient has been previously treated with steroids for allergic bronchopulmonary aspergillosis [82]. Fama and colleagues used the lens opacity meter in a cohort of patients with CF aged 5–34 years of age and found that their lenses were significantly less transparent than the control group, though these lens changes were not evident on slit lamp exam [83]. The authors proposed that micronutrient deficiencies may also contribute to this finding.

The second major component of xerophthalmia is night blindness (nyctalopia) due to a defect in the synthesis of rhodopsin [57]. It is the earliest symptom of vitamin A deficiency and may occur as an atypical presentation of CF [84] or during the course of disease, manifesting as complaints of night blindness or found on dark adaptation testing [67, 70, 85]. Vitamin A deficiency restricts rhodopsin production, raising the scotopic visual threshold, until a perceptive threshold is reached that leads to recognition of nyctalopia [57]. As mentioned previously, zinc deficiency may contribute to the development of nyctalopia in vitamin A deficiency [70, 79]. Of the 31 patients with CF over 12 years of age examined by Neugebauer and colleagues, none complained of eye symptoms but 10 % had conjunctival xerosis and 19 % had abnormal dark adaptation testing [67]. Elevation of the dark adaption threshold is associated with marked decreases in plasma retinol below 15–30 micrograms/dL [67, 86]. The level at which patients appreciate nyctalopia may be even lower.

Electroretinography (ERG) studies of patients with CF including infants and children have shown variable results. In vitamin A deficiency, scotopic ERG is affected before photopic ERG [87]. Tsinopoulos found normal scotopic waveforms in patients with CF, even those found to have low serum retinol levels, as compared to a control group [88]. The authors suggested that this may be attributed to an inconsistency between serum retinol levels and hepatic stores or total body vitamin A [80]. Suttle and colleagues demonstrated restoration of initially absent scotopic waveforms in one infant after treatment for cystic fibrosis which included vitamin A supplementation [89]. The infant's photopic ERG remained normal. Visual evoked potentials to luminance-modulated and chromatic stimuli, however, remained abnormal with significant latency delay, the etiology of which was unclear [89]. Whatham and colleagues compared ERGs for children and adolescents with CF with pancreatic insufficiency receiving supplementation and without pancreatic insufficiency with similar serum retinol levels and found no significant difference in the ERGs between the two [90]. Electro-oculogram (EOG) and contrast sensitivity have also been reported to be abnormal in CF patients with vitamin A deficiency, with improvement after treatment [91, 92].

Optic neuropathy in patients with CF has been reported primarily in those treated with the antibiotic chloramphenicol, which is now infrequently used due to its well-known adverse effects including bone marrow suppression, "gray syndrome" in neonates, and toxic optic neuropathy [43]. When a case of toxic optic neuropathy attributed to chloramphenicol was reported in 2011, the authors stated that the last reported case in the English literature was in 1988 [93]. Chloramphenicol is not, however, the only cause of optic nerve disease in CF, and optic neuropathy has been reported in patients with CF without a history of chloramphenicol treatment [94]. Other antibiotics, vitamin deficiencies, and chronic hypoxia could also adversely affect the optic nerve [24, 94].

Chloramphenicol toxic optic neuropathy (termed optic neuritis by some authors) was reported numerous times in the 1960s–1970s in children with CF presenting with sudden or subacute bilateral vision loss [42, 95–98]. Often, there had been prolonged use of the antibiotic [43, 46, 97–99]. Fundus exam showed varying degrees of blurred optic disc margins with or without elevation, flame hemorrhages and venous engorgement [42, 97, 99]. The fundus exam may also appear normal, and later optic atrophy may be seen [95, 98]. Central scotomas as well as peripheral constriction are present in those patients in whom visual field examination is possible [43, 95, 97, 99]. Color vision may be affected, and there may be orbital pain and limb paresthesias as well [95, 99]. Godel also demonstrated abnormal visual evoked potentials and photopic ERGs in affected patients [95]. The course of visual impairment is variable, with recovery over weeks to months, and permanent deficits may remain [43, 95, 97, 98]. In some cases, reversal of the visual defect follows cessation of the drug [95, 97, 99], or in response to treatment with vitamin B complex, although no vitamin B deficiency is found [95, 97, 99]. Improvement, often to normal vision with no residual effects, occurs in over half of cases [98]. Due to increasing antibiotic resistance, chloramphenicol is being used again, as reported in 2013 [42], and may potentially need to be considered in the treatment of infections in CF. To prevent chloramphenicol-induced optic neuropathy, the antibiotic is recommended to be used for less than 4–6 weeks [46, 98] with dosage based on age and weight [43]. Serum chloramphenicol levels and blood cell counts should be followed [43].

Pupillary dysfunction has been described in patients with CF [94, 100–102] where the pupils have a diminished rate and absolute level of pupillary dilatation, suggesting that there is concomitant dysfunction of the autonomic nervous system [100, 101, 103]. With pharmacologic pupillary testing, Spaide and colleagues showed that patients with CF display a preganglionic oculosympathetic paresis that corresponds to the disease severity [94]. Reduced cardiovascular response to beta-adrenergic stimulation has also been shown, demonstrating autonomic dysfunction in other organ systems as well [102].

With supplementation according to current standard of care, there are conflicting reports of the prevalence of vitamin E deficiency in children with CF [77, 104]. Vitamin E deficiency can occur, however, irrespective of pancreatic function and pancreatic enzyme and vitamin supplementation [77, 78]. Deficiency can lead to neurologic changes of spinocerebellar degeneration, as well as decreased visual acuity with abnormal visual-evoked potentials indicating deficits in the visual pathway, which have been reported in young adults [105, 106]. Ptosis and abnormal eye movements have also been described [106, 107]. After vitamin E supplementation, the symptoms often improve and VEP abnormalities resolve [105–107]. Vitamin E also increases absorption of vitamin A [108] and may be used in conjunction with vitamin A supplementation for vitamin A deficiency.

Paranasal mucoceles rarely occur in the pediatric age group, but have been reported in patients with CF due to chronic sinus disease and suppuration, usually affecting the ethmoid sinuses and more rarely the frontal sinuses [109]. Presenting symptoms include proptosis or enophthalmos, epiphora, diplopia, headache and nasal obstruction [109, 110].

Diagnosis

Guidelines for the diagnosis of CF have been published by the CF Foundation and the European Union CF Diagnostic Working Group [111, 112]. Diagnosis is based on a combination of phenotypic signs or symptoms with biochemical or genetic markers of *CFTR* dysfunction. Clinical characteristics were described above. Biochemical diagnostic criteria of "classic CF" include [1] sweat chloride of greater than 60 mmol/L or [2] intermediate range sweat chloride (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. Individuals with mild clinical characteristics, normal to intermediate ranges of sweat chloride and *CFTR* mutations of unknown clinical significance may be diagnosed with "*CFTR*-related disease" or "non-classic CF." Final diagnosis should be done with analysis and interpretation by persons familiar with CF disease and genetics at a CF center.

Quantitative measurement of chloride concentration in sweat is stimulated by pilocarpine iontophoresis and is done according to strict guidelines [113]. Causes of false-negative sweat chloride include dilution of sample, malnutrition, peripheral edema, low sweat rate, hypoproteinemia, dehydration, and *CFTR* mutation with normal *CFTR* function. Select causes of false-positive sweat chloride include atopic dermatitis, malnutrition, congenital adrenal hyperplasia, nephrogenic diabetes insipidus, adrenal insufficiency, and hypothyroidism.

Detection of *CFTR* mutations is done with mutation panels using discrete mutation probes. Various geographic regions have created specific mutation panels to capture the majority of cases for specific populations [114]. Full *CFTR* sequence analysis is commercially available. This type of analysis has led to detection of polymorphisms or mutations of unknown clinical significance. Researchers have created coalitions to help investigate *CFTR* mutations and create an updated database on whether *CFTR* mutations are disease causing or not [115].

Other biochemical markers of *CFTR* function are performed in the research setting such as nasal transepithelial potential difference and sweat rate [111, 112, 116]. Currently, these measurements are technically difficult, labor intensive and not approved for diagnosis.

Newborn screening for CF has also been adopted in various areas with different algorithms. Most start with a measurement of immunoreactive trypsinogen (IRT) in blood spots of newborn infants. IRT is elevated in infants with CF possibly due to pancreatic injury consistent with CF, but IRT elevation could also be due to other causes [117]. Infants with elevated IRT can then undergo further testing with a repeat IRT (IRT/IRT) on a second blood spot 1–3 weeks later or *CFTR* mutation analysis with panel or full sequence (IRT/DNA) on the original blood spot [114, 118]. Sweat chloride is then done to confirm the diagnosis.

Systemic Management

CFTR modulator, Ivacaftor, used to reverse the defect in CFTR function in a subset of patients with CF with a specific mutation and also associated with cataracts in children—recommended that patients undergo eye exam prior to starting and during therapy.

Improved care and treatment of patients with CF has extended the life span from a median survival of 10 years in 1966 to 38 years in 2012 in the US [119, 120]. Treatment with antibiotics, chest physiotherapy, and anti-inflammatory agents is directed towards maintaining pulmonary health and preventing progressive pulmonary destruction [121, 122]. Episodes of acute worsening of symptoms are also treated with aggressive airway clearance and enteral or parenteral antibiotics [123]. Close monitoring and treatment to maintain optimal nutrition (BMI > 50%tile or BMI > 22) are recommended for patients with CF [124]. Pancreatic enzyme

replacement and fat-soluble vitamin supplementation are important for nutrition and pulmonary health of patients with CF. Some patients require up to 12,000 IU of vitamin A and 200 mg of vitamin E in order to maintain normal serum concentrations [24]. Periodic screening for cystic fibrosis complications such as liver disease and diabetes is recommended for all patients with CF [125, 126].

Ophthalmic Management

Patients with CF should undergo regular dilated ophthalmologic examinations with special attention to early signs of xerophthalmia and those patients who have been treated with steroids or chloramphenicol. Regular screenings for vitamin A deficiency with measurement of serum retinol or retinol-binding protein levels are recommended [67, 70, 77, 81]. Positive or uncertain cases of vitamin A deficiency should be referred to an ophthalmologist to evaluate for evidence of early manifestations with slit-lamp examination, dark adaption testing and/or ERG [68]. Recognition of early signs of vitamin A deficiency allows for treatment of reversible changes and prevents serious corneal complications and problems with night vision including driving at night, which is important to consider in the teenage and young adult age group [84].

Xerophthalmia is treated with 2 oral doses of oil-miscible vitamin A (200,000 IU) [64]. Intramuscular administration of 100,000 IU of water-miscible vitamin A retinol palmitate may replace the first dose if oral dosing is not possible. Infants younger than 12 months should be given half the dose [57, 64]. In patients who fail to respond to additional vitamin A supplementation despite achieving normal serum levels, the possibility of zinc deficiency should be considered, treatment of which has been reported to be effective in resolving xerophthalmia signs and symptoms [70, 79, 127]. Zinc interacts with vitamin A in the retina, regulates the light-rhodopsin reaction within the photoreceptor and is involved in mobilization of retinol from the liver and synthesis of retinol-binding protein [79, 127]. Corneal lesions can be treated with topical antibiotics for prophylaxis of infection. Corneal xerosis typically improves within 1–4 weeks depending on the severity of the lesion, and nyctalopia resolves within 24 h of treatment with vitamin A [57]. Vitamin A supplementation may then be continued at a lower dose.

Contact lenses may be used with caution, keeping in mind the ocular surface and tear film changes described. Additionally, the high rate of colonization in patients with CF with *Pseudomonas* should be considered if conjunctivitis or a corneal ulcer develops.

Paranasal mucoceles should be co-managed with otolaryngology with consideration for surgery if the mucocele is problematic.

Ophthalmologic problems that arise in patients with CF may have a significant impact on quality of life, are potentially preventable and fortunately are often treatable when they occur.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

Definition

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic syndrome which can include small to medium-vessel vasculitis, granulomatous inflammation, asthma and eosinophilia [128]. Clinical presentation can be heterogeneous. There are several clinically distinct subgroups. 30–40 % of cases are associated with antineutrophil cytoplasmic antibody (ANCA) [129–131].

History

Eosinophilic granulomatosis with polyangiitis (EGPA) was first described in 1951 based on clinical and autopsy data by Jacob Churg and Lotte Strauss, who initially named the disease allergic angiitis and granulomatosis [132]. They described generalized extravascular and vascular granulomatous lesions and proposed that allergic granulomatosis is a more benign form of the disease, and angiitis more severe [132, 133]. The nomenclature was revised by the International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides in 2012 which changed the name to eosinophilic granulomatosis with polyangiitis [134].

Epidemiology

Churg-Strauss syndrome is rare with an estimated incidence of 2.4 per million adults per year [135]. The reported adult male-to-female ratio ranges from 1 to 3 [136], and there is limited data regarding racial variations in occurrence [137]. In the pediatric age group, the incidence is unknown due to its rarity, with most information derived from case reports [138]. A 2009 review of childhood Churg-Strauss syndrome identified 33 published cases with a mean age of 12 years and a male-to-female ratio of 0.74 [139].

Systemic Manifestations

EGPA evolves through phases starting with a prodromic phase (allergic, asthma, sinusitis), an eosinophilic phase (peripheral eosinophilia and organ involvement - lung, cardiac, gastrointestinal), then a vasculitic phase (small-vessel vasculitis) [140]. Asthma is a hallmark feature of EGPA with 90 % of cases of EPGA also having asthma at the time of

diagnosis [131]. Infiltrates on chest imaging, including interstitial thickening, ground-glass opacities, bronchial wall thickening, and bronchiectasis, are part of the criteria for EGPA classification [141]. Allergic rhinitis, recurrent sinusitis, and nasal polyposis are also observed during the prodromic phase. The eosinophilic infiltration phase can affect the myocardium and gastrointestinal system. Cardiac disease is a poor prognostic factor and includes left-ventricular dysfunction, myocardial ischemia, or arrhythmias from eosinophilic infiltration [142]. The vasculitic phase has constitutional symptoms (fever, weight loss, fatigue), peripheral neuropathy, and renal disease.

While the original syndrome was described as having necrotizing vasculitis, eosinophilic infiltration, and extravascular granulomas [132], these features are not seen together in living patients [143]. The pathologic features depend on which stage of disease the affected tissue is sampled. Early disease is associated with extravascular tissue infiltration by eosinophils [144]. Later, inflammation is seen in small to medium sized vessel walls with eosinophilic infiltration. Tissues potentially affected include the lungs, myocardium, gastrointestinal tract, peripheral nerves, skin, and kidney [128, 144].

Ophthalmic Manifestations

Ophthalmic manifestations of EGPA have been described but are unusual [133]. While various conjunctival, corneal, uveitic, retinal, orbital, optic nerve and cranial nerve manifestations have been reported in adults with EGPA [145–147], only two cases of ophthalmic involvement in pediatric EGPA patients have been reported.

In 1995, Heine and colleagues reported a 4-year-old girl presenting with acute pneumonia who had developed an inflammatory lesion in the right orbit [148]. Biopsy of the lesion revealed necrotizing vasculitis, an extravascular epithelioid granuloma and eosinophilic tissue infiltration, which were suggestive of EGPA. Laboratory findings showed eosinophilia, elevated IgE and positive polynuclear antineutrophil cytoplasmic antibodies (p-ANCA) titers at 1:320. Conjunctival involvement was not discussed.

Partal and colleagues reported a case of bilateral optic neuropathy with vasculitis and multiple branch retinal artery occlusions involving the macula in a child with EGPA [149]. The patient was a 10-year-old African-American girl who developed sudden painless vision loss in both eyes to hand motions during a hospitalization for a yet undiagnosed multisystem disease which included asthma, renal failure with hypertension, and elevated liver enzymes. Fundus exam revealed large retinal opacities within the papillomacular bundle, extending into the peripapillary regions in both eyes. There was also macular edema and venous sludging with extensive intraretinal hemorrhages. Fluorescein angiography revealed bilateral blocking defects and non-perfusion in the macula, with pruning and non-perfusion of the small retinal capillaries and choroidal vessels. There was leakage from the vasculature and from the optic nerves as well. The diagnosis of EGPA was made on the presence of only three of the six American College Rheumatology diagnostic criteria, which were asthma, eosinophilia and non-fixed pulmonary infiltrates.

The ocular manifestations in EGPA have been classified into two groups by Takanashi and colleagues based on adult case reports: orbital inflammatory pseudotumour type and ischemic vasculitis type [133], which may represent the two essential characteristics of EGPA which are granulomatosis and angiitis. Orbital inflammatory pseudotumor type has a chronic onset, conjunctival involvement, abnormal orbital imaging and is ANCA-negative with a good visual prognosis. This type may represent the eosinophilic phase of EGPA. The ischemic type has a sudden onset with no conjunctival involvement, no abnormal orbital imaging, occasional oculomotor or trochlear nerve involvement and is ANCA-positive, sometimes with a poor visual prognosis [133]. This type may present the vasculitic phase of the disease.

Diagnosis

EGPA involves eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, necrotizing vasculitis predominantly affecting small to medium vessels, and is associated with asthma and eosinophilia [128]. There are no commonly accepted diagnostic criteria for EGPA. Per the 1990 American College of Rheumatology classification criteria, a vasculitis is classified as EGPA if at least four out of six of the following criteria are present: (1) asthma, (2) eosinophilia >10 % of differential white blood cell count, (3) neuropathy, (4) pulmonary infiltrates on chest imaging, (5) paranasal sinus abnormality, (6) extravascular eosinophils on biopsy [141].

The hallmark histologic findings associated with EGPA are not required for diagnosis since many patients receive glucocorticoids prior to diagnosis which lowers the severity of the histopathologic lesions [140].

Systemic Management

Therapy depends on the severity of disease and prognosis, and ranges from glucocorticoids alone, for mild disease, or in combination with cyclophosphamide, for patients with a poor prognosis [150]. Steroid-sparing therapies include azathioprine and methotrexate [151].

Ophthalmic Management

The patient in the case reported by Heine and colleagues was treated with parenteral corticosteroids with which her symptoms improved, but recurrence occurred while tapering the steroid. The steroid dose was thus increased and azathioprine was added [147, 148]. In the second case by Partal and colleagues, the patient was treated with high-dose intravenous corticosteroids, cyclophosphamide, as well as intravitreal triamcinolone in the right eye, which improved the macular edema. However, vision did not improve beyond 20/400 in either eye [149].

Takanashi has recommended that patients with positive ANCA EGPA who do not have visual symptoms should be followed carefully and treated systemically with corticosteroids to prevent potentially irreversible vision loss from ischemic vasculitis type ocular involvement [133, 149].

Sarcoidosis

Pulmonary Manifestations

Sarcoidosis has been described to involve every organ system [152]; however, the most common manifestations are found in the lymph nodes, lung, skin, and eyes. Two-thirds of patients with sarcoidosis have remission within 10 years after diagnosis with few sequelae, while one-third of patients have chronic disease leading to organ impairment such as pulmonary fibrosis [153]. Older children and adolescents with sarcoidosis present with similar symptoms as adults. There is a form of early-onset childhood sarcoidosis that occurs before 4 years of age and is characterized by an abnormal chest radiograph, skin lesions, arthritis, and uveitis [154]. In this section, we will focus on the pulmonary manifestations of sarcoidosis. Other systemic and ocular manifestations of sarcoidosis are covered in the Rheumatology section of the book.

Pulmonary disease is present in 75–90 % of sarcoidosis cases and is almost universal (97 %) among children aged 8–15 years [155–157]. Respiratory symptoms include dyspnea, cough, chest discomfort and wheezing. Chest pain, an uncommon symptom in children, occurs in 20 % of affected children [152]. Abnormalities found on chest radiographs have been classified into four stages or radiographic patterns that do not correlate with duration of disease or changes in pulmonary function [158, 159]: stage 1, bilateral hilar lymphadenopathy without infiltrates; stage 2, bilateral hilar lymphadenopathy with infiltrates; stage 3, infiltration alone; stage 4, fibrotic bands, bullae, hilar retraction, bronchiectasis, and diaphragmatic tenting. Abnormalities on pulmonary function include both restrictive and obstructive defects, decreased diffusion capacity, and airway hyper-reactivity [160, 161]. The majority of patients who have abnormalities on spirometry return to normal within 2 years [159]. Pulmonary fibrosis occurs in 20–25 % of patients with sarcoidosis [153]. Pulmonary fibrosis and granulomatous infiltration of the pulmonary arterioles have been suggested as causes of pulmonary hypertension which can occur in up to 25 % of patients with sarcoidosis [162, 163].

Pleuropulmonary Blastoma Family Tumor and Dysplasia Syndrome (*DICER1* Syndrome)

Definition

Pleuropulmonary blastoma family tumor and dysplasia syndrome (PPBFTDS) is a familial tumor susceptibility syndrome that increases the risk of pleuropulmonary blastoma (PPB), ovarian sex cord-stromal tumors, cystic nephroma and thyroid gland neoplasia [164]. Several less commonly observed tumors have also been reported: ciliary body medulloepithelioma (CBM), botryoid-type embryonal rhabdomyosarcoma of the cervix and other sites, nasal chondromesenchymal hamartoma, renal sarcoma, pituitary blastoma and pineoblastoma [164]. This section will discuss pleuropulmonary blastoma, a rare dysembryonic tumor of childhood occurring in the lung and pleura [165, 166], and the ocular manifestation of PPBFTDS, ciliary body medulloepithelioma, a rare embryonal ocular tumor of childhood.

History

PPB was first described in 1988 by Manivel and colleagues in a report of 11 pediatric intrathoracic neoplasms that shared clinicopathologic features [167]. Priest and colleagues described PPB as the sentinel disease of a familial tumor susceptibility syndrome [168] in 1996, and in 2009, Hill and colleagues identified heterozygous germline loss-of-function mutations in *DICER1* on chromosome 14q31 as the first known genetic cause for this syndrome [169]. *DICER1* encodes an RNase III enzyme which functions in the microRNA pathways cleaving precursor RNAs into their active forms [164].

CBM was initially termed “carcinoma primitif” by Badel and Lagrange in 1892, and then “teratoneuroma” by Verhoeff in 1904 [170]. In 1908, Fuchs renamed the tumor “dictyoma” due to the prominent findings of a network of medullary epithelial bands. “Medulloepithelioma” was introduced by Grinker in 1931 and has been the favored terminology since then [170].

Priest and colleagues [165] first described in 2010 an association between CBM and PPB and suggested that CBM is an additional neoplasm of the PPBFTDS. They reviewed 299 confirmed cases of PPB and found that three (1 %) were subsequently diagnosed with CBM. Subsequent

reports have also documented an association between the two conditions [170].

Epidemiology

PPB is rare, and the prevalence is not known [164]. About 25–30 cases of PPB from the United States are reported annually to the International Pleuropulmonary Blastoma Registry, which was organized in 1988 [164, 165, 171]. It accounts for 0.5 % of all pediatric malignancies [166]. However, it is one of the most common primary lung malignancies in children [172], with more than 90 % of cases occurring in infants and children less than six years of age [164–166]. About 35 % of families affected by PPB may also manifest a distinct group of other neoplastic conditions comprising PPBFTDS [164], and 25 % of PPB cases appear to be a marker for familial tumor susceptibility [168]. It should be noted that PPB does not occur in all families with *DICER1* mutations, and although the inheritance of the *DICER1* syndrome is autosomal dominant, most mutation carriers are unaffected, indicating that tumor risk is modest with reduced penetrance [164, 173].

Intraocular medulloepithelioma is rare, but it is the second most common primary intraocular neoplasm in children under 10 years of age [174]. Incidence and prevalence are unknown.

Systemic Manifestations

The pulmonary manifestation of PPBFTDS is PPB, which is a potentially aggressive intrathoracic dysembryonic neoplasm in children [166]. The tumor is usually located in the lung periphery, arising from primitive pleuropulmonary mesenchyme [167], but may be extrapulmonary with involvement of the mediastinum, diaphragm, heart, thoracic great vessels and/or pleura [164, 175, 176]. PPB is subdivided into three main subtypes (Table 18.1) on a tumor progression pathway [171]. Type I regressed (type Ir) was described in 2008 as a purely cystic tumor without a primitive cell component, signifying regression or nonprogression, and has a wider age range [171]. Median age at diagnosis, survival rate, risk of metastasis and recurrence are included in Table 18.1. PPB subtype is the strongest predictor of outcome [171]. Type I occurs in the youngest age group, with most diagnosed during the first year of life. Some patients' lung cysts have been detected on prenatal ultrasound at a gestational age of 31–35 weeks [171]. Type I has the most favorable prognosis. Types II and III present in older children with a poorer prognosis and risk of distant metastasis (9 % at diagnosis). Ninety-five percent of types II and III PPB are diagnosed by 6.8 years of age, with rare cases found in adolescents and the oldest reported patient diagnosed at 36 years [171]. Type I can recur, and 10 % can progress after treatment, to type II or III at a median of 23 months after diagnosis, which in turn worsens the prognosis [171, 177]. Metastasis is an independent unfavorable prognostic factor.

Not all PPB cases are found to have a germline *DICER1* mutation [171]. About 65 % of PPB cases have a detectable germline DICER1 mutation, of which 80 % have inherited the germline mutation from a parent, while 20 % are de novo mutations [164]. *DICER1* status does not seem to correlate with outcome [171].

Ophthalmic Manifestations

The ophthalmic manifestation of PPBFTDS is CBM, which is a rare embryonal ocular tumor arising from primitive medullary epithelium, occurring most commonly in children in the first decade of life, with a mean age at diagnosis of 5 years [165, 170, 178]. CBM occurs rarely in adults. The tumor arises from the nonpigmented ciliary epithelium of the pars plicata and rarely from the iris, retina or optic nerve head [179–182]. CBM is histopathologically classified as nonteratoid (50–63 % of cases with 10–31 % benign and 19–40 % malignant) or teratoid (37–50 % of cases with 0–31 % benign and 19–50 % malignant). Overall, 20–34 % are benign and 66–80 % are malignant [170, 178]. Heteroplastic tissue including cartilage, striated muscle and/or neuroglia is present in teratoid CBM [170]. Associated clinical features of

Table 18.1 Subtypes of pleuropulmonary blastoma

Subtype	Median age at diagnosis [171, 187]	Proportion of PPB cases [171, 187]	Histopathology [171]	Distant metastasis [187, 188]	Recurrence [171, 187]	Overall survival [171, 176, 187]
Type I	8–10 months	14–33 %	Purely cystic	Has not been reported	14–20 %	83–91.7 % (deaths followed progression to type II or III)
Type II	34–35 months	35–48 %	Cystic and solid	• Brain 11 % • Bone • Liver (rare)	40–46 %	71 %
Type III	41–44 months	32–38 %	Purely solid	• Brain 54 % • Bone • Liver (rare)	46–60 %	53 %

CBM include secondary glaucoma (44–50 % of cases), iris neovascularization (51 %), cataract (26–50 %), lens subluxation (27 %), lens coloboma (20 %), retrolental neoplastic cyclitic membrane (51 %), intratumoral cysts (61 %) and extraocular extension (10 %) [170, 178, 183]. A neoplastic epiretinal membrane has been observed in some enucleated eyes with CBM. In one larger case series by Kaliki and colleagues [170] of 41 patients with CBM, 2 cases (5 %) were associated with PPB. Less than 1 % of patients with PPB develop CBM, and 5 % of CBM patients have a history of PPB [170]. CBM has not been reported as a chemotherapy-related secondary tumor in childhood cancer patients [184]. Metastasis is uncommon, but in cases with extrascleral extension of tumor at presentation due to a delay in diagnosis, systemic metastasis to cervical lymph nodes and the parotid gland can occur [170, 183]. Intraocular tumor recurrence may also occur after primary treatment, frequently after local resection by partial lamellar sclerouvectomy. Tumor-related death occurs in cases with orbital involvement and/or intracranial extension [178, 183].

There has been one report of choroidal metastasis of PPB in a 3.5-year-old girl with a large PPB tumor of unknown type who developed a choroidal relapse 15 months after diagnosis and five months after treatment with surgical resection and chemotherapy [185]. Chemotherapy was given, and she received radiation therapy to the eye and was disease-free at 35 months.

Diagnosis

No guidelines regarding surveillance of those with a known germline *DICER1* mutation have been established, but annual physical examination, targeted review of systems and imaging based on patient age, presence or absence of clinical findings and suspected tumor type are recommended [164]. Due to the rarity of PPB and its nonspecific symptoms, it may not be considered in the differential diagnosis of children with respiratory distress, persistent pneumonitis, cough, chest pain, fever and/or atelectasis, resulting in a delayed diagnosis [166, 186]. Some present with pleural effusion (type II or III) or pneumothorax (type I or II) [164, 171]. There may no history of familial disease [166]. Computed tomography (CT) of the chest and investigation for associated diseases is recommended in the workup of possible PPB [166, 171]. Magnetic resonance imaging (MRI) of the brain and bone scan are recommend in new diagnoses of type II or III to evaluate for metastasis. In infants, type I PPB may be mistaken for a congenital cystic lesion of the lungs such as congenital pulmonary airway malformation. In these patients, PPB is more likely if there is a family history of PPB or associated tumors but pathological examination is required [171]. In all cases, diagnosis is confirmed on pathologic examination. Interestingly, in a report of 350 pathology-confirmed cases by the International Pleuropulmonary Blastoma Registry, 435 cases were initially included but 85 (20 %) were another entity [171], demonstrating the importance of central pathology review for rare tumors.

The diagnosis of CBM is often delayed due to difficulty in visualizing the ciliary body mass until gradual enlargement leads to secondary effects [170]. The most common presenting signs and symptoms are decreased visual acuity, red and painful eye and leukocoria. On slit lamp exam, CBM is irregularly shaped with a smooth surface and gray to fleshy pink color. Vessels may be visible on or near the surface. In about half of cases, cysts or tumor are present in the anterior chamber [174]. Definitive diagnosis is by histopathologic examination or by the presence of the clinical findings of a ciliary body mass with intratumoral cysts on ultrasound biomicroscopy and/or anterior segment optical coherence tomography, with associated iris neovascularization, corectopia, ectropion uveae, lenticular changes or retrolental neoplastic cyclitic membrane [170]. MRI and CT have also been used to determine the extent of the tumor and distinguish CBM from other intraocular tumors [164]. The intratumoral cysts can occasionally dislodge from the tumor and float in the aqueous or vitreous. Fluorescein angiogram of the retrolental neoplastic cyclitic membrane that often develops in CBM reveals rapid filling of large disorganized vessels emanating from the ciliary body across the hyaloid face [170]. This can help differentiate CBM with a retrolental cyclitic membrane from a retinoblastoma or Coats disease with a total retinal detachment.

While repeated formal ophthalmologic screening of PPB patients may not be warranted by the low risk of CBM development, standard vision screening is recommended, along with the awareness of the relationship of CBM to PPB and the possibility of a familial tumor susceptibility syndrome [165].

Systemic Management

Treatment of PPB is multi-modal and includes surgical resection, adjuvant chemotherapy and radiation therapy [171, 186]. Type I PPB may be treated with primary surgical resection only or with adjuvant chemotherapy in some cases [171]. The use of chemotherapy to prevent progression to type II or III is unclear. Gross total surgical resection of the tumor is associated with improved prognosis, though this may be difficult in type II and III tumors [164, 166, 175, 176, 186]. Type II and III PPB are aggressive sarcomas that require chemotherapy after the first surgery. Chemotherapeutic agents may include vincristine, cyclophosphamide, dactinomycin, doxorubicin and irinotecan [186]. Radiation therapy may be used in type II or III PPB, especially in cases of recurrence or metastasis, or in tumors that cannot be removed [164, 171]. Myeloablative chemotherapy followed by rescue treatment with transplantation of autologous stem cells has

been reported but is controversial and reserved for cases of relapse or poor response to standard therapy [166, 171].

Ophthalmic Management

Primary tumor treatment options for CBM include enucleation, local resection by partial lamellar sclerouvectomy, plaque radiotherapy, external beam radiotherapy, cryotherapy and observation [165, 170]. The role of systemic chemotherapy is not well-established. Treatment selection primarily depends on size of the tumor. Small tumors may be controlled by plaque radiotherapy or local resection. Enucleation is recommended for larger tumors and for smaller tumors that failed to respond to more conservative treatment. Exenteration is required in cases with extensive orbital invasion. Observation of a clinically diagnosed non-progressing CBM monitored every 6 months, without secondary glaucoma and with good visual acuity has been reported [165].

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Ocular Manifestations of Pediatric Renal Diseases

19

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Introduction

The kidneys perform a multitude of functions on top of the obvious activities of waste excretion, maintenance of fluid and electrolyte balance, and assistance in keeping the body's pH within an acceptable limit. Other renal functions that may be overlooked include the synthesis of erythropoietin, 1-hydroxylation of 25-cholecalciferol (i.e., synthesis of active vitamin D_3), synthesis and release of renin (which plays a role in blood pressure control and aldosterone release), synthesis of autocoids, and metabolism of a variety of substances [1].

The kidney interacts with many other organs and, like the eye, is impacted by a myriad of diseases [2]. The oculorenal disorders are listed in Table 19.1 [3, 4]. This chapter will cover only those disease entities that are primarily of a renal nature with the remaining syndromes being covered in other chapters. Listed in the table, but not discussed, are isolated case reports of oculorenal syndromes, as well.

The oculorenal disorders exist for a variety of reasons. A systemic anomaly may result in deposition of abnormal material in both the eye and the kidney (e.g., Fabry disease). A second mechanism of disease occurs when there is a similarity between antigens in both the eye and the kidney (e.g., tubulointerstitial nephritis and uveitis syndrome). Thirdly, systemic effects may injure both the eye and the kidney, as in the case of hypertension. Fourthly, both organs may be affected by a chromosomal abnormality (e.g., Wilms tumor and aniridia). Fifthly, the renal abnormality may secondarily impact the eye as in the cases of dialysis and kidney transplantation. Lastly, the kidneys and eyes develop at similar times embryologically, and hence, developmental defects may coexist (e.g., Alagille syndrome).

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Renal Failure, Dialysis, and Transplantation

Definition

Renal failure is divided into acute kidney injury (AKI) and chronic kidney disease (CKD). AKI is a relatively sudden decline in glomerular filtration rate (GFR). Etiologies fall into three general categories: (1) pre-renal disease, reflecting inadequate renal perfusion; (2) intrinsic renal disease, including acute tubular necrosis, glomerulonephritis, and interstitial nephritis; and (3) post-renal disease secondary to an obstruction of urinary flow.

Chronic kidney disease signifies irreversibility. Recently revised guidelines define CKD as abnormalities of kidney structure or function present for greater than 3 months with some implication for health. CKD is further staged for those over the age of 2 years by GFR ranging from > 90 mL/min/1.73 m^2 to < 15 mL/min/1.73 m^2 [5]. End-stage renal disease (ESRD) defines those with GFR < 15 mL/min/1.73 m^2 [6]. The caveat made for those less than 2 years old reflects the age at which children's GFR begins to approximate adult norms. Etiologies for pediatric CKD vary. In younger children the most common causes are congenital anomalies of the kidney and urinary tract (CAKUT), while glomerulonephritides predominate in adolescents [7, 8].

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Table 19.1 Oculorenal disorders

Malformation/hypoplasia	Renal-coloboma syndrome
	Wilms tumor-aniridia (WAGR contiguous deletion syndrome)
	CHARGE syndrome
	Alagille syndrome
	Branchio-oto-renal syndrome (BOR)
	Fraser syndrome
Ciliopathies	Nephronophthisis (NPHP) syndromes (see Table 18.3) including:
	Senior-Løken syndrome
	Bardet-Biedl syndrome
	Joubert syndrome
	Mainzer-Saldino syndrome
Common structural defects	Alport syndrome
	Nail-patella syndrome
	Pierson syndrome
	Williams-Beuren syndrome
	Marfan syndrome
	Alagille syndrome
	IFAP ± BRESHAK syndrome
	Zellweger syndrome
Metabolic	Lowe syndrome
	Oxalosis
	Cystinosis
	Lecithin cholesterol acyltransferase (LCAT) deficiency/Norum syndrome
	Osteopetrosis with tubular dysfunction
	Galactosemia
	α-galactosidase A deficiency/Fabry disease
	Familial hypercalciuric hypomagnesemia with nephrocalcinosis (FHHNC)
Phakomatosis	von Hippel-Lindau disease
	Tuberous sclerosis complex
Vascular	Diabetes mellitus
	Hypertension
Inflammatory	Tubulointerstitial nephritis and uveitis syndrome
	Sjögren syndrome
	Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
	Systemic lupus erythematosus

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History

While aspects of CKD have been noted since ancient Greek times, the first to associate blindness with renal disease was Bright in 1836. Subsequently, Liebreich was the first to report funduscopic changes associated with uremia in 1859 and named it albuminuric retinitis [9]. The advent of chronic dialysis and renal transplantation in the 1950s has allowed people with renal failure to extend their lives and consequently develop ocular complications that were not previously observed.

Epidemiology

AKI occurs in 33–50 % of acutely ill, hospitalized children while the need for renal replacement therapy (RRT) is almost 25 per 100,000 person-years [10]. With respect to CKD, epidemiologic data is somewhat limited for various reasons, including inconsistent definitions and a relatively asymptomatic early course of the disease [11]. European data reflect an incidence of 11–12 per million of the age-related population for CKD stages 3–5 and 8 per million of the age-related population for CKD stages 4–5 [8]. The mode of RRT varies dependent on the underlying disease process, age (e.g., in the US and Europe, children younger than 14 years tend to obtain peritoneal dialysis, while older adolescents tend to obtain hemodialysis), and location (e.g., Japan and Turkey prefer peritoneal dialysis). Approximately 60–85 % of pediatric patients on RRT undergo kidney transplantation [8].

Systemic Manifestations

Systemic findings of CKD are multi-organ in nature. Fluid retention in the form of edema can be seen in those with a glomerular etiology of CKD. Anemia results from decreased erythropoietin production [12], iron deficiency, and a state of chronic inflammation. Additionally, red blood cell lifespan is shortened in those with CKD further contributing to the anemic state [13]. Metabolic acidosis results from diminished ability to effectively excrete the generated daily acid load [14]. Metabolic bone disease is another common systemic sequel of CKD, resulting from both the impaired renal excretion of phosphorus as well as the decreased synthesis of calcitriol—the active form of vitamin D. The combined effects lead to secondary hyperparathyroidism. Growth failure is a multifactorial manifestation of CKD with average height falling 1.5 standard deviations below the norm [15]. In addition to the aforementioned metabolic bone disease, metabolic acidosis, malnutrition, and a disturbed growth hormone-insulin-like growth factor axis all play a part [11].

The most important systemic features of CKD that impact the eyes are: (1) phosphate retention and decreased 1,25-dihydroxycholecalciferol synthesis with consequent hypocalcemia and secondary hyperparathyroidism; (2) salt and fluid retention resulting in edema and hypertension; and (3) consequences of drug therapy, including immunosuppression and steroid-induced side effects.

Drug therapy may include medications such as steroids, tacrolimus, cyclosporine, mycophenolate mofetil, azathioprine, and antithymocyte globulin. Complications of cyclosporine use include nephrotoxicity, neurologic disorders ranging from tremor to seizure, hirsutism, gingival hyperplasia, hypertension, hyperkalemia, and hepatotoxicity. The principle side effect of azathioprine is suppression of the hematologic system. Antithymocyte globulin, which is a monoclonal antibody to lymphocytes, has many acute side effects including pulmonary edema. None of these treatments, however, have any known direct ocular toxicity. On the other hand, steroids have a broad range of systemic side effects such as adrenal insufficiency, gastric ulceration, impaired glycemic control, mood instability, osteoporosis, elevated intracranial pressure, and hormonal changes to name a few. There are also direct ophthalmic complications, including cataract formation, ocular hypertension and glaucoma, delayed corneal epithelial healing, and reactivation of latent herpetic/fungal infection.

Ophthalmic Manifestations

The effects of ESRD on the eye have been more regularly reported since the 1960s. Symptomatology can vary between mild ocular hyperemia and irritation to significant eye pain and vision loss, depending on the etiology. While difficult to document, there is a belief that maintaining patients in a more normal metabolic balance has decreased the number of ophthalmic complications. The following discussion illustrates the importance of the ophthalmologist in the care of patients with CKD regardless of the modality of support.

Ocular calcifications are usually asymptomatic and typically seen in dialysis patients since it takes time to develop the calcium abnormality. Band keratopathy, similar to that seen in primary hyperparathyroidism, may occur [16, 17]. Brown tumors of the orbit as a manifestation of dysregulation in the calcium-parathyroid axis have also been reported [18, 19]. The frequency of cataracts has been reported to be up to 50 %, and punctate stippling of the lens cortex appears to correlate with hypocalcemia (calcium < 8 mg/dL) [20]. The deposition of calcium phosphate and apatite crystals occurs frequently in the cornea and conjunctiva with reports ranging from 28 to 100 % of the time [21, 22]. One individual has been reported with calcified eyelid margins [23]. Pathologically, the calcium phosphate deposits are seen primarily in the subepithelial and, to a lesser degree, in the basal epithelial layers. The precipitation of calcium phosphate in the conjunctiva may cause acute inflammation and consequent red eye with concomitant, inadequate tearing playing a role [22]. The propensity for calcification in the cornea and conjunctiva is secondary to: (1) alkalinity that results from decreased carbon dioxide concentration from diffusion at the exposed eye surface; (2) the calcium × phosphate product being at least 70 $mmol^2/L^2$ in many cases (although some suggest a lack of association with serum calcium and phosphorus levels) [24]; and (3) local degenerative changes [25]. The predisposition to calcium precipitation improves with reduction of the calcium × phosphate product [26–28].

Exudative or serous retinal detachment may occur in renal failure apart from the presence of a retinal hole, tear, or break [29]. The pathogenesis is believed to be related to hyponatremia, osmotic disequilibrium, and hypertension—which may lead to obstruction at the choriocapillaris level and subsequent leakage of fluid into the subretinal space potentially causing secondary retinal detachment [17]. Chorioretinal degeneration is found in approximately 18 % of cases and is manifested by peripapillary, segmental, or triangular patches. Localized retinal pigment epithelial alterations on fluorescein angiography may also be seen [30]. Spontaneous retinal hemorrhages, retinal vascular accidents, macular edema, and papilledema may also occur [21, 31].

The marked fluid shifts and accompanying hypotension that occur with dialysis can also impact the eyes through potential complications such as central retinal vein occlusion, cortical blindness, and anterior ischemic optic neuropathy [32–35]. Optic neuropathy has also been linked to the uremic milieu in several cases [36]. Patients with CKD have an accelerated diffuse vasculopathy that impairs the optic nerve from handling blood pressure fluctuations as seen in dialysis and renal hypertension. This can lead to an increased risk of optic disc ischemia [37]. Irregular macular pigmentation has been described; however, whether it is an actual consequence of dialysis or merely scarring from retinal pigment epithelial changes secondary to prior hypertension and choroidopathy is subject to discussion [38]. Fluorescein angiography (which can be safely utilized in dialysis patients and, in fact, has improved fluorescence in the setting of anemia) demonstrates choroidal sclerotic changes with simultaneous filling of the retinal and choroidal vessels [39]. Some of the signs of hypertension may improve or even resolve if volume status is adequately controlled, but changes associated with arteriosclerosis will persist.

Intraocular pressure (IOP) and intracranial pressure (ICP) tend to rise with dialysis with IOP even increasing by 13.5 mmHg during hemodialysis [40–42]. Since both organs have semipermeable membranes that limit the diffusion of urea, levels of urea will be lowered in most of the body while they are initially maintained in the aqueous humor and cerebrospinal fluid. This osmotic disequilibrium results in water diffusion into the aqueous humor and cerebrospinal fluid, and consequently, the IOP increases [43, 44]. The IOP elevation is more problematic if there is an underlying history of glaucoma. In fact, there is a case report of acute glaucoma precipitated by hemodialysis [45]. However, others have disputed the findings of the above authors and contend that

there is an insignificant rise in IOP—or even a decrease in IOP—during dialysis with improved technique and better uremia control [46, 47]. Regardless, this potential problem could be addressed through less rapid urea removal (e.g., lower dialysis clearance rates, increased frequency of dialysis, and less efficient artificial kidneys), use of an alternative osmotic agent (e.g., mannitol), or symptomatic glaucoma treatment with agents other than acetazolamide—which may precipitate metabolic acidosis [17].

Dialysis patients can also be exposed to toxic substances such as desferoxamine through the use of phosphate binders [48]. Desferoxamine has been noted to cause cataracts, pigmentary retinal degeneration, color vision disturbances, nyctalopia, visual field defects, and a predisposition to mucormycosis. These may resolve or chronically remain and have further been reported to occur with one or multiple doses of desferoxamine [33, 49, 50].

In addition to the above, dialysis can be associated with other ocular complications. Conjunctival and retinal hemorrhages are seen in the setting of both CKD and hemodialysis. Their presence may be secondary to uremic bleeding diathesis, heparinization during hemodialysis, or may be coincidental [17]. Unilateral exophthalmos has been reported in one instance related to an occluded arteriovenous fistula and subsequent orbital swelling with retro-orbital edema [51].

Renal transplantation has reportedly stabilized some of the ocular abnormalities that occur with dialysis, including corneal and conjunctival calcification; however, it has been shown to neither reverse nor prevent the progression of diabetic retinopathy [52, 53]. Steroid-related complications are noted elsewhere in this book; however, it needs to be emphasized that glucocorticoid therapy enhances the possibilities of cataract formation and glaucoma [54]. The incidence of posterior subcapsular cataracts has been stated as 17–58 % in the transplant population [54, 55]. The posterior subcapsular cataract of renal transplantation reportedly can be distinguished from age-related posterior subcapsular cataract. The axial thickness of the lens is larger than normal, and the opacity lies in the superficial cortex at a depth proportional to the time from transplant with the lens maintaining a normal anterior clear zone [56]. In several series, 17–19 % of affected individuals ultimately required cataract extraction; a third of those were bilateral procedures [21]. Several authors believe that the cataracts are related to steroid use in the peritransplant period and stabilize or even regress when the steroid doses are reduced [56, 57]. Anterior subcapsular opacities are seen in approximately 18 % of cases [58]. Unlike the posterior cataracts, these subcapsular opacities are non-progressive and may be related to underlying renal failure rather than immunosuppressive treatment. They may also represent glaukomflecken i.e., signs of lens epithelial necrosis secondary to elevated IOP. Alterations in IOP attributable to glucocorticoids have been noted in 4–33 % of patients with 2–30 % of those patients requiring IOP-lowering agents [59]. Patients generally were noted to have increased ocular tension between 2 and 6 months post-transplant with normalization that allowed discontinuation of therapy anywhere from 2 months to 3 years after therapy was initiated. Finally, dendritic ulcerations of the cornea have been reported in approximately 2 % of renal transplant patients [21]. The infections with ocular involvement that are seen post-transplant include cytomegalovirus, herpes simplex keratitis and retinitis, *Staphylococcus*, *Pseudomonas*, *Candida*, *Nocardia*, coccidiomycosis, aspergillosis, toxoplasmosis, and *Pneumocystis* [54, 55, 60, 61]. Squamous cell carcinoma of the eyelid, malakoplakia of the eyelid, keratoacanthoma, ocular lymphoma, and reactivation of malignant melanoma have all been reported, as well [62–65].

Diagnosis

Renal failure may be diagnosed under varied circumstances. Signs and symptoms such as high blood pressure, edema, or gross hematuria may prompt an evaluation. Alternatively, the diagnosis may be made incidentally either through routine screenings or when evaluating other conditions. Ultimately, it is the finding of elevated serum creatinine (translating to reduced GFR), abnormal urinalysis, and/or radiographic evaluation that confirms the diagnosis. Once renal failure has been identified, the distinction should be made between acute and chronic conditions.

Management

With regards to AKI, determining the underlying cause (i.e., pre-renal, intrinsic renal, post-renal) can help guide the management both of the etiology as well as secondary effects (e.g., edema, hypertension). A discussion of therapeutic options for the varied etiologies of AKI is beyond the scope of this chapter.

Medical therapy can be utilized to mitigate the systemic effects of CKD. Anemia is managed with iron supplementation and erythropoietin. Metabolic acidosis is treated with systemic bicarbonate therapy. Mineral bone disease requires phosphate control—either through diet alone or with the assistance of phosphate binders, repletion of 25-hydroxyvitamin D, and provision of active vitamin D. Growth failure necessitates adequate calorie intake and management of secondary hyperparathyroidism before consideration of growth hormone therapy.

Renal replacement therapy encompasses both dialysis and transplantation. The decision to pursue dialysis occurs when diet and medical therapy no longer suffice to manage the sequelae of CKD or when symptomatic uremia develops. Typically, this occurs when GFR falls below 15 mL/min/1.73 m^2. Chronic dialysis modalities include hemodialysis

(HD) and peritoneal dialysis (PD). Regardless of modality, the goals of dialysis are the same: namely, to purify the blood of accumulated toxins (clearance) and to remove excess fluid (ultrafiltration) in order to maintain a state of euvolemia. HD necessitates creation of vascular access (e.g., central venous catheter, arteriovenous graft, or fistula). Heparin is utilized to minimize the risk of blood clotting in the extracorporeal dialyzer. PD requires the placement of an intraperitoneal catheter.

Renal transplantation is the preferred RRT given reduced morbidity and mortality as compared to dialysis. In some instances, pre-emptive transplantation occurs without time spent on dialysis in those with ESRD whom medical therapy suffices. Transplant-related ocular abnormalities are relatively more common in children.

From an ophthalmologic perspective, treatment of underlying kidney disease is the most crucial aspect of management. Complications of steroid and RRT (e.g., cataracts and glaucoma) should be monitored and addressed accordingly with medical and surgical intervention as needed. Furthermore, due to the impact of renal failure and transplant on one's immune status, ocular infections should be closely evaluated and treated aggressively to avoid potentially serious ocular morbidity.

Alport Syndrome

Definition

Alport syndrome (AS) is a hereditary renal disease that is clinically and genetically heterogeneous with frequent sensorineural hearing loss (SNHL) and occasional ocular findings. It is best defined as a progressive hereditary renal dysfunction with a high risk of progression towards end-stage renal disease (ESRD).

History

Initially reported in a kindred in 1927 [66], Alport syndrome is characterized by hematuria, proteinuria, renal failure, and progressive deafness with a higher preponderance in males [67]. Prior to Alport's report, there were multiple other case reports of hereditary nephritis; however, Alport was awarded the eponym for recognizing the association of progressive sensorineural deafness with familial hemorrhagic nephritis. The cause of the syndrome was largely unknown [68] until the discovery of mutations in type IV collagen [69, 70].

Epidemiology

AS is the underlying cause of ESRD in up to 3 % of children and 0.2 % of adults [71]. It appears to have a gene frequency of 1 in 5000 [4] without a racial predilection [72]. At its basis

Table 19.2 Genetic basis and expression of type IV collagen [73]

Gene	Chromosome	Chain	Heterotrimers	Expression
COL4A1	1	α1	α1α1α2	All BM
COL4A2		α2		
COL4A3	2	α3	α3α4α5	Glomerular BM
COL4A4		α4		Bowman's capsule
				Distal tubule BM
				Ocular BM
				Cochlear BM
COL4A5	X	α5	α3α4α5	Glomerular BM
COL4A6		α6		Bowman's capsule
				Distal tubule BM
				Ocular BM
				Cochlear BM
			α5α5α6	Bowman's capsule
				Distal tubule BM
				Collecting duct BM
				Epidermal BM

BM basement membrane

AS is a disease of type IV collagen. Six genes (*COL4A1*–*COL4A6*) encode six distinct chains (α1–α6), which arrange to form three major heterotrimers expressed in a variety of tissues [73] (see Table 19.2).

The majority of cases of AS arise from an X-linked inheritance pattern. Though there is inevitable progression of X-linked affected males to ESRD, the rate appears at least somewhat influenced by the type of mutation. Those with large deletions, nonsense mutations, and small mutations altering the reading frame of *COL4A5* have a 90 % probability of progression towards ESRD before 30 years of age. This is in contrast to splice-site mutations that confer a 70 % risk and missense mutations that confer a 50 % risk of development of ESRD in the same time frame [74].

The ophthalmologist may assist in prognosticating given that the retinal changes correlate with earlier onset of renal failure. As noted earlier, male gender has a negative impact on renal survival as does increasing proteinuria. The mode of inheritance also plays a role with X-linkage having a median renal survival of 25 years in males versus 51 years in autosomal dominant inheritance patterns [67].

Systemic Manifestations

Though the clinical manifestations of AS vary somewhat depending on the mode of transmission, the classic findings are largely based on males affected by the X-linked mode of inheritance. In early childhood, affected males present with isolate, persistent microscopic hematuria though renal function is usually well preserved. Episodes of gross hematuria can occur, as well—notably in conjunction with respiratory illness [75]. With time, progressive renal dysfunction develops with rising serum creatinine, worsening proteinuria, and hypertension.

The progression to ESRD largely depends on the mode of inheritance. ESRD is unavoidable in males with X-linked AS with 50 % progressing by age 25 and 100 % by age 60 [74]. Females with X-linked AS also have a significant risk of progression with 12 % reaching ESRD by the age of 45 [76]. Both genders with the autosomal recessive inheritance pattern follow a similar course. Autosomal dominant inheritance, however, tends to follow a much slower rate of progression [67].

Auditory defects are present in the majority of those with both X-linked and autosomal recessive disease though better characterized in the X-linked population with 90 % of X-linked males affected by age 40 and only 10 % of X-linked females affected in the same time frame [74, 76]. SNHL may be initially subtle—starting in the second decade of life—but tends to be bilateral, symmetric, and progress with time in a manner proportional to the progression of kidney disease [77]. The nerve deafness is felt to be due to degeneration of the stria vascularis and the hair cells of the organ of Corti [78] that causes inappropriately functioning hair cells, which still allow for generally good speech discrimination [77].

Ophthalmic Manifestations

Ocular abnormalities occur in 15–30 % of patients with AS [75, 79, 80]. The most common findings are a perimacular dot-and-fleck retinopathy (85 %) and anterior lenticonus (25 %) [79] while posterior polymorphous corneal dystrophy is a reportedly rare but possibly often overlooked manifestation [81].

Anterior lenticonus is most typically associated with AS and is bilateral in 75 % of patients with a preponderance in males [4]. It is a highly specific finding and is an almost pathognomonic suggestion of AS [79, 82–84]. Anterior lenticonus may be difficult to diagnose, even by slit-lamp exam (see Fig. 19.1). The lens may be normal at birth [84], while the lenticonus develops during the second decade of life, displaying an oil-droplet reflex on retinoscopy. Electron microscopy and histopathologic examination of lenses with anterior lenticonus has revealed thinning of the lens capsule, decreased number of epithelial cells, bulging of the lens substance, and capsular dehiscences with fibrillar deposition and vacuolation [82, 86]. The defective nature of the α(IV) collagen in AS has been shown to lead to the fragility of the lens capsule, causing progressive weakening, lenticonus, and risk for cataract formation or lens rupture [87–89]. With respect to lens opacities, anterior polar cataracts are more commonly noted, but cases of posterior subcapsular cataracts have been reported. Anterior polar cataracts are not of specific diagnostic value and can be difficult to differentiate from anterior pyramidal cataracts in the setting of lenticonus [4, 83, 84, 90]. Other anterior findings include calcium crystals in the conjunctiva [91], partial atrophy of the iris [92], flat lenses [93], spherophakia [79], angle-closure glaucoma, strabismus [94], antimongoloid palpebral slant [92], and nystagmus [92, 93].

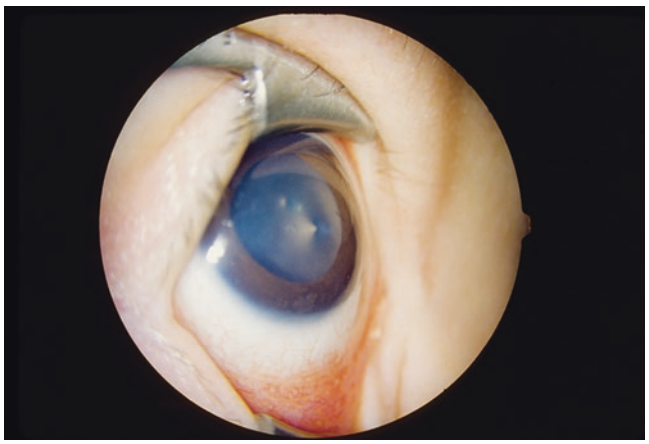

Fig. 19.1 Anterior lenticonus in Alport syndrome [85] (Reprinted from *The Hospital for Sick Children's Atlas of Pediatric Ophthalmology*, Levin AV, Wilson TW, Buncic JR: Metabolic. In: Levin AV, Wilson TW, eds, 2007, © Wolters Kluwer, with permission from Wolters Kluwer)

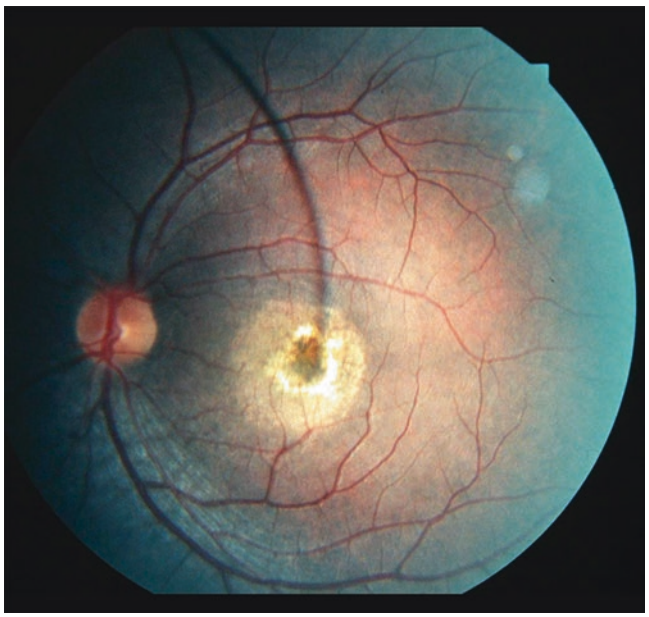

Fig. 19.2 Maculopathy in Alport syndrome demonstrating circumferential exudates in the perifoveal region and clustered pigmentary migration within the fovea [85] (Reprinted from *The Hospital for Sick Children's Atlas of Pediatric Ophthalmology*, Levin AV, Wilson TW, Buncic JR: Metabolic. In: Levin AV, Wilson TW, eds, 2007, © Wolters Kluwer, with permission from Wolters Kluwer)

Macular and perimacular lesions are more common than lenticonus—again, affecting males more commonly than females; and, in the context of familial hematuria, are diagnostic for AS [79, 95]. The appearance can range from scattered yellow-white dots and flecks, typically in the temporal macula, to a more consolidated ring in the perifoveal region that causes a duller macular reflex [90, 96] (see Fig. 19.2). Visual acuity is unaffected by the retinal lesions [97]. Electroretinography (ERG) is typically normal; however,

some authors have found the ERG to have a reduced b-wave while the electro-oculogram (EOG) tracings are normal [98, 99]. Other posterior segment findings include pseudopapilledema [100], retinal drusen [100], retinal detachment [72, 101], macular hole [102, 103], coloboma [104], abnormal macular reflex, hypopigmentation of the retina, tortuosity of the retinal vessels, peripheral pigmentary alterations [93, 98, 105], vitelliform macular lesions [106], bull's eye maculopathy [106], and macular degeneration [107].

Given that α(IV) collagen is also present in the cornea, it is of no surprise that Alport-related mutations have resulted in corneal anomalies. The most common association is a posterior polymorphous corneal dystrophy (PPCD or PPMD) where aberrant endothelium grows in an epithelial-like manner with abnormal basement membrane formation [79, 81, 84, 108–110]. One particular gene, *TCF8*, has been implicated in the development of PPMD and has been found to interact with the promoter region of *COL4A3*, which encodes the α3 subunit of type IV collagen [111]. Other corneal findings include arcus cornealis [90], fine punctate corneal opacities [92], megalocornea [93], progressive bilateral keratoconus [112], microcornea [79], ring abscesses of the cornea [99], and endothelial pigmentation [98].

Diagnosis

The diagnosis of AS is clinically made in those with glomerular hematuria and a family history of the disease. If family history is absent or unknown, the role of either renal or skin biopsy or molecular genetic testing can be discussed.

At its basis, both glomerular and interstitial abnormalities occur due to a defect in the collagen heterotrimer α3α4α5(IV), which is a major component of the basement membrane in the glomerulus (GBM), cochlea (stria vascularis), and eye (e.g., lens capsule) [113]. The α3(IV)–α5(IV) collagen chains have also been found within the internal limiting membrane (ILM) of the retina and basement membrane of the retinal pigment epithelium (RPE)—accounting for the fundus findings in AS [96]. About 85 % of cases are X-linked mutations in the α5(IV) chain (*COL4A5* on Xq22.3) with the majority of the remaining kindreds showing autosomal recessive inheritance from defects in the α3(IV) or α4(IV) chains (*COL4A3* or *COL4A4* on 2q36.3) [4]. Autosomal dominant inheritance due to heterozygous mutations in *COL4A3* or *COL4A4* remains less common and tends to be less pathogenic given that some normal α3(IV) or α4(IV) components are still being formed [114].

Renal biopsy can be quite useful in diagnosing X-linked and autosomal recessive AS. The characteristic electron microscopy finding of GBM lamellation (longitudinal splitting of the lamina densa) is pathognomonic for the disease though the percentage of glomeruli affected in males with X-linked AS is largely influenced by age with split basement membrane present more frequently in older versus younger males. This is not so, however, with either gender affected by autosomal recessive AS [115].

Immunofluorescence can help confirm the diagnosis, especially in young patients not yet displaying the characteristic GBM findings [116]. Males with X-linked AS have an absence of staining for α3(IV), α4(IV), and α5(IV) collagen chains throughout the kidney while heterozygote females show an interrupted expression. Both genders with autosomal recessive disease will show an absence of the α3(IV), α4(IV), and α5(IV) collagen chains in the GBM; however, α5(IV) staining in Bowman's capsule and the distal tubule is maintained [117].

Skin biopsy is a less invasive means of diagnosing X-linked AS given the epidermal expression of α5(IV) collagen chain (but not α3(IV) or α4(IV) chains) [118]. Molecular genetic testing is available to assist in both making the diagnosis of Alport syndrome as well as a means of screening family members at risk [119].

Management

There is no targeted therapy or cure for AS. Therefore, treatment is largely aimed at mitigating the sequelae of CKD. Angiotensin-converting-enzyme (ACE) inhibitors can reduce urinary protein excretion and delay onset of ESRD [120]. In those progressing to ESRD, renal transplantation poses no risk of disease recurrence; however, both X-linked males and both genders with autosomal recessive AS can develop an anti-GBM-like disorder [121–123]. Genetic counseling is important given the hereditary nature of the disease.

The treatment of ocular abnormalities is not warranted historically since the development of significant lenticonus or cataract in the pediatric age is rare; however, reports suggest lensectomy with implantation of an intraocular lens may have a role by the second and third decades of life [124–126]. Certainly, visually significant lens changes should be surgically addressed via pediatric cataract extraction techniques. Subsequent visual rehabilitation with aphakic spectacles, contact lens, or intraocular lens implantation then has merit.

Lowe Syndrome

Definition

Lowe syndrome (LS) an X-linked recessive, multisystem disorder that is characterized by cataracts, mental retardation, and proximal tubule dysfunction, leading to a renal Fanconi-type syndrome [127]. Oculocerebrorenal (OCRL) syndrome is its alternate name owing to the primarily affected organ systems.

History

In 1952, Lowe, Terrey, and MacLachlan described the first three cases [128] of what they termed oculocerebrorenal syndrome. Surprisingly, the original three cases were unrelated despite the currently known genetic inheritance pattern. From 1952 through present day, at least 200 cases of Lowe syndrome have been reported in the literature. It was not until 1992, however, that a genetic basis for Lowe syndrome was discovered as an inborn error of inositol phosphate metabolism due to a mutation in *OCRL* on Xq25–q26 [129].

Epidemiology

Lowe syndrome is a rare diagnosis with an overall prevalence of 1–10 males in 1,000,000 according to the Lowe Syndrome Association (LSA); as of 2000, the LSA noted 190 individuals living with the disease [130]. There does not appear to be a racial predilection. Renal failure usually occurs towards the middle of the third decade [131]. Patients frequently survive into the third and fourth decades of life with the metabolic problems typically decreasing after reaching 5–8 years of age. Given the X-linked nature of inheritance, fathers are not carriers, and there are no reports of affected males fathering children [132]. There have been rare reports of females manifesting the full syndrome [133] likely due to X-autosome translocations. In LS as many as one third of patients represent *de novo* mutations, while 4.5 % are noted to have germline or somatic mosaicism [130].

Systemic Manifestations

Outside of the ocular and renal manifestations, males affected by LS display central hypotonia at birth. Despite the hypotonia, muscle biopsies reveal no abnormalities [134]. Electromyography (EMG) and nerve conduction studies are also normal. The level of muscle enzymes vary with a report of creatinine kinase, aspartate aminotransferase, and lactate dehydrogenase being elevated [131]. Poor development of the anterior fetal brain is one hypothesis accounting for the hypotonia. Central nervous system abnormalities are pronounced and frequently appear in the second 6 months of life [135]. Cognitive deficits are present with only 25 % of patients displaying borderline to normal IQ, resulting in impaired intellectual function [136]. The cognitive deficits are less severe with early systemic intervention and promptly addressing the ophthalmologic deficits. Maladaptive behaviors, including tantrums, stubbornness, and stereotypic mannerisms, are common [136]. Seizures, including infantile spasms, generalized tonic-clonic seizures, and staring spells, may be present in 33–50 % of patients [137, 138]. Anticonvulsant therapy may be required for major motor seizures.

Patients typically have a characteristic phenotypic appearance consisting of microcephaly, frontal bossing, high forehead, hypotonic facies, and short stature [139]. Linear growth decreases after 1 year [131]. Renal failure, rickets, and specific metabolic abnormalities related to the syndrome all may contribute to explain the short stature. Reported musculoskeletal anomalies include joint hypermobility, tenosynovitis, joint effusions, scoliosis, kyphosis, platyspondyly, subluxed or dislocated hips, and cervical spine abnormalities [140, 141].

Renal abnormalities can appear as early as the neonatal period [142] with the urinary excretion of low molecular weight protein reflecting impaired proximal tubular reabsorption. Over the first few years of life, additional proximal tubular wasting can be seen including aminoaciduria, hypercalciuria, kaliuria, phosphaturia, and renal tubular acidosis [131, 139], leading to metabolic acidosis, hypokalemia, and hypophosphatemia. The tubulopathy that develops over time is not consistent with a typical Fanconi syndrome given the absence of glycosuria [143]. Chronic kidney disease generally occurs, which may progress to end-stage renal disease (ESRD) and dialysis dependency. Glomerular filtration rate progressively decreases with age, making ESRD common by early adulthood [144]. Renal biopsies performed early in the disease (less than 10 years old) reflect interstitial fibrosis and tubular dilatation without glomerular involvement—while those biopsied after 10 years of age display a secondary glomerulosclerosis and a more pronounced interstitial disease [131].

Ophthalmic Manifestations

Pathognomonic ocular findings are among the earliest and most consistent clinical observations in LS. The prominent signs are congenital cataracts and congenital glaucoma. Therefore, LS should be considered in any male infant with both of these presenting signs.

Dense bilateral nuclear or posterior cortical cataracts are present in nearly 100 % of cases of affected males at birth [145]. Microspherophakia is common with lenses that are often malformed and discoid in appearance from reduced anterior-posterior and equatorial dimensions. The cataracts occur in small, thin lenses, which may assist with the differential diagnosis [146]. Further findings include an absence of demarcation between the nucleus and cortex, retention of lens nuclei, and irregularities in the thickness of the lens capsule. The lens changes in LS appear to be caused by a defect in early embryogenesis that involves the primary lens fibers [146, 147] and have even been detected prenatally by fetal ultrasound [148].

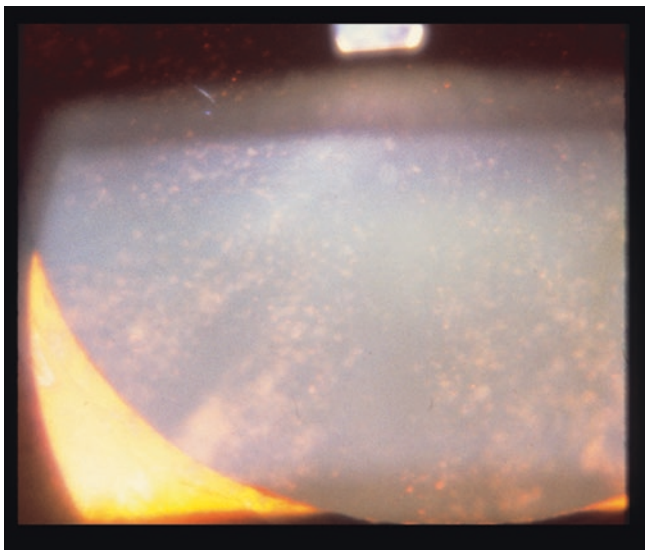

Fig. 19.3 Characteristic lens findings in a female carrier of Lowe syndrome highlighting peripheral, wedge-shaped clusters of punctate and plaque-like subcapsular opacities [85] (Reprinted from *The Hospital for Sick Children's Atlas of Pediatric Ophthalmology*, Levin AV, Wilson TW, Buncic JR: Metabolic. In: Levin AV, Wilson TW, eds, 2007, © Wolters Kluwer, with permission from Wolters Kluwer)

Female carriers may have opacities of the lens and can be diagnosed in their teenage years although the absence of lens opacities does not exclude the carrier state. The typical appearance is punctate and plaque-like opacities in wedge-shaped aggregates outside the nucleus. The superficial opacities and subcapsular plaque-like cataracts continue to develop into adulthood (see Fig. 19.3). Posterior lenticonus is seen frequently. Excrescences are seen on the anterior and equatorial aspects of the lens capsule [149, 150]. These characteristic lens changes permit accurate genetic counseling for female carriers in families with LS.

Glaucoma with or without buphthalmos occurs in over half of cases by 6 years of age [145] and demonstrate histologic anomalies of the anterior chamber [151]. The anatomically abnormal angle of the anterior chamber in LS is indistinguishable from congenital glaucoma. The iris root inserts high on the trabecular meshwork. Other findings include segmental hypoplasia of the iris dilator muscle with adhesions to the anterior lens surface, anteriorly displaced rudimentary ciliary processes, and fenestrations of the iris blood vessels [151]. Strabismus, amblyopia, and pendular nystagmus have all been reported and are most likely secondary to poor vision.

Another typical finding in LS is the formation of corneal keloids that extend through the full thickness of the cornea. In those patients who are at least 6 years old and who have had successful management of their cataracts and/or glaucoma, corneal keloids are the major cause of visual impairment [152]. The pathogenesis of these keloids is unknown although there is a belief, based on several reports of keloid formation, that amino acids may leak into the cornea after an injury or inflammatory reaction, resulting in exuberant fibrovascular proliferation [153, 154].

Diagnosis

Lowe syndrome should be suspected in any male child born with cataracts [128], especially in the setting of hypotonia. Lowe syndrome is an X-linked recessive disease [128] attributed to mutations in the *OCRL* gene at Xq.25–26 [155]. Wadelius et al. initially utilized DNA examination to make carrier detection and prenatal diagnosis feasible [150]. OCRL-1, the enzyme product of the gene, is an inositol 5-phosphatase [129]. Diagnosis is made through identification of reduced function (less than 10%) in inositol polyphosphate 5-phosphatase activity of OCRL-1 in cultured skin fibroblasts [156]. The Lyon hypothesis accounts for the finding of intermediate levels of inositol 5-phosphatase as well as the lens findings in female carriers [157]. Each cell in the lens with the mutated X chromosome causes a punctate or placoid cataract.

Management

Treatment is largely supportive. Renal tubular acidosis is treated with bicarbonate therapy. Supplementation of phosphate and vitamin D are necessary to counteract urinary losses. Renal replacement therapy in the form of dialysis and kidney transplantation is offered to those who progress to ESRD. There is no reported risk of disease recurrence in the transplanted kidney [158, 159]. Speech therapy, physical therapy, and occupational therapy are all disciplines that should be consulted to allow patients to reach their full potential. Additional information on support groups and the disease may be obtained from the Lowe Syndrome Association, PO Box 864346, Plano, Texas, 75086-4346.

Prompt ophthalmologic evaluation and treatment is required to minimize the visual impairment and maximize the potential of these developmentally delayed children. The cataracts are most commonly bilateral and very dense, necessitating early removal. In a series of 14 eyes, Kruger et al. reported cataract surgery at a mean age of 1.25 months [160]. Lensectomy and anterior vitrectomy may be performed via a pars plicata or limbal approach. The former may be beneficial to minimize surgical trauma to the anterior chamber and corneal endothelium given the milieu of goniodysgenesis. One report highlighted intracameral hemorrhage after the removal of an anterior chamber maintainer for a limbal-based lensectomy, which was hypothesized to be from iris vessels in the abnormal angle [161]. However, Kruger et al.

noted a limbal approach in their 14 eyes without intraoperative complications [160]. Another consideration in these patients is the commonly associated iris dilator muscle hypoplasia that may require the use of intraoperative iris hooks. The poor mydriasis also makes satisfactory postoperative retinoscopy and funduscopy a challenge. Given the high risk of glaucoma that may be a result of underlying anterior chamber dysgenesis and post-lensectomy environs, primary intraocular lens (IOL) implantation is ill-advised. The axial length growth these glaucomatous eyes undergo make initial IOL power selection difficult [160].

The glaucoma of LS is best treated surgically by either goniotomy or trabeculotomy even though the angle may appear open or not respond to angle surgery in a manner similar to congenital glaucoma [162]. Correction of surgical aphakia, most often bilateral, is best corrected with aphakic spectacles. Furthermore, since inflammation and/or minor trauma may play a role in corneal keloid formation [153], aphakic contact lenses are relatively contraindicated. And because corneal keloids involve the full thickness of the cornea with risk of regrowth, lamellar keratoplasty is not a viable option. Thus, keloid resection should be limited to those cases with significant visual impairment [153].

Strabismus, amblyopia, and nystagmus occur commonly in LS as a result of aphakia, poor vision, and defective binocularity. Standard treatment is appropriate. Aggressive ophthalmologic treatment is warranted since these children do not necessarily have severe mental retardation. Those who are visually rehabilitated do better than children suffering from visual deprivation [146]. However, despite early intervention, nystagmus and poor visual outcomes may still occur with postoperative care limited by difficulty in vision assessment and funduscopic exam. Finally, conscientious perioperative anesthesia is an important aspect of ophthalmologic care as these patients are likely to have multiple ocular surgeries and exams under anesthesia, which necessitate control of their metabolic and electrolyte abnormalities [163].

Tubulointerstitial Nephritis and Uveitis Syndrome

Definition

Tubulointerstitial nephritis and uveitis (TINU) syndrome is a disorder characterized by tubulointerstitial nephritis with uveitis preceding, concurrent to, or following the development of renal disease. As the name suggests, this syndrome comprises the involvement of the renal tubules and interstitium by an acute process and an associated anterior uveitis without evidence of other predisposing conditions [164].

History

The association of uveitis with tubulointerstitial nephritis may occur in a variety of situations including infection, immunologic dysfunction, and drug-related [165, 166]. The first case of TINU syndrome was described by Dobrin et al. in 1975 [167]. They presented two patients who had anterior uveitis, renal failure, bone marrow granulomas, hypergammaglobulinemia, and increased erythrocyte sedimentation rates (ESR) while excluding other known inciting causes. Since their initial report, multiple case reports and series have been published with increased detection due to a better understanding of the presentation and features of this disease.

Epidemiology

The incidence of TINU syndrome is uncertain given its rarity and likely underdiagnosis; however, Rosenbaum [168] previously stated it made up 2% of his general uveitis clinic. A large review of the world medical literature highlighted 133 cases by 2001 [164], and another review in 2009 found 237 published cases [169]. More recently, there was a mention of at least 250 described cases with more than 60% of those presenting in children [170]. The disease spans a range of ages from 11 to 59 years with a preponderance of teenage subjects. TINU has been reported in all ethnicities with a particularly high prevalence in Japan where it was found to be the second most common cause of pediatric uveitis after sarcoidosis [171]. Although previously believed to be more common in females [164], a lack of gender predilection may be the case. Recently, Mackensen et al. described 33 patients with TINU syndrome of whom 60% were male overall and 70% were male in the subgroup younger than 20 years old [172].

The prognosis is for universal improvement with complete resolution in most cases. Mild proteinuria or pyuria rarely persists. The ophthalmologic manifestations also resolve; however, recurrences of uveitis are frequent for several months.

Systemic Manifestations

The primary sites of involvement are recognizably the eyes and the kidneys. The signs and symptoms of this syndrome, however, suggest a systemic disease. Of 129 identified cases, 53% presented with fever, 47% with weight loss, and 44% with malaise. Additional noteworthy signs and symptoms included anorexia, weakness, myalgias, and headache [164]. In addition to elevated serum creatinine and urinary abnormalities noted below, laboratory studies reflected generalized inflammation, including elevated erythrocyte sedimentation rate (ESR) and anemia [164]. Other laboratory findings of

note include several case reports of bone marrow positivity for granulomatous disease [167, 173]. However, more cases reported normal bone marrow [174–178], suggesting the presence of bone marrow granuloma may represent a different, as yet unrecognized, disorder. The differential diagnosis includes a wide range of entities constituting autoimmune/inflammatory disorders (e.g., sarcoidosis, Behçet disease, HLA-B27-related disease, juvenile idiopathic arthritis, Sjögren syndrome, granulomatosis with polyangiitis [formerly Wegener granulomatosis], and systemic lupus erythematosus); infections (e.g., toxoplasmosis, histoplasmosis, syphilis, leptospirosis, tuberculosis, typhoid fever, brucellosis, streptococcal, infectious mononucleosis, and other viral infections); lymphoma; and drug exposure. The entries that have particular relevance to children include streptococcal infections, toxoplasmosis, infectious mononucleosis, other viral infections, and drug-related.

The renal manifestations of TINU syndrome are consistent with acute interstitial nephritis (AIN) as seen in other etiologies. Findings are quite variable, ranging from isolated, asymptomatic urinary abnormalities such as pyuria and white-blood-cell casts to both non-oliguric and oliguric renal failure [179]. The primary site of injury is the renal tubule epithelium with laboratory abnormalities reflective of which tubular segment is damaged [180]. For example, proximal tubular damage is evidenced by aminoaciduria, glycosuria, phosphaturia, renal tubular acidosis, and can encompass a complete Fanconi syndrome [181]. Although the presence of urinary eosinophils had been associated with AIN in the past, it has ultimately been found not to reliably distinguish AIN from other etiologies of AKI [182]. As the clinical picture of AIN is fairly nonspecific, renal biopsy may be warranted to confirm the diagnosis.

Ophthalmic Manifestations

TINU syndrome essentially presents in a manner similar to anterior uveitis of any other etiology. Symptoms include pain, photophobia, redness, and less commonly diminished vision. The uveitis is characteristically bilateral, anterior, and of acute onset. In a large review of 1985 uveitis patients, Mackensen et al. noted that TINU-related uveitis represented a small fraction (1.6%), but when viewed in the context of sudden-onset bilateral acute anterior uveitis (10%) and in patients younger than 20 years (32%), this prevalence was much higher [172]. Some have noted posterior uveitis or panuveitis in TINU [164, 183], while others suggest this is due to spillover disease or secondary posterior involvement from a primarily anterior uveitis [172]. There have been, however, rare reports of associated unilateral neuroretinitis [184], unilateral posterior uveitis with papillitis [185], bilateral vitritis [186], and focal chorioretinitis [187]. Posterior segment involvement may represent atypical presentations along the spectrum of TINU syndrome or may be complications such as with a report of two cases with choroidal neovascularization [188] and a report of one case with retinal pigment epithelium detachments [186].

The timing of ocular inflammation is variable. Onset of uveitis can sometimes precede the renal disease and at other times occur concurrently or several months after renal manifestations. Duration may also be variable from a short course up to a few months to more chronic courses that may be refractory to typical anti-inflammatory therapy. Recurrences are not the norm, but may occur [189]. There does not appear to be a correlation between age of onset and duration of uveitis [172].

Overall, prognosis is good with detriments to visual acuity often related to uveitic complications such as macular edema and optic disc edema [164, 171, 172, 184]. Signs such as nongranulomatous keratic precipitates and iris synechiae may be present as in other types of anterior uveitis.

Diagnosis

The diagnosis of TINU is made by the presence of uveitis and renal histology consistent with interstitial nephritis. Light microscopy demonstrates interstitial edema with inflammatory cell infiltration predominantly by T cells [190]. Given that the uveitis may not present concurrent to the renal manifestations, a high level of clinical suspicion must be maintained [164]. Noninvasive testing may play a role in the pediatric population. Hettinga et al. looked at a Dutch population of 45 patients with uveitis in TINU syndrome under the age of 23 years and found a good sensitivity and high positive predictive value when assessing for elevated urine β_2-microglobulin and serum creatinine in these patients [191].

The pathogenesis of TINU syndrome is currently unknown. Some authors believe it is cell mediated due to the finding of decreased T cells. A cell-mediated mechanism is further supported by the fact that (1) several other types of acute interstitial nephritis are cell mediated; (2) there is a cellular reaction in the kidney while immunofluorescence staining for immunoglobulins has been found to be negative in 18 of 19 cases with TINU; and (3) anterior uveitis is frequently thought to be cell mediated [173, 174]. Other authors, however, believe that the pathogenesis is more likely related to a humoral mechanism based on (1) the increase in serum immunoglobulins seen in most patients; (2) uveitis and interstitial nephritis have occurred in both experimental and clinical diseases [192–194]; and (3) circulating immune complexes have been reported in several cases of TINU syndrome [195].

The basic etiology remains unidentified. Despite this, there has been a strong association noted with specific human leukocyte antigen (HLA) alleles such as HLA-DRB1*01, HLA-DQA1*01, and HLA-DQB1*05, which may prove

helpful in diagnosis and better understanding of the pathogenesis of this syndrome in the future [183]. Mackensen et al. also showed a higher incidence of HLA-DRB1*0102 allelic frequency in patients that had bilateral acute anterior uveitis in the setting of TINU syndrome compared to normals, whereas those with isolated tubulointerstitial nephritis did not show that specific HLA subtype [196].

Management

The management of TINU syndrome is best separated into therapy for the kidneys or the eyes since the manifestations in these organ systems may occur at different times and require different treatments. Renal involvement is largely addressed through supportive care. Rarely, patients require renal replacement therapy, while the overall renal outcome is excellent for the majority of patients [164, 197]. Given the lack of randomized control trials to date, the role of systemic steroids remains unclear. Most patients with TINU syndrome who have been reported, however, received moderate amounts of oral prednisone therapy for variable lengths of time to treat the renal manifestations.

The anterior uveitis is generally self-limited and well addressed with standard therapy (e.g., topical ophthalmic steroids and cycloplegics). Generally, those patients that are refractory to local therapy do well with oral corticosteroids [171, 172]. Treatment is directed at minimizing the secondary complications of uveitis and its treatment, namely: glaucoma, cataracts, posterior synechiae, macular edema, and optic disc edema. If a patient persists with anterior uveitis and systemic symptoms, it would be prudent to check serum creatinine and a urinalysis for evidence of renal involvement.

Wilms Tumor

Definition

Wilms tumor (nephroblastoma) is an embryonal renal malignancy typically arising in children. The principal differential diagnosis is nephroblastomatosis, hydronephrosis, polycystic kidney disease, and neuroblastoma. Wilms tumor (WT) may occur as part of the WAGR continuous deletion syndrome (WT, aniridia, genitourinary anomalies, and retardation).

History

Max Wilms first described nephroblastoma in 1899 [198]. In 1964, Miller reviewed 440 cases of WT and found six patients with aniridia [199]. Miller et al. also described other malformations such as hemihypertrophy in their cohort. DiGeorge and Horley brought the syndrome to the ophthalmic literature in 1967 [200].

Epidemiology

Roughly 7 % of childhood malignancies originate from the kidney, and in those younger than 15 years, the majority are WT [201]. There is a male:female ratio of 0.89:1 [202]. Median age at diagnosis is 38 months though affected females tend to present later, while those with bilateral disease present earlier [203]. Bilateral disease is present in 4–13 % of patients [201]. The prognosis of WT is 90 % 5-year survival in well-differentiated tumors, which constitute 85–90 % of cases [204, 205]. WAGR continuous deletion syndrome has a prevalence of approximately 0.75–1 % in patients with WT [199, 206].

The presence of metastatic disease does not have a major negative impact on prognosis in those with favorable histology; however, anaplastic histology confers a poorer prognosis, especially with more diffuse involvement [207]. Marked atypia or sarcomatous pattern is unfavorable with 25 % cure rate although it only makes up 10–15 % of tumors. See Table 19.3 for information on tumor staging from the National Wilms Tumor Study (NWTS) with associated survival rates [207–210].

Aniridia occurs in 1 % of WT as opposed to the aniridic incidence of 1 in 50,000–100,000 in the general population. Conversely, 25–33 % of aniridic patients will develop WT before age three. The patients affected by both aniridia and WT frequently have other systemic malformations [211].

Table 19.3 National Wilms Tumor Study (NWTS)-3 staging of Wilms tumors with associated survival rates [208]

Stage	Description	Overall survival (favorable histology/anaplastic histology) (%)
I	Limited to one kidney and completely excised with intact renal capsule and no tumor rupture; clean surgical margins	92–97/83
II	Local extension outside kidney (including from previous biopsy or tumor spillage) but completely removed; clean surgical margins	90–95/81
III	Residual non-hematogenous, intra-abdominal involvement (including regional lymph nodes, diffuse peritoneal contamination, extension beyond surgical margins, or not completely resectable)	86/58–72
IV	Hematogenous metastases (e.g., lung, liver, bone, brain)	82/36–56
V	Bilateral renal involvement at diagnosis—each side staged separately as above	–/55

There are a couple of reported cases with a family history of aniridia in whom WT was not also present [212, 213]. Aniridia is severe if associated with other congenital abnormalities. Patients less than 5 years old with aniridia should be screened with a physical exam and ultrasound of the kidneys every 6 months for the presence of WT [214].

Systemic Manifestations

Wilms tumor classically presents as incidental detection of an asymptomatic abdominal mass, although pain can be present in up to 40 % of cases [201]. In up to 24 % of affected children, hematuria, more commonly microscopic, has been noted, as well [215]. Furthermore, hypertension is a common symptom though the true incidence is difficult to discern due to questionable accuracy of blood pressure determination in some children; one series reported a 63 % incidence [216]. The hypertension may be secondary to tumor production of renin [217], local compression of renal parenchyma by the tumor that causes ischemia, or involvement of the renal artery. Systemic symptoms, including fatigue, fever, and weight loss, are late findings in cases of nephroblastoma.

The nephroblastoma-aniridia patients have severe mental retardation (75 % of cases), craniofacial dysmorphism (75 % of cases), genitourinary abnormalities (66 % of cases), frequent growth retardation, and occasional microcephaly. Hemihypertrophy of the body and urogenital malformations such as cryptorchidism, hypospadias, and pseudohermaphroditism are also seen in association with WT. In conjunction with these abnormalities, WT typically presents earlier.

Ophthalmic Manifestations

Aniridia is a panocular disorder that not only involves the iris, but also the cornea, angle of the anterior chamber, lens, retina, and optic nerve [218]. Aniridia is actually a misnomer since, although a large portion of the iris is missing, the iris root is always present. However, the name is still appropriate since the iris appears to be missing on examination by non-ophthalmologic clinicians (see Fig. 19.4). Absence of a well-formed pupillary aperture can lead to visually significant and symptomatic photophobia, glare, and refractive errors.

While hypoplasia of the iris is the most notable finding, it is not the major impediment of visual function [219]. A survey of 83 aniridic patients in 2011 showed associated issues with nystagmus (83 %), cataract (71 %), dry eye (53 %), glaucoma (46 %), keratopathy (45 %), foveal hypoplasia (45 %), strabismus (31 %), and retinal disease (5 %) [220]. Diminished vision correlates more closely with the presence of cataracts, glaucoma, foveal hypoplasia, and optic nerve hypoplasia.

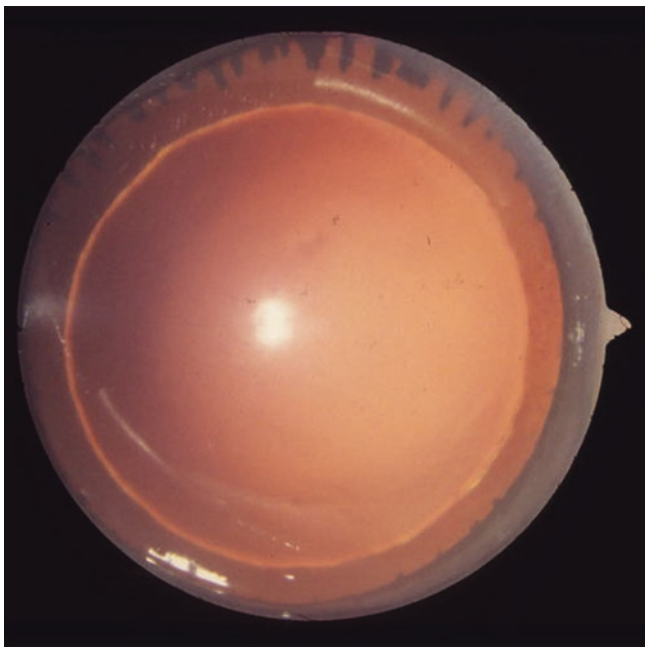

Fig. 19.4 Aniridia in a non-dilated patient, which allows for visibility of the entire lens and scattered ciliary processes on retro-illumination [85] (Reprinted from *The Hospital for Sick Children's Atlas of Pediatric Ophthalmology*, Levin AV, Wilson TW, Buncic JR: Metabolic. In: Levin AV, Wilson TW, eds, 2007, © Wolters Kluwer, with permission from Wolters Kluwer)

Aniridia is often associated with anterior chamber dysgenesis and glaucoma. Corneal development is highly dependent on *PAX6* (located on 11p13), and thus, abnormalities such as thinned corneal epithelium with poor cellular adhesion and migration during wound healing, infiltration of goblet cells, impaired limbal stem cells, and absence of Bowman's layer can lead to aniridia-associated keratopathy [221]. Symptoms can vary from mild to severe based on the level of limbal stem cell insufficiency. Some patients may suffer from significant photophobia, tearing, recurrent erosions and scarring of the cornea, and visual disability [222].

Glaucoma is felt to be an outcome of progressive angle closure within a milieu of abnormal angle development. On gonioscopic exam, broad areas of peripheral anterior synechiae and less commonly anterior rotation of the iris root can be seen [223]. Monitoring via tonometry should be assessed in the context of the increased central corneal thickness that can often be found in aniridic patients [224], highlighting the importance of evaluating the optic nerve, angle, and visual field changes in following these patients.

Lens abnormalities may include ectopia lentis, lens coloboma, and cataract with a notably fragile lens capsule. Reduction in vision can further be compounded by macular and optic nerve hypoplasia. Optic nerve hypoplasia has been found in 10 % of aniridic patients, and foveal hypoplasia is more commonly found in those patients with hypoplastic

optic nerves, although it can also be independently observed [225]. Sensory nystagmus often develops as a consequence of the reduced vision [221, 226].

Diagnosis

Evaluation begins with ultrasonography given ease and availability. Associated Doppler interrogation can assess for infiltration into the inferior vena cava (IVC) or renal vein [227]. Commonly, contrast-enhanced computed tomography (CT) is the subsequent imaging study of choice by better delineating the mass as well as sites of metastases. Other than local extension, WT may also metastasize to the lymph nodes, lungs, and liver [228]. Involvement of the bone marrow suggests an alternative diagnosis (e.g., neuroblastoma). Definitive diagnosis is made via histologic confirmation.

Seven percent of patients diagnosed with WT have an associated syndrome such as WAGR, Beckwith-Wiedemann, or Denys-Drash. Therefore, close attention should be paid to any associated anomalies suggestive of syndromic diagnoses [201]. A definite genetic basis has been identified in WAGR continuous deletion syndrome. Hittner et al. found a deletion of the short arm of chromosome 11 (11p13) [229]. This region was later found to contain the transcription factor, Wilms tumor 1 gene (*WT1*) [230]. Nearby to *WT1* in the 11p13 location is the paired box 6 gene (*PAX6*), which is associated with the majority of aniridia cases and the previously mentioned panocular abnormalities. There have been reports of familial aniridia without WT in which case a single break in 11p13 due to a translocation was hypothesized to cause the isolated aniridia phenotype but a full 11p13 deletion was required for associated WT to occur [212, 213]. Moreover, there have been cases of aniridia with no identified *PAX6* mutation, or deletion [221].

Management

Management is largely driven by research protocols. Two varying approaches are taken by the National Wilms Tumor Study (NWTS) group and the International Society of Pediatric Oncology (SIOP) with one distinction being the timing of chemotherapy versus pre-emptive surgical resection at diagnosis [231]. Partial nephrectomy and nephron sparing surgery (NSS) are being utilized in an attempt to lower morbidity, especially in cases of Stage V Wilms tumor, solitary kidneys, or underlying renal dysfunction [232, 233]. As noted above, radiation and chemotherapy are adjunctive treatments to surgery.

Given the background of an abnormally developed eye that has a propensity towards progressive scarring and the potential of further fibrotic changes with intervention, there are potential avenues of management, but the prognosis can be guarded [221, 234]. Children with significant foveal hypoplasia should be rehabilitated with low vision aids. Visually significant cataracts should be extracted, and a pars plana approach is a reasonable option to avoid further damage to limbal stem cells. Given that cataracts are often bilateral, correction with aphakic spectacles or contact lenses is indicated. Furthermore, abnormalities in the lens capsule and iris can make lensectomy challenging and preclude the use of a standard intraocular lens (IOL). This, in addition to the symptomatology of photophobia and glare, which may not sufficiently be addressed with colored contact lenses, corneal tattooing, and artificial irides, has led to the potential use of a black iris diaphragm IOL to manage both the congenital aniridia and surgical aphakia [221, 235, 236].

Management of aniridic glaucoma has been a challenge. Medical and laser therapy have not shown good control while goniotomy/trabeculotomy appears to have a better effect when done prophylactically to angle closure rather as a therapeutic option down the road [237]. Others have advocated trabeculectomy as first-line therapy [238] while tube shunt implantation has also shown evidence of good intraocular pressure control [221]. Despite aggressive intervention—or possibly even due to it—long-term visual prognosis in the setting of aniridic glaucoma is guarded. Risk factors towards poorer visual outcome include familial aniridia, higher intraocular pressure at baseline, and increased number of intraocular surgeries [239].

Keratopathy can be treated with ocular surface lubrication but may require more intense management with limbal stem cell transplants, lamellar keratoplasty, or the use of the Boston keratoprosthesis, which has shown promising results in vision improvement but can have variable outcomes [240–243]. In conclusion, the treatment of WT and aniridia can have successes but requires a multidisciplinary approach.

Nephronophthisis

Definition

Nephronophthisis (NPHP) literally means "disintegration/damage of nephrons." It is a cystic kidney disease with both childhood and adult types and has also been known as progressive hereditary nephropathy and chronic idiopathic tubular interstitial nephropathy. It is the most common genetic cause of ESRD up to the third decade of life. NPHP is characterized by an autosomal recessive inheritance pattern with severe tubulointerstitial disease and renal corticomedullary cysts although the presence or absence of cysts has not withstood the scrutiny of all authors [244]. Definitive diagnosis is based on renal biopsy and mutational analysis as histopatho-

logic review alone cannot completely differentiate between autosomal recessive (NPHP) and autosomal dominant disease (medullary cystic disease). Several reviews of the condition recommend the terms nephronophthisis complex [245] and renal-retinal dysplasia [246]; however, we will use the more conventional term of NPHP for general recognition while specifying particular syndromes of ophthalmologic interest.

History

In 1945, Smith and Graham first described the condition as congenital medullary cysts of the kidney [247]. Six years later, Fanconi et al. described the disorder and coined the term familial juvenile nephronophthisis (FJN) [248]. Interestingly, the term Fanconi syndrome (i.e., aminoaciduria, renal tubular acidosis, and glycosuria) was based upon the description of FJN. With better understanding of the histopathology and genetics of this disorder, the general term of NPHP has been used to identify this spectrum of disease. The association of this disorder with retinal degeneration was first noted in 1960 by Contreras and Espinoza [244], and in 1997, the first disease gene, *NPHP1*, was discovered by Hildebrandt et al. [249] and Saunier et al. [250].

Epidemiology

The incidence of NPHP has not been well established and ranges from 1 in 50,000–900,000 depending on varying reports [251]. The true incidence may be under-recognized given the relatively recent advent of molecular diagnostics and genetic understanding of this disease. The majority of cases reported thus far in the North American and European literature have been in Caucasians. The prevalence of NPHP in pediatric cases of renal failure is 5 % in the USA and 6.5 % in the UK [251]. The typical course is that of renal failure by early adulthood with a median age of 13 years [251]. Life expectancy has increased with dialytic intervention and renal transplantation. The most commonly mutated gene is *NPHP1*, which causes disease in 20–25 % of patients with NPHP [252].

Systemic Manifestations

Differentiated by their age of ESRD onset, NPHP is divided into three clinical forms: infantile, juvenile, and adolescent [253]. The most common form of NPHP is the juvenile variant. The clinical presentation is frequently insidious, usually manifesting itself between 6 years of age and adolescence [254]. The vast majority of affected children initially present with signs of impaired renal concentrating ability (e.g., polyuria, polydipsia, nocturia, and enuresis). Unlike most disorders causing renal failure, edema and hypertension in NPHP are uncommon due to the accompanying salt wasting [254]. As the early disease manifestations are fairly mild without edema or elevated blood pressures, diagnosis is often delayed. With progression of CKD, anemia and linear growth impairment occur [255]. ESRD is reached by a mean age of 13 years [256]. The infantile and adolescent forms of NPHP progress to ESRD at a mean age of 4 years and 19 years, respectively [257].

A variety of extra-renal abnormalities has been identified with the disease beyond the ophthalmic manifestations: central nervous system abnormalities such as mental retardation [245, 247, 258] and cerebellar ataxia [245, 259], hepatic fibrosis [245, 260–262], skeletal abnormalities such as cone-shaped epiphyses [245, 259, 263] and postaxial hexadactyly [261, 264], obesity [262, 264], hypogonadism [264], and asphyxiating thoracic dystrophy (also known as Jeune syndrome) [265].

Renal ultrasonography early in the disease may show normal to slightly reduced sized kidneys. With disease progression, the kidneys demonstrate increased echogenicity and cyst formation at the corticomedullary junction [266].

The differential diagnosis of NPHP includes other forms of renal cystic disease, including medullary sponge kidney, autosomal recessive polycystic kidney disease (ARPKD), and oligomeganephronia. Medullary sponge kidney is an uninherited disorder confined to renal findings that do not progress to renal failure. ARPKD is a major consideration as it additionally affects the liver; however, the kidneys are typically enlarged with increased echogenicity. Oligomeganephronia may resemble NPHP and consists of bilateral renal hypoplasia with a reduced number of nephrons.

Ophthalmic Manifestations

The first descriptions of an associated retinal degeneration were in the early 1960s by Contreras and Espinosa [244], Senior et al. [267], and Løken et al. [268]. All of the above cases had diminished vision, nystagmus, and a generalized abnormality of the retina that was clinically and histologically similar to Leber congenital amaurosis (LCA). By 1965, Meier and Hass described findings akin to retinitis pigmentosa (RP)—such as narrowed retinal arterioles and clumps/strands of pigment in the retina—in association with NPHP [269]. The RP was characterized by poor night vision (nyctalopia), poor peripheral vision with good central vision in the early stages, and absence of nystagmus as opposed to the findings in LCA. Several kindreds have members with either the retinal disorder or the renal disorder while other members have both manifestations. “Atypical” RP has been associated with NPHP, including retinitis punctata albes-

cens, RP sine pigmento, and central RP [270]. Abnormal ERG that indicates a rod-and-cone degeneration—some cases showing extinction of both the photopic a-wave and the scotopic b-wave—has been reported. Several reports note abnormal ERG or EOG in heterozygotes [271], but these findings are not consistent enough to identify the carrier state [272, 273].

A variety of other ocular abnormalities have been described in association with NPHP, including a yellow spot in the fovea with surrounding hyperpigmentation, chorioretinal coloboma, strabismus, amblyopia, significant refractive errors (myopia or hyperopia), and optic nerve atrophy [245, 264, 267, 268, 274]. The frequency of ocular abnormalities is variable with one series reporting 13 of 27 children having ocular manifestations [245], and retinal dysplasia clearly being the most common. For more information on specific ocular abnormalities noted with various NPHP syndromes, see Table 19.4 [4, 275].

Table 19.4 Spectrum of nephronophthisis (NPHP) syndromes

Name of syndrome	Ophthalmologic findings	Other extra-renal findings
Alström	Retinitis pigmentosa	Obesity
	Nystagmus	Diabetes mellitus, type 2
	Early loss of central vision	Neurosensory hearing loss
		Dilated cardiomyopathy
Arima (cerebro-oculo-hepato-renal syndrome)	Retinitis pigmentosa	Agenesis of the cerebellar vermis
		Hepatic fibrosis
Bardet-Biedl	Retinitis pigmentosa	Obesity
	Early loss of central vision	Deafness
	Early loss of night vision	Postaxial polydactyly
		Mental retardation
		Hypogonadism
Cogan	Oculomotor apraxia	
Ellis-van Creveld	Retinitis pigmentosa	Postaxial polydactyly
		Skeletal dysplasia
		Chondrodysplasia
		Congenital heart defects (atrial septal defect in 60 %)
Jeune (asphyxiating thoracic dysplasia)	Retinitis pigmentosa	Hypoplastic lung disease
		Postaxial polydactyly
		Hepatic fibrosis
		Chondrodysplasia
		Short ribs
Joubert	Nystagmus	Postaxial polydactyly
	Oculomotor apraxia	Cerebellar vermis aplasia/ataxia
	Chorioretinal coloboma	Hypotonia
		Neonatal tachypnea
		Hepatic fibrosis
Mainzer-Saldino	Tapetoretinal degeneration	Cone-shaped epiphyses
		Ataxia
		Polydactyly
Meckel-Gruber	Microphthalmia/microcornea	Occipital encephalocele
	Optic nerve and retinal dysplasia	Situs inversus
	Cataract	Mental retardation
	Iris hypoplasia	Postaxial polydactyly
	Persistent tunica vasculosa lentis	Oral malformations
	Sclerocornea	Cardiac anomalies
	Anophthalmia	Pulmonary hypoplasia
	Cryptophthalmia	Hepatic fibrosis
RHYNS	Retinitis pigmentosa	Hypopituitarism
		Skeletal dysplasia
Senior-Løken (SLNS)	Retinitis pigmentosa	

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Diagnosis

Clinically, NPHP should be considered in any normotensive child with evidence of CKD, relatively bland (non-glomerular) urinary sediment, and normal to slightly small kidneys as visualized on ultrasound.

Overall, NPHP is a genetically heterogeneous disease. An increased molecular understanding has better elucidated the underlying defect to be of the primary cilium of the cell: responsible for sensing and subsequently signaling changes in the extracellular space. The disorders have therefore been classified as ciliopathies with specific genetic mutations [276, 277]. At present, 16 NPHP syndromes have been identified based on mutations in the end-product nephrocystins, which are implicated in the pathogenesis of NPHP. The most common form, NPHP type 1, is due to a mutation in *NPHP1* and accounts for roughly 20–25 % of all NPHP [249, 250]. Clinically, the NPHP syndromes are often referred to by their eponymous names as related to the phenotypic constellation of associated findings rather than the genetic cause. For instance, a mutation in *NPHP1* causing NPHP and retinitis pigmentosa has been named Senior-Løken syndrome, while a mutation in *NPHP1* causing NPHP, cerebellar vermis hypoplasia, oculomotor apraxia, and chorioretinal coloboma is denoted Joubert syndrome (see Table 19.4).

Renal biopsy, though not specific for NPHP, provides highly suggestive features of chronic tubulointerstitial disease, tubular atrophy/dilatation, and thickened/thinned tubular basement membrane [245, 278, 279].

Management

No targeted therapy exists for NPHP; therefore, treatment is focused on managing the sequelae of CKD. Anemia is managed with iron supplementation and erythropoietin; metabolic acidosis is managed with bicarbonate supplementation; and secondary hyperparathyroidism is managed with phosphorus control and vitamin D supplementation in the forms of both 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol [280]. Renal transplantation is ultimately the treatment of choice, and to date there has been no evidence of disease recurrence in transplanted kidneys [281, 282], including a large review of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Registry that showed no NPHP recurrence in 224 patients [283]. Family counseling is important, and careful examination of siblings may allow earlier intervention and prevention of some of the abnormalities attributable to ESRD. A multidisciplinary approach is essential to deal with the medical, psychological, and dietary issues of a child with CKD.

From an ophthalmic perspective, the primary association to evaluate and manage is retinitis pigmentosa. Because of its generally progressive nature that leads to significant impact on visual acuity, peripheral vision, and nighttime vision, visual function should be optimized—often with the assistance of low vision aides. However, there is ongoing research with regards to treating the baseline issue of retinal degeneration and loss of function. Stem cell therapy from embryonic/adult stem cells, induced pluripotent cells, and bone-marrow-derived stem cells have shown promise in terms of differentiation into retinal cells, but the ability of safely and effectively delivering these cells in a manner that will provide physiological function and avoid host rejection is still being studied [284–286]. Similarly, gene therapy has shown promise in certain retinal degenerative diseases (e.g., Leber congenital amaurosis); however therapeutic delivery and attainment of proper physiologic response in a long-term manner requires further insight. Moreover, there is a belief that gene therapy may be more efficacious with less loss of function, thus making the early detection of RP a more crucial element [284, 287]. Nutritional supplementation would be a promising, noninvasive therapy; however, a Cochrane review in 2013 showed no clear evidence that vitamin A and fish oils (docosahexaenoic acid) were beneficial in treating RP [288]. Finally, another therapeutic possibility exists with a surgically implanted, retinal prosthetic such as the Argus® II, which has shown the ability to improve some vision in RP patients but requires appropriate patient selection, intensive investment in visual rehabilitation, and close monitoring for surgical complications [289–292].

Nephrotic Syndrome

Definition

Nephrotic syndrome refers to the clinical triad of proteinuria (>50 mg/kg/day in children), hypoalbuminemia (<2.5–3.0 g/dL), and generalized edema that is often found in association with hyperlipidemia and lipiduria. Urinary wasting of protein and protein-bound molecules can further run the risk of hypothyroidism, microcytic anemia, hypocalcemia, and thrombophilia [293]. It is further defined based on the age presentation according to the following types: congenital (birth–3 months), infantile (4–12 months), or childhood (older than 1 year).

History

Hippocrates described frothy urine suggestive of albuminuria without knowing a cause. Proteinuria in conjunction with edema was first noted by Domenico Cotugno in 1770 [294],

prior to which dropsy had been observed. The first complete description of nephrotic syndrome was by Richard Bright in 1827 [295]. A chemist and physician, John Bostock, added to Bright's description by quantitating the levels of urine and serum proteins and making the observation that greater proteinuria was associated with lower levels of serum albumin [296]. Thus in the 1800s, nephrotic syndrome was defined as profuse albuminuria, hypoalbuminemia, and edema secondary to diseased kidneys, including the possible diagnoses of diabetes mellitus, syphilis, and mercury poisoning [297]. From that time forward, the history of nephrotic syndrome revolves around defining pathologic etiologies, particularly with the advent of the kidney biopsy in the 1950s.

Epidemiology

The incidence of nephrotic syndrome in children less than 16 years old varies from 2 to 7 cases per 100,000 [298, 299]. Genetic etiologies leading to mutations in the glomerular filtration barrier predominate in the congenital and infantile forms [300]. Prognosis varies depending both on the etiology as well as the rate of complications, which have a huge impact on morbidity and mortality of these patients. Studies have shown up to 16% of children hospitalized with nephrotic syndrome sustain a severe complication such as thromboembolism and peritonitis [301].

Systemic Manifestations

Childhood nephrotic syndrome is most often idiopathic in nature, largely reflective of one of two diseases: minimal change disease (MCD; also known as Nil disease) and focal segmental glomerulosclerosis (FSGS) though additional conditions, including membranous nephropathy and membranoproliferative glomerulonephritis, also fall within the differential [302]. As per the International Study of Kidney Diseases in Children (ISKDC), MCD was the histopathologic diagnosis in 76.6% of those presenting under the age of 16 years and 79.6% in those 6 years and under [303]. After the age of 5 years, the incidence of MCD decreases, but it still comprises almost a quarter of nephrotic syndrome cases in adulthood.

The chief systemic features of nephrotic syndrome arise secondary to both the urinary protein losses as well as the compensatory responses to the consequent hypoproteinemia. The clinical hallmark of the disease is excess fluid retention resulting in edema that is often initially noted periorbitally (though with time progresses to ascites), pitting lower extremity edema, or frank anasarca. Pleural effusions are common, as well. Theories exist surrounding edema formation, including an "underfill hypothesis" where edema results from decreased oncotic pressure [304] and an "overfill hypothesis" [305] where edema results from an intrarenal retention of sodium and water. The hypoalbuminemia/hypoproteinemia stimulates compensatory hepatic lipoprotein synthesis, and urinary loss of lipoprotein lipase decreases lipid catabolism—both of which result in hyperlipidemia. Furthermore, elevated serum lipid levels increase the risk of premature vascular disease.

Nephrotic syndrome also predisposes to a hypercoagulable state. Urinary losses of antithrombin III, plasminogen, and protein S lead to decreased endogenous anticoagulants [306]. Additionally, nephrotic syndrome predisposes to an increased number of procoagulants such as fibrinogen, factor VIII, and plasminogen activator inhibitor-1. The hypercoagulable state is further exacerbated by a state of intravascular depletion owing to diuretic therapy that is commonly utilized to treat edema. The pattern of thrombosis is different between adults and children. The former tend to develop venous thrombosis, whereas the latter develop arterial thrombosis.

Children with nephrotic syndrome also have an increased propensity for infection, particularly with encapsulated bacteria (e.g., *Haemophilis influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitides*). This is due to immunoglobulin deficiency [307] and impaired antibody opsonization [308].

Finally, perturbations in metabolism can occur as evidenced by loss of vitamin-D-binding protein, resulting in vitamin D deficiency.

Ophthalmic Manifestations

Nephrotic syndrome has broad systemic effects (e.g., hypercoagulability, diabetes mellitus, hypertension, and hyperlipidemia) that can in turn lead to ophthalmic complications (e.g., retinal vascular occlusions, retinopathy, and retinal ischemia). Due to the influence on circulation, it is not uncommon to see asymptomatic tortuous and dilated retinal vessels [298]. Nephrotic syndrome-related hypercoagulability has even led to cerebral sinus venous thrombosis and associated presentations of papilledema and sixth-nerve palsies [309, 310]. Depending on the duration of disease, both acute and chronic changes can be seen.

More commonly, ophthalmic manifestations of steroid therapy are encountered: cataracts (especially posterior subcapsular opacities), steroid-response elevation in intraocular pressure, and glaucoma [298, 311–315]. Immunosuppression as related to steroid or other immunomodulatory therapy can lead to potential ocular complications, as well. There have been reports of choroidal melanoma [316] and Purtscher-like retinopathy secondary to septicemic disseminated intravascular coagulation [317]. On the other hand, there is thought that just as nephrotic syndrome may be a immunologic

phenomenon, these patients may have uveitic manifestations [318]; however, it is difficult to accurately parse out this association as these patients are typically being treated with high doses of immunosuppression prior to ophthalmologic evaluation [298].

Finally, a specific form of congenital nephrotic syndrome with diffuse mesangial sclerosis, known as Pierson syndrome, is a result of loss-of-function mutations in *LAMB2*. Several associated ocular findings have been reported, most commonly severe microcoria, but also posterior embryotoxon, iris hypoplasia, persistent fetal vasculature, retinal detachment, and abnormal lens shape with or without cataract [319–322]. Although Pierson syndrome can have early lethality, there is belief that a phenotypic spectrum of severity exists, which may help explain findings of Mittendorf dots in nephrotic children [312, 323, 324].

Diagnosis

Nephrotic syndrome is diagnosed by the classic triad of nephrotic range proteinuria (>50 mg/kg/day) or spot urine protein-to-creatinine ratio >2, hypoalbuminemia (<2.5–3.0 g/dL), and edema. Additional laboratory studies, including complement levels, help identify those cases of nephrotic syndrome with a secondary etiology. Nephrotic syndrome is a genetically heterogeneous entity although mutations in genes such as *NPHS1*, *NPHS2*, and *WT1* have been associated with congenital nephrotic syndrome of the Finnish type, familial steroid-resistant nephrotic syndrome, and Denys-Drash syndrome, respectively [299].

As per the ISKDC, MCD is the presumptive diagnosis in those children under the age of 6 years who have both normal renal function and complement levels and are otherwise normotensive without gross hematuria [303]. As 93 % of children with MCD respond to systemic steroids, treatment can be initiated without preceding renal biopsy. Renal biopsy at disease presentation is indicated for children presenting under the age of 1 year, over the age of 12 years, with gross hematuria, with persistent renal dysfunction, or with low complement 3 (C3) levels [325, 326].

Management

Symptomatic treatment of edema is tailored to the degree of volume overload. Mild edema can be managed with salt and water restriction. More pronounced edema may warrant diuretic therapy as well as albumin infusion to help mobilize fluid. First line therapy for MCD is systemic steroids dosed at 2 mg/kg/day (maximum 60 mg/day) for 4–6 weeks, initiating a taper thereafter. Steroid-sparing therapy in the form of mycophenolate mofetil, cyclophosphamide, or rituximab is warranted for those children who (1) are steroid dependent, (2) relapse once a taper is initiated, (3) frequently relapse, (4) or suffer unacceptable steroid side effects, including ocular disease and growth impairment. For those children who fail to enter remission after the designated course of steroids, renal biopsy is warranted, as well. Therapy is tailored to the histopathologic diagnosis. If biopsy findings are consistent with MCD or FSGS, tacrolimus may be utilized [327]. It goes without saying that the complications of nephrotic syndrome need to be monitored and addressed, as well.

From an ophthalmic perspective, monitoring for complications as related to nephrotic syndrome and its treatment is important (particularly cataracts and glaucoma). These should be followed carefully and addressed accordingly, keeping in mind that children with nephrotic syndrome often have long-term steroid therapy or undergo multiple pulses of high-dose steroids to control their underlying disease.

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Ocular Manifestations of Pediatric Rheumatic Diseases

20

R. Christopher Walton, Clara Lin, and Robert W. Enzenauer

Introduction

Ocular manifestations are relatively common among many of the rheumatic diseases affecting children. A number of these ocular conditions can lead to significant visual morbidity including blindness. Unfortunately, ocular symptoms may not be reported by some children or family members. This may occur for a number of reasons including the limited verbal ability of younger children, absence of or minimal symptoms in some conditions, or lack of knowledge by the family about the ocular complications associated with the underlying disease. In addition, several of the medications used to treat these rheumatic diseases as well as the ocular complications have side effects that may lead to visual impairment. These ocular manifestations may influence the management of the underlying disease as well as the child's overall quality of life. Therefore, pediatricians and ophthalmologists should be familiar with the ocular manifestations of these diseases as well as the possible ocular complications of their treatment. A team approach between the pediatrician, pediatric rheumatologist and ophthalmologist is essential to the optimal management of these conditions.

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Juvenile Idiopathic Arthritis (JIA)

Definition

Juvenile idiopathic arthritis (JIA) is the term used to describe a group of disorders characterized by chronic arthritis of unknown etiology with onset prior to 16 years of age and persisting more than 6 weeks [1]. It is a multifactorial autoimmune disease with genetic susceptibility factors and environmental triggers [2, 3]. JIA is the most common chronic arthritis of childhood worldwide and in the United States, affecting an estimated 300,000 children [4]. It is also the most common cause of chronic uveitis among children [5]. JIA is a leading cause of disability as well as blindness in children.

Prior to 1995, two major classification systems were used to describe children with chronic arthritis of unknown etiology. Criteria for each of the systems were developed and published in the late 1970s by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). Juvenile rheumatoid arthritis (JRA) was the ACR classification used throughout North and South America while juvenile chronic arthritis (JCA) was adopted by the EULAR and used predominantly in Europe (Table 20.1) [6]. With significant differences between the two systems, neither gained universal acceptance. Additionally, the lack of a widely accepted classification hindered research and communication among clinicians and scientists. Therefore, in 1997 the International League of Associations for Rheumatology (ILAR) developed the JIA classification scheme to provide a more homogeneous and internationally accepted description of the different subtypes of childhood arthritis [1, 7–10]. The 1997 ILAR classification (edited in 2001) retains some elements of the two previous classifications but uses unique definitions and exclusions. This system defines eight categories of JIA each differing in clinical and laboratory features, exclusion criteria, prognosis, and risk for uveitis (Table 20.2). Unlike the previous systems, the subtypes of psoriatic arthritis and enthesitis-related arthritis were created in the ILAR classification.

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Table 20.1 Comparison of juvenile rheumatoid arthritis and juvenile chronic arthritis classification systems [9]

	Juvenile rheumatoid arthritis (JRA)	Juvenile chronic arthritis (JCA)
Minimum duration arthritis	≥6 weeks	≥3 months
Subtypes	Systemic	Systemic
	Pauciarticular	Pauciarticular
	Polyarticular	Polyarticular
		Juvenile rheumatoid arthritis[a]
		Juvenile psoriatic arthritis
		Juvenile anklyosing spondylitis

[a]Term used in patients with polyarticular disease and positive rheumatoid factor

In addition, it does not utilize the terms "rheumatoid" and "chronic." With these differences in mind, it is clear that the JIA terminology cannot be used interchangeably with the prior nomenclature of JRA or JCA [11]. As it is difficult to retrospectively reclassify patients in published reports prior to the ILAR classification, we will retain the original terminology used by authors of works referenced in this chapter.

History

Juvenile-onset arthritis was first described in 1897 by Still [12]. He noted that chronic arthritis in children differed from adult rheumatoid arthritis both in articular and extra articular manifestations. Still also was the first to describe different subsets of the disease. Today, systemic onset JIA is often referred to as "Still's disease." The first record of the association of JIA and uveitis is attributed to Ohm in 1910 [13]. Additional reports of iridocyclitis and band keratopathy were later described in the German literature [14].

Epidemiology

JIA is the most common rheumatic disease affecting children. Worldwide, the incidence ranges between 0.8 and 22.6 per 100,000 children per year [15]. Reported prevalence rates range from 7 to 401 per 100,000 children. In the United States, the prevalence ranges between 1.6 and 86.1 per 100,000 [16]. The wide variability in these estimates is due to several factors including differences in classification, nomenclature, and heterogeneity of the disease. Differences in geographic region and among ethnic groups further contributes to this variation [16, 17]. As a result, the frequency of many of the subtypes of JIA also varies widely (Table 20.2) [7].

The onset of JIA is bimodal, peaking at two age groups: 1–2 years and 9–15 years [18–22]. The proportion of affected males differs among the subtypes of JIA. Oligoarticular and polyarticular subtypes affect females more than males. Males on the other hand develop the enthesitis subtype more commonly [22]. In the systemic onset subtype, females and males are equally affected.

Children of European ancestry have the highest risk of developing JIA except the systemic onset and rheumatoid factor (RF) positive polyarticular subtypes. Asian ancestry is a predisposing factor for the development of enthesitis-related arthritis. Children of African American or Indian subcontinent ancestry are at increased risk for developing RF-positive polyarticular JIA. Native North American ancestry predisposes children to development of RF-positive or RF-negative polyarticular JIA [17].

Systemic Manifestations

Systemic Onset

Systemic onset JIA (SOJIA) is defined by the presence of arthritis in at least one joint with or preceded by quotidian fever of at least 2 weeks duration. The arthritis is often polyarticular affecting both large and small joints [23, 24]. It is accompanied by one or more of the following: evanescent rash, lymphadenopathy, hepatomegaly or splenomegaly, or serositis. SOJIA occurs in 5–15 % of children with JIA. Males and females are equally affected with no predominant age of onset. Laboratory findings include leukocytosis, thrombocytosis, anemia, increased transaminases, and markedly increased ferritin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP); however, macrophage activation syndrome is a complication of SOJIA which presents similarly to secondary hemophagocytic lymphohistiocytosis with extremely elevated ferritin, hypoalbuminemia, elevated PT, PTT, low fibrinogen, and cytopenias (especially thrombocytopenia) [23, 25]. ESR may be low or normal due to disseminated intravascular coagulation. This complication must be recognized promptly, and treatment should be initiated as quickly as possible.

The course of systemic onset JIA is variable with a mean duration of activity of 6 years [26]. Up to 40 % of children with this subtype will experience a monophasic course with complete remission; however recent studies have shown over half of these children have chronic disease [23].

Oligoarthritis

Oligoarthritis affects 1–4 joints during the first 6 months of the disease [1, 7, 10]. This is the most common subtype accounting for 50–88 % of children with JIA [23]. It is more common in females with onset usually before the age of 6 years. The ILAR classification divides this group of children into two categories; persistent oligoarthritis and extended oligoarthritis. Children with persistent oligoarthritis have no more than four joints affected during the course of the disease while those with extended oligoarthritis develop arthritis in more than four joints after the first 6 months of the disease.

Table 20.2 International League of Associations for Rheumatology classification for chronic arthritis in children [10]

Category	Frequency	Definition	Exclusion criteria
Systemic arthritis	10–20 %	Arthritis with documented quotidian fever of at least 2 weeks duration and at least one of the following:	a, b, c, d
		– Evanescent rash	
		– Lymphadenopathy	
		– Hepato- or splenomegaly	
		– Serositis	
Oligoarthritis, persistent	50–60 %	Arthritis in ≤ 4 joints throughout the course of the disease	a, b, c, d, e
Oligoarthritis, extended		Arthritis in ≤ 4 joints during the first 6 months of the disease but affecting a cumulative total of ≥ 5 joints after the first 6 months	a, b, c, d, e
RF-negative polyarthritis	30–35 %	Arthritis in ≥ 5 joints during the first 6 months with negative test for rheumatoid factor	a, b, c, d, e
RF-positive polyarthritis		Arthritis in ≥ 5 joints during the first 6 months with positive test for rheumatoid factor at least twice 3 months apart	a, b, c, e
Psoriatic arthritis	2–15 %	Arthritis and psoriasis or arthritis and at least two of the following:	b, c, d, e
		– Physician-diagnosed psoriasis in first-degree relative	
		– Dactylitis	
		– Nail abnormalities (pitting or onycholysis)	
Enthesitis-related arthritis	1–7 %	Arthritis and enthesitis or arthritis or enthesitis plus any two of the following:	a, d, e
		– Physician diagnosed HLA-B27-associated disease in first or second degree relative	
		– Symptomatic anterior uveitis	
		– Male > 8 years old at onset of arthritis	
		– Sacroiliac joint tenderness and/or inflammatory spinal pain	
		– Presence of HLA-B27	
Undifferentiated arthritis	2–23 %	Arthritis that does not fulfill any of the above categories or fits into > 1 category	None

a—Psoriasis or family history of psoriasis in first-degree relative
b—Arthritis in an HLA-B27-positive male with onset after the sixth birthday
c—Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or history of any of these disorders in a first-degree relative
d—Presence of IgM rheumatoid factor on at least two occasions at least 3 months apart
e—Presence of systemic JIA in the patient

Oligoarthritis typically affects the lower extremities; especially the knee and ankle [25]. Rheumatoid factor is always negative but antinuclear antibodies (ANA) are present in up to 80 % of children [27]. Overall, the prognosis is good for children with oligoarthritis. However, up to 50 % progress to extended oligoarthritis [27]. Risk factors for development of extended oligoarthritis include upper extremity arthritis, positive ANA, and elevated ESR [23, 28–30].

Rheumatoid Factor Negative Polyarthritis

Rheumatoid factor negative polyarthritis is defined as arthritis that affects five or more joints during the first 6 months of the disease with a negative RF. This subtype affects 20–30 % of children and is more common in females [7, 23]. This category is the most heterogeneous subtype of JIA and may include two subsets of disease. The first subset includes children less than 6 years old, primarily female, with asymmetric arthritis, and positive ANA. These children have an increased risk for development of uveitis [31]. The second subset includes children 7–9 years old with symmetric arthritis affecting large and small joints and a negative ANA [25, 32, 33].

Children with RF negative polyarthritis typically have mild anemia as well as an elevated ESR and CRP. Up to 40 % have positive ANA. These children have a variable clinical course which is likely dependent upon the subset of the disease. Even so, approximately one-third experience a long-term remission [34].

Rheumatoid Factor Positive Polyarthritis

This subtype includes children with arthritis affecting five or more joints during the first 6 months of the disease with two positive tests for RF separated by at least 3 months. This category accounts for 5–10 % of children with JIA [7, 23]. RF positive polyarthritis is more common in adolescent females.

Symmetric polyarthritis of multiple joints especially the small joints of the hands, wrist, and feet are characteristic. Rheumatoid nodules may also occur along the forearm and elbow. Low grade fever is not uncommon at the onset of the disease. Laboratory features include a positive RF, positive anti-cyclic citrullinated peptide (anti-CCP), elevated ESR and CRP, as well as mild anemia.

Rheumatoid factor positive polyarthritis is likely an early form of adult rheumatoid arthritis since the two diseases share several human leukocyte antigen (HLA) associations as well as serologic markers [23]. This group of children has a poor long-term prognosis characterized by severe erosive disease [35–37].

Psoriatic Arthritis

Juvenile psoriatic arthritis (JPA) includes children with arthritis and psoriasis or arthritis with any two of the following: psoriasis in a first-degree relative, dactylitis (inflammation of an entire digit due to synovitis and tenosynovitis), and nail pitting or onycholysis (separation of the nail from the nail bed). JPA accounts for 2–15 % of children with JIA. The onset has a bimodal distribution with one peak at toddler age, similar to oligoarticular JIA, and another peak during the pre-teen to teenage years [21, 23, 38]. There is a slight female preponderance with onset typically between the ages of 7–10 years old.

The arthritis of JPA is asymmetric involving both the large and small joints. The knee and ankle as well as small joints of the hand and foot are most commonly affected [39]. Up to 20 % of children develop uveitis which may be more resistant to therapy compared to oligoarthritis associated uveitis [27, 31, 40–43]. Laboratory features include mild anemia as well as an elevated ESR and CRP. Up to one-half of children will have a positive ANA test.

The long-term outcome of these children is less clear than the other subtypes of JIA. Previous studies using a different classification system indicated that many children have chronic active disease [44].

Enthesitis-Related Arthritis

Enthesitis-related arthritis (ERA) is defined by the presence of arthritis or enthesitis (inflammation at the insertion of a ligament, tendon, fascia, or joint capsule to bone or cartilage) with at least two of the following: history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain, positive HLA-B27, arthritis onset after 6 years old in a male, acute symptomatic uveitis, history of an HLA-B27 related disease (ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease (IBD), Reiter's syndrome, or acute anterior uveitis) in a first-degree relative. This subtype occurs in up to 1–7 % of children with JIA and is more common in boys older than 8 years [23, 45]. Genetic factors such as HLA-B27 may predispose to the development of ERA [2].

The arthritis of ERA usually affects the peripheral joints before axial involvement occurs. The peripheral arthritis typically presents with asymmetric lower extremity oligoarthritis [27]. Axial involvement typically follows but may take years to manifest. Axial disease typically begins in the hip joint, progresses to the sacroiliac joint and then up the spine. Most patients will eventually develop sacroiliitis and lumbosacral spine disease [46].

Children with ERA may have mild as well as a variably elevated ESR. Up to 90 % of patients will have positive HLA-B27. Long-term outcomes tend to be worse than those children with polyarticular or oligoarticular JIA [47].

Undifferentiated Arthritis

This subtype is defined as children who do not fulfill the inclusion criteria of any category or are excluded because of filling criteria in two or more categories of JIA. This group accounts for 2–23 % of children with JIA [7].

Ophthalmic Manifestations

Uveitis is the most common extra articular manifestation of JIA affecting up to 24 % of children [48, 49]. Uveitis is extremely rare in children with systemic onset JIA [27, 50]. Chronic anterior uveitis occurs in up to 45 % of children with oligoarthritis [41, 48, 51–53]. Most cases of uveitis are bilateral with onset within 4 years of developing arthritis [27, 29, 54]. Uveitis is very rare in RF positive polyarthritis [27, 55]. Uveitis occurs in up to 15 % of patients with ERA; especially older adolescents [27]. The uveitis is usually acute, unilateral, and symptomatic. The fellow eye is often involved but not necessarily simultaneously.

Chronic asymptomatic bilateral nongranulomatous anterior uveitis is the most common type of uveitis in JIA although a small number of patients may have granulomatous inflammation (Fig. 20.1) [56]. Acute, recurrent anterior uveitis may also occur but is less common and typically seen in children with HLA-B27 associated ERA. Panuveitis has been rarely reported in patients with JIA [57]. Symptomatic patients may describe ocular pain, redness, blurred vision, photophobia, and occasionally headache but most children remain asymptomatic for long periods, sometimes until they present with anisocoria and/or decreased visual acuity.

Arthritis precedes the onset of uveitis in most children; typically during the first 5 years following the diagnosis of JIA [14, 58]. Approximately 18 % of children develop uveitis simultaneously with the onset of arthritis. Although less common, up to 10 % of children develop uveitis as the initial presentation of JIA [59]. The course of the arthritis and uveitis

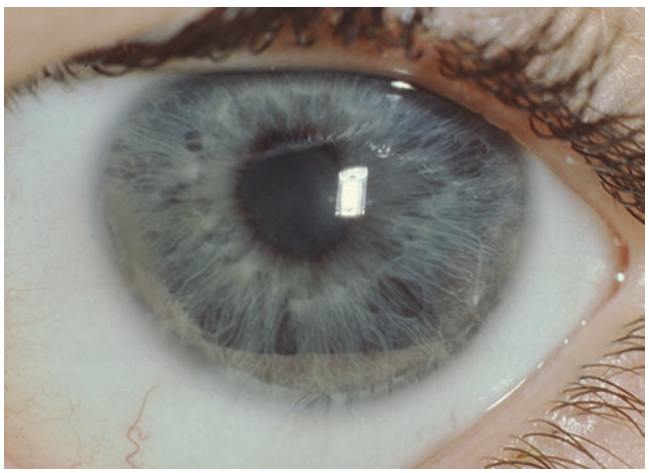

Fig. 20.1 Chronic anterior uveitis with posterior synechiae in a 12-year-old female with ANA-positive, JIA-associated chronic anterior uveitis. Note the absence of conjunctival injection characteristic of chronic uveitis in these children

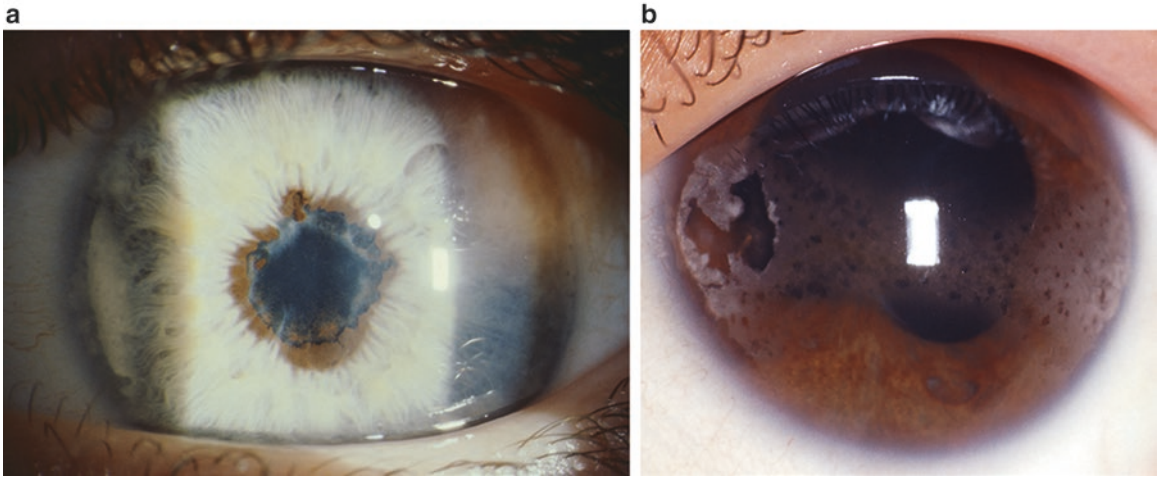

Fig. 20.2 Posterior synechiae with early band keratopathy (**a**) and extensive band keratopathy (**b**) in JIA-associated chronic anterior uveitis

are often independent although a parallel course occurs in a minority of children. The arthritis of JIA tends to improve in most patients by adulthood; however the uveitis often persists and can last for many years [59].

The course of uveitis in JIA may be acute, recurrent-relapsing, and chronic [48]. Historically, the course in most children has been described as chronic and relapsing. However, recent research suggests that uveitis in JIA may have a biphasic course [60]. In this group of children, initial high disease activity was followed by a quiescent stage with subsequent increased activity during the early teenage years. The uveitis activity peaked 9 years following diagnosis. The authors further noted that during this peak of activity, 74 % of the children were between 10 and 15 years of age.

A number of risk factors for the development of JIA-associated uveitis have been identified including young age, female gender, positive ANA, and oligoarticular and RF-negative polyarticular subtypes [17]. Girls who are ANA-positive appear to be at highest risk, especially those with arthritis diagnosed prior to the age of 2 years [61]. The risk of developing uveitis among ANA-positive children appears similar among the different subtypes of JIA [32, 62]. Risk factors for severe uveitis at the time of diagnosis include male gender and shorter interval between the onset of arthritis to the diagnosis of uveitis [62].

Ocular complications of uveitis are common in children with JIA. Studies from tertiary care centers have reported complications in up to 84 % of patients [5, 63, 64]. In a long-term follow-up study of adults with JCA in Denmark, ocular complications were noted in 20 % of patients with half of the complications occurring after the age of 16 years old [65]. Thorne and coworkers recently reported an incidence of any ocular complication of 0.33/eye-year [66]. The most important ocular complication in children with JIA is visual loss and impairment [48]. Up to 66 % of patients with uveitis will experience some degree of visual loss [41, 48, 52, 54, 63, 67–71]. Other common complications include band keratopathy, posterior synechiae, cataract, increased intraocular pressure, and glaucoma (Fig. 20.2) [48, 60, 68, 71]. Less common complications include macular edema, papillitis, epiretinal membrane, chronic hypotony and amblyopia. The rates for each specific complication vary and may reflect differences among published studies such as duration of disease and follow-up, patient populations, treatment centers, and time periods. In addition, early aggressive use of immunosuppressive therapy has become widely advocated and likely altered the incidence and prevalence of complications in JIA.

Several risk factors for ocular complications have been identified. Children with at least 1+ anterior chamber flare and a history of intraocular surgery have a greater risk of visual loss and impairment [57, 64]. Additional risk factors for development of ocular complications include shorter duration between the diagnosis of arthritis and the onset of uveitis, uveitis onset prior to arthritis, male gender, positive ANA and use of oral prednisone [57, 64, 72]. The presence of posterior synechiae, 1+ or greater anterior chamber flare, and an abnormal intraocular pressure (>21 mm Hg or <5 mm Hg) have also been associated with an increased risk of complications [66]. Risk factors for development of cataracts include active uveitis, posterior synechiae, and use of topical corticosteroids at initial presentation. The use of topical corticosteroids is an independent risk factor for cataract development regardless of uveitis activity; especially when doses exceed three times daily [73]. The presence of posterior synechiae during the initial diagnosis of uveitis increased the risk of cataracts requiring surgery [74].

Keratoconjunctivitis sicca (KCS) has been reported in up to 75 % of children with JIA [75–78]. The risk for development of KCS appears to be greater in boys and children with longer duration of disease [75]. Establishing the diagnosis of dry eye may be difficult in younger children who are unable to verbalize their symptoms or cooperate with diagnostic testing [79]. In addition, patients with uveitis who are receiving

topical corticosteroids may have minimal or no symptoms of dry eye leading to a delay in the diagnosis.

Juvenile idiopathic arthritis has also been associated with Brown syndrome [80–83]. Manifestations include pain, tenderness, "clicking sensation" with eye movement, palpable mass near the trochlea, and intermittent diplopia. Some patients have experienced spontaneous resolution while others required treatment with systemic corticosteroids or injections of corticosteroids in the region of the trochlea.

Diagnosis

Juvenile idiopathic arthritis is a diagnosis of exclusion and other causes of arthritis must be ruled out before a diagnosis of JIA is established (Table 20.3). A detailed history and meticulous physical examination are essential. There are no confirmatory laboratory studies although several tests are useful in classifying patients with JIA. Rheumatoid factor, ANA, and HLA-B27 are often obtained to further define the subtype of JIA and may also provide prognostic information in some children. Mild anemia, as well as an elevated ESR and CRP are relatively common in children with JIA. Anti-CCP antibodies have been found in some children with JIA; especially children with RF-positive polyarthritis [84, 85]. Several studies suggest that children with anti-CCP antibodies have a more severe disease course and may benefit from early aggressive therapy [86–88].

Table 20.3 Etiologies of joint pain in children

Reactive arthritis
Post-infectious arthritis
Rheumatic fever
Poststreptococcal
Infectious
Septic arthritis
Osteomyelitis
Lyme disease
Trauma
Mechanical joint pain
Idiopathic joint pain
Sarcoidosis
Inflammatory bowel disease
Connective tissue diseases
Systemic lupus erythematosus
Juvenile dermatomyositis
Juvenile systemic sclerosis
Systemic vasculitis
Henoch-Schönlein purpura
Kawasaki's disease
Polyarteritis nodosa
Behçet's disease
Systemic diseases
Hemoglobinopathies
Diabetes mellitus
Cystic fibrosis
Hyperparathyroidism
Malignancy

Diagnostic imaging may be helpful to rule out other etiologies of joint pain including infection, trauma, or malignancy [89]. Imaging is also used to monitor progression of synovial inflammation. Structural damage is typically assessed with plain radiography [90, 91]. Magnetic resonance imaging (MRI) allows visualization and assessment of synovitis without radiation exposure. However, the prolonged examination time, need for general anesthesia in many children, and cost of the procedure limits the utility of this imaging modality [92]. With advances in ultrasound technology, musculoskeletal ultrasound may play an important role in diagnosis and management of JIA since it is relatively quick, inexpensive, and poses no radiation or sedation risk.

Management

The management of children with JIA requires a multidisciplinary approach. This often includes but is not limited to physical therapists, occupational therapists, specialty nurses, podiatrists, psychologists, social workers, pediatricians, rheumatologists, orthopedic surgeons, ophthalmologists, dentists, and pain management specialists. Goals of this team based approach are to reduce long-term sequelae of the disease through early, complete remission of uveitis and or arthritis, minimize treatment related side effects, preserve normal joint function, prevent joint deformity and disability, and optimize the potential for normal growth and development [35, 93].

Until the 1990s, the treatment of children with JIA was based upon a pyramid approach beginning with non-steroidal anti-inflammatory drugs (NSAIDs) [94, 95]. For children with only a few joints affected, long-acting intra-articular corticosteroid injections were used in combination with NSAIDs. Subsequent treatment included disease modifying antirheumatic drugs (DMARDs) and or systemic corticosteroids [96]. More recent studies have demonstrated improved outcomes with early aggressive therapy [97–100].

Currently, there are no universal guidelines regarding treatment of children with JIA. However, numerous studies have demonstrated that aggressive therapy with early use of DMARDs reduces morbidity and improves outcomes in these children [98, 101–107]. The American College of Rheumatology (ACR) has recently published recommendations for the treatment of juvenile idiopathic arthritis [108]. These recommendations were based upon five treatment groups rather than the different categories of JIA. Treatment groups included: history of arthritis of four or fewer joints, history of arthritis of five or more joints, active sacroiliac arthritis, systemic arthritis with active systemic features, and systemic arthritis with active arthritis without active

systemic features. Each treatment group included specific criteria for disease activity and prognosis to aid in selection of the most appropriate treatment.

Among all treatment groups, the ACR recommended the continuation of methotrexate when starting therapy with a TNFα inhibitor and allows the use of intra-articular corticosteroid injections for active arthritis regardless of other systemic therapy. Joint injection with triamcinolone hexacetonide typically results in clinical improvement for at least 2–3 months in most patients. For patients beginning treatment with etanercept or adalimumab, methotrexate should be continued if they experienced any degree of clinical improvement previously [109, 110].

Children with a history of arthritis of four or fewer joints, no poor prognostic signs and low disease activity are initially treated with NSAID monotherapy. Those children with high disease activity and poor prognostic features should receive methotrexate as initial therapy. A TNFα inhibitor should be initiated for persistent disease despite intra articular injections and 3 months of the maximal dose of methotrexate. Sulfasalazine is recommended for children with enthesitis-related arthritis with moderate to high disease activity following intraarticular corticosteroid injection or a 2 month trial of NSAIDs. If disease activity does not improve, a TNFα inhibitor is recommended for these children.

Treatment of children with arthritis of five or more joints with low to moderate disease activity typically begins with NSAID monotherapy. For patients with high disease activity, methotrexate is recommended as initial therapy. Within this group, patients with features of poor prognosis may be treated with leflunomide as an alternative to methotrexate. Children with low disease activity and poor prognostic features should receive methotrexate after 1 month of therapy with NSAIDs. Those children with moderate disease activity without poor prognostic features should be started on methotrexate after 1–2 months of NSAID treatment. TNFα inhibitors are useful in patients treated with maximal dosages of methotrexate or leflunomide for at least 3 months with moderate to high disease activity. Children with low disease activity despite maximal dosages of methotrexate or leflunomide for 6 months should also be treated with a TNFα inhibitor. Switching to another TNFα inhibitor is recommended in patients with moderate to high disease activity after 4 months of treatment with a TNFα inhibitor. For patients who have high disease activity despite treatment with a TNFα inhibitor and abatacept; rituximab or tocilizumab may be considered.

Children with active sacroiliac arthritis are initially treated with NSAIDs, however TNFα inhibitors are recommended for axial disease. Methotrexate or sulfasalazine can be used concomitantly with TNFα inhibitors in children with peripheral arthritis in addition to axial disease. In addition, children treated with sulfasalazine for 3 months with persistent moderate activity or 6 months with low activity should begin treatment with a TNFα inhibitor.

The treatment of children with SOJIA differs based upon the presence of active arthritis. In patients with active systemic features and no active arthritis, initial treatment consists of systemic corticosteroids. Before the diagnosis has been established, patients may be treated with NSAIDs. Anakinra is recommended for patients who develop a fever during corticosteroid therapy as well as children with poor prognostic features. In children with active arthritis and no active systemic features, initial therapy includes NSAIDs for up to 1 month followed by methotrexate. Anakinra or a TNFα inhibitor is recommended for patients with moderate to high disease activity after 3 months of methotrexate. If disease activity remains moderate to high, switching between a TNFα inhibitor or anakinra should be considered. Children with persistent high disease activity or moderate disease activity and a poor prognosis after 4 months of a TNFα inhibitor may benefit from abatacept therapy.

Management of JIA-associated uveitis and its complications begins with screening and early detection. Recommendations for screening have been established by the American Academy of Pediatrics [111]. These guidelines are based upon the JRA classification system and as a result there are no screening recommendations for children with psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. Several suggested modifications to these guidelines were published by the German Uveitis in Childhood Study group [112, 113]. These modifications used the ILAR classification system to describe recommendations for screening children with each specific subtype of JIA (Tables 20.4 and 20.5). Saurenmann and coworkers suggested that the subtype of JIA should not guide ophthalmic screening recommendations except for those children with polyarticular RF-positive JIA or SOJIA [61]. Furthermore, they recommended the most frequent screening examinations should be performed in ANA-positive girls diagnosed with JIA prior to the age of seven and all children diagnosed with JIA prior to 5 years of age. In those children diagnosed with JIA before the 5 years old, screenings should continue until 7 years after the JIA diagnosis.

The treatment of uveitis in children with JIA is often challenging. Most children have chronic bilateral anterior uveitis although children with HLA-B27 associated ERA may

Table 20.4 Ophthalmologic screening recommendations for children with ANA positive JIA

Age at onset of JIA (years)	Duration of JIA (years)	Screening intervals (months)
≤6	≤4	3
≤6	>4	6
≤6	≤7	12
>6	≤2	6
>6	≥2	12

Adapted from Heiligenhaus, et al. [112] with permission from Oxford University Press. © Oxford University Press

Table 20.5 Ophthalmic screening recommendations for children with ANA negative JIA

JIA category	Age at onset of JIA (years)	Duration of JIA (years)	Screening intervals (months)
Oligoarthritis, RF-negative polyarthritis, psoriatic arthritis, undifferentiated arthritis	≤6	≤4	6
	≤6	>4	12
	>6	Any	12
RF-positive polyarthritis, enthesitis-related arthritis, systemic arthritis	Any	Any	12

Adapted from Heiligenhaus, et al. [112] with permission from Oxford University Press. © Oxford University Press

develop acute, recurrent anterior uveitis [55]. Early aggressive therapy is essential to minimize ocular complications in all of these children. To this end, the overarching goal in the treatment of JIA uveitis is complete elimination of all cells in the anterior chamber. In chronic cases, this may not be achievable and trace cells may persist. Yet, similar to the treatment of arthritis, there are no universal guidelines regarding therapy of uveitis in JIA.

Recently the German Ophthalmological Society and the Society for Childhood and Adolescent Rheumatology published evidence-based guidelines for the interdisciplinary treatment of uveitis in JIA [114]. These guidelines outline a three phase approach to the treatment of JIA associated uveitis with shared management by the ophthalmologist and pediatric rheumatologist. Initial therapy consists of high potency topical corticosteroids such as prednisolone acetate 1 % at a frequency based upon the severity of inflammation. Topical corticosteroid ointment may also be used at bedtime. The frequency of topical therapy should be decreased within 6 weeks based upon the degree of inflammation. Topical and or systemic NSAIDs are not recommended for treating attacks of uveitis. For children with poor prognostic signs including poor initial vision, cataract, glaucoma, macular edema, dense vitreous opacities, or hypotony; systemic corticosteroids are recommended in addition to topical corticosteroids. The initial dose of prednisolone is 1–2 mg/kg followed by tapering to less 0.15 mg/kg within 4 weeks. The total duration of systemic corticosteroid use should not exceed 3 months. Corticosteroid side effects should be considered in these children including weight gain, growth retardation, impaired glucose metabolism, increased intraocular pressure, and cataracts.

Step two treatment is begun if the uveitis remains active after 12 weeks with topical corticosteroids at least four times daily or systemic corticosteroid dose of 0.15 mg/kg or greater. These children should be treated with traditional immunosuppressive agents. However, there are no randomized, controlled trials using these agents in treating children with JIA associated uveitis. Therefore the recommendations for these drugs were based upon the consensus from the authors of these guidelines. Methotrexate or azathioprine was recommended as step two treatment options. Methotrexate has a good safety profile and is the first choice for most patients with corticosteroid resistant uveitis [115]. Dosages of each drug should be individualized for each child. Typical dosages of methotrexate for children with uveitis are 10–15 mg/m^2 weekly (oral or subcutaneous). The dosage of azathioprine for most children is 2–3 mg/kg daily [115, 116]. Topical corticosteroids should be decreased to three times daily or less based upon the degree of inflammation. Other traditional immunosuppressive drugs including cyclosporine, chlorambucil, cyclophosphamide and mycophenolate mofetil were not recommended based upon lack of efficacy as a primary immunosuppressive agent or severe side effects.

Step three therapy is reserved for children with persistent uveitis despite 16 weeks of therapy with a traditional immunosuppressive drug or those who develop new complications of uveitis. In these children, a TNFα inhibitor or cyclosporine should be added to the treatment regimen [117, 118]. Adalimumab or infliximab are both effective in the treatment of JIA associated uveitis. Adalimumab is a fully humanized monoclonal antibody and is the preferred TNFα inhibitor among these children. Etanercept is less effective than the other two agents and is not recommended for the treatment of uveitis in JIA. Cyclosporine is another option in patients who have persistent uveitis despite methotrexate or azathioprine. The initial dose in children with JIA is typically 3 mg/kg daily. Topical corticosteroids should be decreased to three times daily or less based upon the degree of inflammation.

Additional treatment options that can be considered during any step of therapy include topical cycloplegics and periocular or intraocular corticosteroid injections. Cycloplegics are useful to prevent or lyse posterior synechiae. They are most useful during acute attacks of uveitis. All of the commonly used cycloplegics have anticholinergic effects that should be considered when treating children. Atropine, homatropine, cyclopentolate, and tropicamide vary in duration of action and side effect profile. Periocular or intraocular corticosteroid injections may be considered in children with severe acute uveitis complicated by dense vitreous opacities, macular edema or hypotony. They may also be useful for patients with severe uveitis with limited response to topical and systemic corticosteroid therapy. However, they should be avoided if there is preexisting glaucoma or a history of steroid response. Periocular or intraocular injections of long acting corticosteroids such as triamcinolone acetonide can provide effective intraocular drug levels over several weeks duration.

Cataract surgery in children with JIA requires meticulous perioperative control of inflammation to maximize visual outcomes. Rarely, children with hyperacute intumescent cataracts or phacolytic glaucoma may require urgent surgery even with active inflammation. For most children, long-standing guidelines emphasize complete control of inflammation using medical therapies for at least 3 months prior to surgery [119, 120]. In JIA, patients on chronic methotrexate therapy are prescribed supplemental corticosteroids beginning approximately 1 week prior to surgery followed by tapering and discontinuation based upon the severity of intraocular inflammation postoperatively [121–123]. Periocular corticosteroids or intraocular corticosteroids may also be used in the perioperative period in children without glaucoma or a history of steroid response [123–125]. There are no widely accepted guidelines regarding the implantation of an intraocular lens (IOL) in children with JIA [126]. Historically, implantation of an IOL has been associated with increased postoperative inflammation that may lead to cyclitic membrane, hypotony, and phthisis [121, 127–130]. Yet, several series have reported good outcomes following cataract extraction with IOL implantation although the specific surgical techniques vary among studies [131–135]. We currently recommend a cautious approach when considering IOL implantation in children with JIA associated uveitis.

Keratoconjunctivitis sicca is a chronic condition requiring ongoing monitoring and treatment. Artificial tears are typically used as first-line therapy in children with dry eye disease. Nonpreserved tears are preferable since most children with JIA will require prolonged daily use of these agents [79]. Topical corticosteroids may be considered as adjunctive therapy for children with symptoms despite use of artificial tears. The risk of cataract and glaucoma associated with the use of corticosteroids must be considered since these children are at high risk for these complications due to their underlying disease. Topical cyclosporine emulsion has been used increasingly among adults with KCS but there are few reports of its use in children except to treat vernal keratoconjunctivitis [136–139]. In severe cases, autologous serum tears may be useful, however this option is less desirable among younger children due to the requirement for periodic blood collection. Punctal occlusion is an option for children with severe disease or those who develop toxicity to topical therapeutic agents. Silicone punctal plugs have been used in children with KCS associated with a systemic disease [140]. Punctal plug insertion may require general anesthesia, especially in young children. Extrusion of the plug is the most common complication occurring in 19 % of children during the 6 months following insertion. Thus far, other complications reported in adults such as infection, pyogenic granuloma, punctal scarring, and canalicular stenosis have not been reported [140].

Systemic Lupus Erythematosus

Definition

Systemic lupus erythematosus (SLE) is an uncommon disease in childhood. It is a chronic relapsing, remitting multisystem autoimmune disease characterized by wide range of manifestations. End organ damage results from autoantibody binding to tissues as well as immune complex deposition. The most widely used classification criteria for the diagnosis of SLE was established by The American College of Rheumatology in 1982 and revised in 1997 (Table 20.6) [141, 142]. Recently the Systemic Lupus International Collaborating Clinics (SLICC) group proposed revised criteria to include

Table 20.6 Revised 1982 American College of Rheumatology Systemic Lupus classification criteria

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging: atrophic scarring may occur
3. Photosensitivity	Skin rash as an unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving at least two peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis or pericarditis
7. Renal disorder	Persistent proteinuria or cellular casts
8. Neurologic disorder	Seizures (without other etiology) or psychosis (not due to drugs or metabolic disorder)
9. Hematologic disorder	Hemolytic anemia or leukopenia on at least two occasions or lymphopenia on at least two occasions or thrombocytopenia (not due to drugs)
10. Immunologic disorder	Positive LE cell preparation or anti-DNA antibody to native DNA in abnormal titer or anti-Sm antibody or false positive serologic test for syphilis (for at least 6 months and confirmed by *T pallidum* immobilization or fluorescent treponemal antibody absorption test)
11. Antinuclear antibody	Abnormal titer of antinuclear antibody by immunofluorescence or equivalent assay in the absence of drugs known to be associated with "drug-induced lupus" syndrome

Adapted from Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis and Rheumatism. 1982;25(11):1271–7 [141] with permission from John Wiley & Sons

Table 20.7 Systemic Lupus International Collaborating Clinics classification criteria [143]

Clinical criteria
1. Acute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral ulcers
4. Nonscarring alopecia
5. Synovitis involving ≥ 2 joints
6. Serositis
7. Renal
8. Neurologic
9. Hemolytic anemia
10. Leukopenia
11. Thrombocytopenia
Immunologic criteria
1. ANA (above laboratory reference values)
2. Anti-ds DNA antibody (above laboratory reference values)
3. Anti-Sm nuclear antigen antibody
4. Antiphospholipid antibody
5. Low complement
6. Direct Coombs' test (without hemolytic anemia)

newer immunologic criteria (Table 20.7) [143]. Using this classification, at least four criteria must be satisfied to establish the diagnosis of SLE. Of these four criteria, at least one must be clinical and one immunologic, or the patient must have biopsy proven nephritis, or anti double-stranded DNA antibodies.

Childhood SLE tends to be more aggressive and has poorer outcomes compared to adults with the disease [144–146]. Numerous studies have demonstrated that renal, neurologic, and hematologic manifestations are more common among children at presentation [145–149]. As a consequence, children and adolescents frequently require higher doses of corticosteroids to control the disease manifestations [150, 151].

History

Although it has been known by various names since the time of Hippocrates, SLE was not described in great detail until the nineteenth and twentieth centuries [144]. With the discovery of the lupus erythematosus (LE) cell phenomenon by Hargraves and coworkers in 1948, it became possible to diagnose SLE more precisely [152]. Retinopathy in SLE was first reported by Bergmeister in 1929 [153]. The incidence of retinopathy in patients with end-stage disease was 50 % prior to the widespread use of corticosteroids, however this has markedly decreased in more recent times [154].

Epidemiology

Approximately 10–20 % of patients with SLE develop the disease during childhood and adolescence [146, 155–158]. The incidence ranges from 0.3 to 0.9 per 100,000 children-years while prevalence rates of 3.3–8.8 per 100,000 have been reported [159]. The median age at diagnosis is 11–12 years but most children are diagnosed during adolescence. Onset prior to 8 years old is less common occurring in only about 20 % of children [159–161]. Similar to adults, the disease is more common in females with a female:male ratio of 4–5:1 [160, 162–164]. Childhood SLE is more common among certain ethnic groups including Native Americans, African Americans, Hispanics and Asians [165, 166]. The disease tends to be more severe among African Americans and Hispanics [167].

Systemic Manifestations

Systemic lupus erythematosus can affect any organ system in children. Renal and central nervous system involvement are more common in children and can lead to significant morbidity [143]. Children with SLE often present with nonspecific constitutional symptoms including fatigue, weight loss, fever, arthralgias, and alopecia. Common presenting signs among adolescents are rash, mucositis, fever, and arthritis [167]. Cutaneous lesions are present in up to 80 % of children at initial diagnosis. The characteristic malar rash as well as a maculopapular rash, photosensitive lesions, vasculitic lesions, palmar erythema, and Raynaud phenomenon are common [168]. Classic discoid lupus is uncommon in children compared with adults [160]. Mucosal ulcers involving the hard palate, tongue and the nasal septum are painless and therefore may not be detected during examination. Arthritis with minimal pain occurs in up to 80 % of children [168]. Similar to the arthritis of JIA, both small and large joints are affected but does not result in bone destruction or deformity in most children. Arthralgias are also common in children with SLE. Renal involvement is a leading cause of morbidity and mortality affecting up to 75 % of children [160]. Up to 20 % of affected children develop end stage renal disease within 10 years of onset [169, 170]. Neuropsychiatric involvement occurs in up to 65 % of patients [171]. Headache is the most common manifestation in up to 95 % of children [172]. Psychosis and seizures are also relatively common among children with SLE [173, 174]. Cranial and peripheral neuropathies are less common than central nervous system (CNS) manifestations. Gastrointestinal involvement is common with abdominal pain a frequent complaint [168]. Pericarditis and or pleuritis

affects up to one-half all children with SLE [156, 160]. Vascular abnormalities have also been reported including cutaneous vasculitis, retinal vasculitis, and small vessel CNS vasculitis [168].

Ophthalmic Manifestations

The ophthalmic manifestations of SLE in adults have been documented in numerous reviews [175–182]. There are few reviews or large series describing the ocular findings among children with SLE [144, 183].

Keratoconjunctivitis sicca is the one of the most common ocular manifestations in children with SLE [156, 183, 184]. The frequency of KCS ranges between 2–13 %, however the methods used to diagnose KCS in these studies differs which may influence the incidence among the published reports. Episcleritis has also been reported in children with SLE [185, 186]. Anterior uveitis may occur but is uncommon in childhood SLE [144, 183, 187]. Orbital pseudotumor has also been reported as the presenting sign of SLE in a 9 year-old girl [188].

Neuroophthalmic manifestations have been described in children with SLE. Ocular motility disorders include oculomotor palsy, abducens palsy, internuclear ophthalmoplegia, and nystagmus [189–194]. Visual field defects, optic neuropathy, optic neuritis, amaurosis fugax, papilledema, and idiopathic intracranial hypertension have also been described in these patients [189, 190, 195–197]. Scintillating scotoma has been reported as the initial symptom in a child subsequently diagnosed with SLE [198].

Retinopathy (Fig. 20.3) is the most common vision threatening complication in patients with SLE affecting up to 29 % of adults with the disease [178]. Retinopathy has been considered an indicator of systemic disease activity in adults; especially CNS disease [180, 182]. In most patients, the retinopathy resolves when the underlying disease is controlled [181]. Patients with anti-phospholipid antibodies may have a greater risk of severe retinopathy with vascular occlusions [199–201]. It is unclear if these same risk factors are true for children with lupus retinopathy.

The most common manifestation of classic lupus retinopathy is the cotton-wool spot. With fluorescein angiography, these lesions appear as avascular zones [202–204]. Intraretinal hemorrhages, capillary dilation, venous engorgement or tortuosity, focal arteriolar constriction, or extensive arteriolar narrowing may be present [204]. The pathogenesis of these manifestations involves immune complex deposition in the vessel wall with endothelial swelling, vascular constriction and thrombus formation [205]. This form of retinopathy tends to have a good prognosis and severe visual loss is uncommon [175, 182].

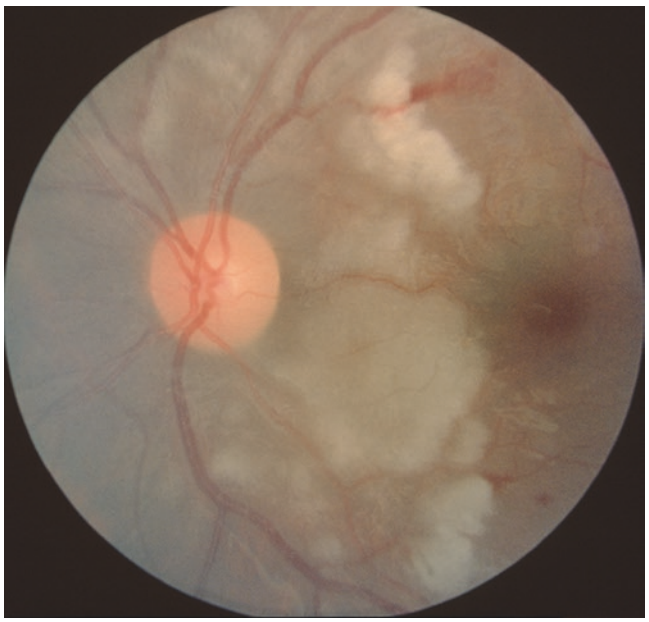

Fig. 20.3 Lupus retinopathy with cotton-wool spots, hemorrhages and areas of retinal whitening

A severe vaso-occlusive retinopathy can develop in patients with SLE. Although rare, this form of retinopathy often results in poor visual outcomes [206–208]. Diffuse capillary nonperfusion, retinal arterial and arteriolar occlusion, retinal neovascularization, and vitreous hemorrhage are characteristic of this occlusive retinopathy [207]. Antiphospholipid antibodies and thrombus formation may contribute to the pathogenesis of this retinopathy since there appears to be a strong association between CNS disease, the presence of antiphospholipid antibodies and severe occlusive retinopathy [209].

In a study of 37 children with SLE, retinopathy was described in only one child. In this child, the retinal lesions regressed and disappeared despite systemic disease progression [210]. In a larger cohort of 108 patients with childhood SLE, 7 % had cotton-wool spots that resolved within several weeks while receiving systemic corticosteroids for other manifestations of the disease [144]. In a more recent publication describing 52 children, 10 % of children developed retinopathy. Most of these children had mild retinopathy although one developed severe occlusive vasculitis [183, 184]. A number of case reports have also described various forms of retinopathy including severe occlusive retinopathy, central retinal vein occlusion, bilateral retinal venous occlusion, macular infarction, and retinal vascular occlusion [186, 189, 211–215].

Choroidal disease has been rarely reported in patients with SLE (Fig. 20.4) [216–219]. Manifestations include multifocal serous retinal detachments, choroidal effusion, secondary angle closure glaucoma, choroidal infarction, and choroidal

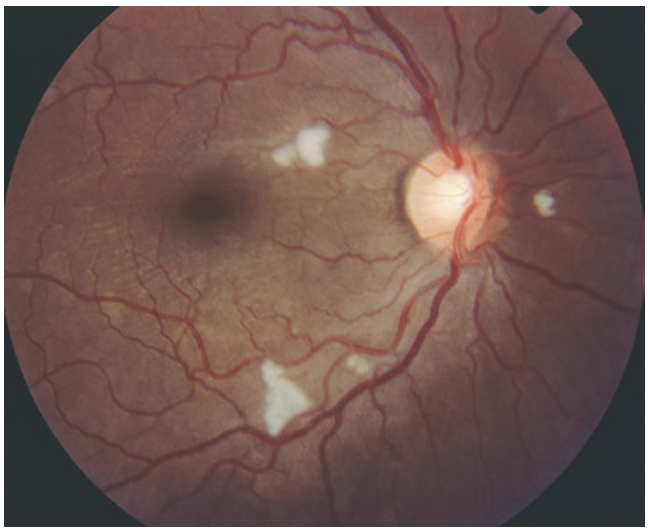

Fig. 20.4 Lupus choroidopathy with resolving serous retinal detachment and scattered cotton-wool spots

Table 20.8 Screening guidelines for patients treated with hydroxychloroquine or chloroquine

Frequency of screening	Baseline (within first 12 months of therapy); annual after 5 years of drug use
Test	Comments
Ophthalmic examination	Complete examination including detailed retina examination
Automated visual field	White 10-2 threshold testing
One or more of the following objective tests if available:	
Spectral domain optical coherence tomography (SD-OCT)	Rapid test; can reveal very early abnormalities
Fundus autofluorescence (FAF)	Can reveal abnormalities earlier than visual field testing
Multifocal electroretinogram (mfERG)	May be useful for evaluation of suspected or unreliable visual field loss; may reveal abnormalities earlier than visual field testing

Adapted from Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF, American Academy of O. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology. 2011;118(2):415–22 [234] with permission from Elsevier

neovascularization. A single case report describes a child with anterior uveitis, vitreous inflammation, and a large serous retinal detachment [220]. It is uncertain if this case represents true lupus choroidopathy since most other reports do not describe simultaneous intraocular inflammation. Central serous retinopathy (CSR) has been reported in two children with SLE [221, 222]. The cause of CSR in these patients is unclear since many have underlying renal disease with hypertension and often are receiving corticosteroid therapy. Most patients with SLE and CSR have good visual outcomes [219].

Antimalarial agents are often used in patients with SLE [223]. They are considered a mainstay of therapy and have been shown to reduce disease activity and improve survival in these patients [224]. In children, hydroxychloroquine and chloroquine are often used as disease maintenance therapy and to treat rash and arthritis [168]. Ocular toxicity of these drugs can occur and some cases result in severe, permanent visual loss [225–230]. Keratopathy is a well-known complication of chloroquine and hydroxychloroquine treatment. Bilateral golden-brown deposits in a whorl-like pattern (vortex keratopathy) are found in the cornea but are not visually significant in most cases [227, 231].

Retinal toxicity is a rare complication of chloroquine and hydroxychloroquine therapy but can result in irreversible visual loss [229, 232]. Recent studies indicate that patient age, daily dose, or patient weight do not influence the risk of retinal toxicity [233]. The risk of toxicity increases with duration of therapy. Incidence rates greater than 1 % have been reported after 5–7 years and 2 % after 10–15 years of therapy [233]. Renal or liver disease may also increase the risk of toxicity due to reduced clearance of the drug [234]. Clinical manifestations of toxicity include central visual loss, impaired color vision, central visual field defects, retinal pigment epithelial abnormalities, and bull's eye maculopathy [235]. Retinal toxicity is often classified as premaculopathy or true retinopathy [236]. Patients with premaculopathy typically are asymptomatic and may have mild macular pigmentary abnormalities. Those with true retinopathy are often symptomatic and have persistent paracentral or central scotomata. In addition, a bull's eye maculopathy with or without a scotoma also suggests true retinopathy. In a series of 117 children with SLE, macular changes were found in eight patients who were treated with chloroquine or hydroxychloroquine for 1–5 years [237]. Despite the low risk of toxicity, all patients treated with chloroquine or hydroxychloroquine should undergo ophthalmologic screening to ensure detection of toxicity at the earliest stage of development. A baseline ophthalmologic examination is recommended during the first year of use of the medication followed by annual screening beginning 5 years after starting therapy [234]. Specific screening procedures are outlined in Table 20.8. Tests not recommend for use in screening include fundus photography, color vision, Amsler grid, fluorescein angiography, time-domain optical coherence tomography, full-field electroretinogram, or electrooculogram [234, 238].

Ocular complications of systemic corticosteroids also occur in childhood SLE. Five percent of children treated with systemic corticosteroids for a mean of 45 months developed posterior subcapsular cataract while glaucoma was reported in 3 % of patients receiving corticosteroids for a mean of 21 months [237]. Both of these complications developed in children receiving higher doses of corticosteroids compared to those without cataract or glaucoma.

Diagnosis

The diagnosis of SLE in children is based upon clinical manifestations and presence of characteristic autoantibodies. The SLICC revised criteria were developed to improve research studies but can be used to establish the diagnosis in many patients [143, 168]. The presence of multiple autoantibodies is characteristic in patients with SLE. Testing for ANA, antids DNA, anti-Sm, and antiphospholipid antibody should be performed in all children. Serum complement levels may reveal hypocomplementemia in patients with major organ involvement [239]. The direct Coomb's test should also be performed since it is also one of the SLICC immunologic criteria. Nonspecific acute phase reactants are often elevated with the exception of CRP which is typically normal or minimally elevated during exacerbations of the disease [168]. Urinalysis is used to monitor for proteinuria and hematuria.

Management

A multidisciplinary team approach is typically required for the treatment of SLE in children and adolescents [168]. Individualized therapy is based upon disease severity, organ involvement, and potential side effects of specific medications [240, 241]. Most children with SLE are treated with systemic corticosteroids and many also receive immunosuppressive therapy to control the disease [242, 243].

Oral and intravenous corticosteroids are a mainstay of therapy in children with SLE. They are highly effective in achieving rapid disease control [168]. Oral prednisone and prednisolone, are used most often in doses up to 2.0 mg/kg. Intravenous methylprednisolone is typically used as intermittent pulse therapy in doses of 30 mg/kg (maximum of 1000 mg/dose). Following control of the disease, the dose is decreased over time to the lowest dose tolerated to reduce the risk of side effects [240, 243, 244]. Steroid-sparing agents may be required in cases resistant to tapering or in children who develop intolerable side effects.

Virtually all children are treated with hydroxychloroquine to reduce disease activity and autoantibody production. It is also useful in the management of cutaneous manifestations and to decrease the risk of thrombotic and premature atherosclerosis [171, 243, 245]. Antimalarial therapy has been shown to reduce disease activity, prolong survival, reduce infections, and possibly protect against osteoporosis [224]. Children treated with hydroxychloroquine should undergo ophthalmologic examinations as previously discussed to screen for potential retinal toxicity.

Several immunosuppressive agents are used in childhood SLE. Methotrexate is used in children with persistent arthritis without other systemic manifestations [168]. Azathioprine is useful for the treatment of arthritis, skin disease, serositis, and renal disease [243]. Mycophenolate mofetil is increasingly used to induce remission in lupus nephritis as well as an overall steroid-sparing therapy [168, 243, 246]. Cyclophosphamide is another treatment option for children with the most severe disease manifestations such as resistant nephritis, neuropsychiatric disease, and other life threatening manifestations [243]. The potential for serious side effects including infertility, future malignancy, bone marrow suppression, infection, and hemorrhagic cystitis should be considered before initiating cyclophosphamide therapy. A number of biologic agents that target B cells, T cells, and several cytokines are currently being investigated for the treatment of SLE. Belimumab is a monoclonal antibody that inhibits the B lymphocyte stimulator and has recently received approval for use in adult SLE [247].

There is little information regarding the optimal treatment of KCS in children with SLE. Therefore, a general treatment approach similar to that used in children with JIA seems reasonable. Artificial tears are first-line therapy in these children. Nonpreserved tears are preferable similar to children with JIA. Topical corticosteroids may be considered as adjunctive therapy but the risk of cataract and glaucoma should be considered. Also, topical cyclosporine emulsion may be useful in resistant cases of KCS. In severe cases or in children who develop toxicity to topical agents, punctal occlusion may be useful.

Patients with mild lupus retinopathy typically require no treatment and have good visual outcomes since the retinopathy improves with treatment of the systemic disease [175, 181, 182]. Severe occlusive retinopathy is treated with systemic corticosteroids and immunosuppressive steroid-sparing agents [175, 176, 178, 201]. Panretinal photocoagulation is recommended for patients with retinal neovascularization. Vitrectomy and anti-vascular endothelial growth factor therapy may be also be useful in patients with neovascularization although their use in children has not been described. Despite treatment, over one-half of affected eyes have a final visual acuity of 20/200 or worse [206, 207].

Lupus choroidopathy may resolve with control of the underlying systemic disease [216, 248]. In most cases, treatment with systemic corticosteroids with or without immunosuppressive agents is effective [178, 216]. In patients who develop CSR while receiving corticosteroids, a reduction in dosage has been suggested by some authors [249, 250]. However, corticosteroid therapy should not be withheld in patients with severe systemic disease especially if CSR develops during a systemic exacerbation [251].

There is no effective treatment for chloroquine or hydroxychloroquine retinal toxicity other than stopping the drug. In some patients, visual loss can progress despite cessation of the drug [234, 252]. Signs of possible toxicity include subtle changes in macular pigmentation, visual field sensitivity, or any of the objective screening tests.

Any of these early changes should be confirmed with additional testing. In patients with early signs of toxicity, discontinuation of the drug or close monitoring at 3–6 month intervals may be considered [234]. The decision to continue the drug should be made in conjunction with the treating rheumatologist based upon the risk and benefits of continued therapy. Any sign of probable toxicity including bull's eye maculopathy or parafoveal abnormalities detected with any objective screening test should prompt cessation of the drug. After the drug is stopped, reevaluation should be performed 3 months later and annually until the abnormalities remain stable [234].

Juvenile–Onset Spondyloarthropathies

Definition

Juvenile-onset spondyloarthropathies (JSpA) are a group of inflammatory disorders characterized by enthesitis, arthritis with involvement of the spinal and sacroiliac joints, strong association with HLA-B27 and onset prior to 16 years old [253–255]. While the majority of patients with juvenile arthritis only develop peripheral arthritis, a subset of these patients is at risk of developing axial joint disease which can potentially progress to spondyloarthropathy (SpA). These patients who share the common characteristics of lower extremity arthritis and enthesitis were previously classified as oligoarticular juvenile rheumatoid arthritis type II or seronegative enthesopathy and arthropathy syndrome [1]. Rosenberg and Petty first described the syndrome of seronegative enthesopathy and arthropathy as distinct group of juvenile arthritis who had a predisposition to developing spondyloarthropathy [256]. Juvenile ankylosing spondylitis (JAS) and reactive arthritis (ReA) represent two of the well-known differentiated juvenile-onset spondyloarthropathies [256–258].

Classification of children with spondyloarthropathies has been difficult with several different systems in use although none are universally accepted [259–261]. The ILAR JIA classification, categorizes children with JSpA into one of three subtypes: ERA, JPA or undifferentiated arthritis [262, 263]. However, the ILAR classification does not specifically address children with JAS and excludes children with ReA[262].

Juvenile ankylosing spondylitis shares a number of features with adult ankylosing spondylitis (AS) but also differs in several characteristics. Similar to adult AS, these children demonstrate radiographic evidence of sacroiliitis and HLA-B27 is often present [264, 265]. Unlike adult AS, classic inflammatory back pain is not a typical presenting feature in JAS. Children tend to have peripheral arthritis and enthesitis as well as worse hip disease compared to adults. Significant delays in the diagnosis are common among children; especially girls with JAS [264]. In addition, children have a higher risk for uveitis [266].

Table 20.9 Diagnostic criteria for reactive arthritis

Typical peripheral arthritis
Asymmetric oligoarthritis; predominantly lower limbs
Plus:
Evidence of preceding infection
Clear history of diarrhea or urethritis within the preceding 4 weeks; laboratory confirmation desirable but not required
No clear preceding infection; laboratory confirmation required
Exclusion criteria
Other known causes of monoarthritis or oligoarthritis such as:
Other defined spondyloarthropathies
Septic arthritis
Crystal arthritis
Lyme disease
Streptococcal reactive arthritis

Adapted from Kingsley G, Sieper J. Third International Workshop on Reactive Arthritis. 23–26 September 1995, Berlin, Germany. Report and abstracts. Annals of the Rheumatic Diseases. 1996;55(8):564–84 [267] with permission from BMJ Publishing Group

The most commonly used criteria for ReA are from the Berlin Third International Workshop of ReA (Table 20.9) [267]. Most cases are due to enteric or genital infections although a small number may be associated with an upper respiratory tract infection. The organisms responsible for most infections in children include *Shigella flexneri, Salmonella* spp., *Yersinia enterocolitica*, *Campylobacter* spp. and *Chlamydia* spp [253]. Infection with Shigella, Salmonella, Yersinia, and Campylobacter presents as a gastroenteritis while Chlamydia presents as a genital infection or less commonly an upper respiratory infection. The pathophysiology of the arthritis is thought to be a localized inflammatory reaction resulting from nonviable bacterial components [268].

History

Ankylosing spondylitis is a disease of ancient times. Ruffer and Raymond in 1912 described AS in the mummies of ancient Egypt [269, 270]. In 1974, Short described 18 cases of AS extending over 3000 years from 2900 B.C. to 200 A.D. derived from Egyptian sources [271]. Separate descriptions by von Bechterew, Strumpell, and Marie at the end of the nineteenth century promoted the general recognition of AS, and the eponyms, "Marie-Strumpell disease" and "von Bechterew's disease" bear their names [272].

A major breakthrough in the understanding of AS came in 1973 when two studies reported the association of HLA-B27 with AS [273, 274]. This genetic disease association accounts for the increased prevalence of AS among relatives of patients, and the rarity of AS in non-Caucasian populations, where the frequency of HLA-B27 is low [272]. It also accounts for the high incidence of uveitis in association with AS, since 50 % of all cases of acute anterior uveitis are HLA-B27 positive [273].

Sir Benjamin Brodie described the triad of urethritis, arthritis, and conjunctivitis in five patients in 1818 [275]. Stoll was probably the first to describe the association of arthritis, conjunctivitis, and urethritis with a diarrhea illness in 1776 [276]. In 1916, Reiter also described the triad of arthritis, urethritis, and conjunctivitis following dysentery [277]. The first description of Reiter syndrome in a 16 year-old was reported 2 years later by Junghanns [278]. In 1947, the initial case of a preadolescent with Reiter syndrome was published [279]. In 1947, Harkness reaffirmed that Reiter syndrome may follow both dysenteric and venereal infections [280]. The association of HLA-B27 with Reiter syndrome was subsequently described in 1973 [281]. Although widely used in the past, the term Reiter syndrome is no longer used. With the discovery of Reiter's Nazi past and complicity with war atrocities, several rheumatology journal editors in 2003 suggested removal of the eponym from the literature and replacing it with the term reactive arthritis [282, 283].

Epidemiology

With no universally accepted classification system, reports describing the epidemiology of JSpA vary widely [14, 284]. The estimated incidence of JSpA in the United States is 2.0 per 100,000 children and 1.4-2.1 per 100,000 children in Canada [38, 285, 286]. Using data extrapolated from adults, the prevalence of JSpA is estimated at 11–86 per 100,000 children [287]. Children of any age can be affected but JSpA is more common between 8 and 12 years of age. Boys are more frequently affected than girls, especially in the prepubescent years. However, the number of girls with JSpA increases with age and eventually equals the prevalence among boys [284, 287].

Systemic Manifestations

Juvenile ankylosing spondylitis is a differentiated JSpA with onset by 16 years of age [288]. Initial manifestation of JAS typically are asymmetric peripheral oligoarthritis, enthesopathy affecting the lower extremities, and hip and shoulder arthritis [289–291]. Most children eventually develop polyarthritis; typically after the first year of the disease [292]. Axial symptoms are uncommon early in the disease occurring in less than 15 % of children [284]. Characteristic axial disease with inflammation involving the vertebral joints tends to occur later [284, 289, 292–295]. Axial disease typically begins at the hip joints and progresses gradually to the sacroiliac joints and up the spine. The unique feature in SpA is the process of abnormal new bone formation in the spine that causes ankylosis (or fusion) [296].

Extra-articular manifestations can also occur in JAS. Nonspecific inflammatory bowel disease may affect up to 80 % of children [297–299]. In addition, recurrent anterior uveitis has been reported in up to 27 % of children with JAS [273, 274, 300–302]. Other extra-articular manifestations such as aortic valve insufficiency, cardiac conduction disturbances, amyloidosis, pulmonary, and renal disease are rare in JAS [291, 301–303].

Reactive arthritis is another differentiated form of JSpA typically occurring after an infection with an arthritogenic bacteria. The clinical course and severity of ReA varies widely. Two disease patterns are common; a short self-limited course or a chronic relapsing course. Symptoms of the inciting infection first develop followed a latent period up to 4 weeks before the onset of a mono- or oligoarthritis usually involving the lower extremities [253, 304]. However, the initial infection may be asymptomatic in some children. The first episode of arthritis typically involves the knees or ankles. Dactylitis, which is caused by inflammation of the joints and tendon sheathes in the finger or toe can also be seen. Due to its appearance, dactylitis is commonly described as a "sausage" digit. Recurrent arthritis is common in children with ReA [305]. Constitutional symptoms such as fever, fatigue, weight loss, and muscle weakness may occur during disease exacerbations. Some children eventually progress to ankylosing spondylitis or ERA [306].

Skin manifestations are relatively common in ReA. Keratoderma blennorrhagica is seen in up to 10 % of patients while circinate balinitis occurs in up to 40 % of males [304]. Rashes, erythema nodosum and nail changes have also been reported. Other extra-articular manifestations include conjunctivitis, uveitis, urethritis, cervicitis, myocarditis, aortic insufficiency and pericarditis [253, 305–309].

Ophthalmic Manifestations

Acute non-granulomatous anterior uveitis is the most frequent extra-articular manifestation in JAS affecting up to 27 % of patients [273, 310]. Children are more likely to develop uveitis or have a history of uveitis compared to adults with AS [266, 289, 311]. Most children with JAS-associated uveitis are boys; reflecting the overall male predominance of the underlying disease [312]. In addition, most children with uveitis and JAS are HLA-B27 positive. The uveitis is usually symptomatic and recurrent but most patients do not experience severe sequelae [273]. In some patients, the uveitis can become chronic which may increase the risk for ocular complications and vision loss [312, 313]. Symptoms in most patients are pain, redness or blurred vision of one or both eyes. The disease is unilateral at presentation in 82–100 % of cases [273, 312]. Bilateral involvement

develops in approximately 25 % of patients with simultaneous involvement of both eyes seen in less than 20 %. In patients with recurrent disease, uveitis tends to reappear within 3–8 months following the initial episode [273]. Acute attacks are characterized by the presence of anterior chamber cell and flare in most cases, while posterior synechiae, cataracts, and band keratopathy are associated with more chronic disease [273]. Posterior segment inflammation has been described in patients with AS but it is difficult to determine the specific manifestations in children since most series include more adults than children. Nevertheless, vitritis, cystoid macular edema, retinal vasculitis, and papillitis have been reported in several studies [313–316].

Uveitis develops within 1–12 years after the onset of arthritis and/or enthesitis in up to 90 % of patients; however, uveitis can occasionally antedate the onset of arthritis by up to a year [273]. Similar to JIA, there appears to be no association between articular or systemic disease activity and uveitis in JAS.

The most common ophthalmic manifestation of ReA is a mucopurulent papillary or follicular conjunctivitis [317]. In a review of 21 cases of pediatric Reiter's syndrome by Lockie, conjunctivitis was the most common initial symptom [318]. The conjunctivitis usually occurs early in the disease course and is typically bilateral, painless and resolves spontaneously. In most cases, symptoms are mild, although some patients may experience severe blepharospasm and photophobia [319].

Additional ocular manifestations in children with ReA include episcleritis, scleritis, and anterior uveitis. Vitritis, macular edema, and optic nerve edema occur rarely [320]. Punctate and subepithelial keratitis have also been reported as well as corneal scarring [317, 321–324].

Diagnosis

The diagnosis of JSpA is based primarily upon clinical manifestations. Laboratory testing may reveal a mild anemia and an elevated ESR. In a retrospective study of 103 patients with JSpA, HLA-B27 was present in 75.9 % of patients [325]. Imaging may help establish the diagnosis and is often useful to monitor disease progression. Conventional radiographs of involved peripheral joints show changes similar to these seen in children with JIA, but evaluation of the sacroiliac joints by conventional radiography is difficult in children. Plain radiography cannot detect active inflammation and can only detect joint damage that occurs after long-standing disease [284]. Contrast enhanced magnetic resonance imaging (MRI) is often used to detect signs of early inflammation of axial skeleton, especially the sacroiliac joint [326].

Diagnostic criteria for ReA are also based upon clinical criteria [268]. Nonspecific laboratory findings are common including elevated ESR and CRP; especially in cases of severe disease [306]. Children with ReA may have mild leukocytosis and elevated neutrophil counts. Testing for HLA-B27 is generally not useful since greater than 50 % of children will have a negative result [327]. Urinalysis may reveal pyuria due to urethritis. Cultures of urine or stool should be obtained based upon the clinical manifestations. In children with chronic disease, conventional radiography may show periostitis, sacroiliitis, joint erosions, and joint space narrowing [327]. MRI may also be useful to identify early joint involvement in these children

Management

The treatment of children with JSpA is challenging due to the variable clinical course and limited reports of efficacy of many drugs used to treat these diseases. NSAIDs are often used to provide symptomatic relief of arthritis and enthesitis. Continuous treatment with NSAIDs may be more beneficial than intermittent therapy based upon studies in adults [328]. Sulfasalazine is also frequently used in children with resistant arthritis and enthesitis [306, 329, 330]. Systemic corticosteroids may be required for patients with severe disabling disease not controlled with NSAIDs. Methotrexate may be useful for patients with anterior uveitis or inflammatory bowel disease [253]. More recently, the TNFα inhibitors etanercept and infliximab have demonstrated significant improvement in disease activity in patients with JSpA [104, 331–333].

Currently there are no guidelines for the use of antibiotics in children with ReA. Many studies have demonstrated no benefit from the use of various antibiotics [327]. However, children with acute *Chlamydia trachomatis* infection should be treated; as well as their sexual partners based upon the most current recommendations [304]. A recent study has also shown that a 10–14 day course of amoxicillin alone or combined with clavulinic acid may be useful during the early stages of ReA prior to identification of the underlying organism [334].

Children with acute anterior uveitis are initially treated with topical corticosteroids and cycloplegics [335]. If the inflammation is especially severe or persists despite frequent topical corticosteroids, periocular corticosteroids are often used. Systemic corticosteroids are reserved for recalcitrant cases [273]. Methotrexate may be considered as a corticosteroid-sparing agent in children requiring prolonged systemic therapy. Complications of chronic anterior uveitis such as cataracts, posterior synechiae, band keratopathy, and glaucoma may require surgical intervention.

Conjunctivitis in children with ReA typically resolves without therapy [317, 335]. Mild episcleritis may require no treatment if asymptomatic. For those with symptoms, artificial tears are often useful. Initial treatment of scleritis is systemic NSAIDs. Systemic corticosteroids or systemic

immunomodulator therapy may be necessary in children with refractory disease [336]. Keratitis may be self-limited requiring no therapy in children with ReA [317, 335]. If symptomatic or persistent, treatment with topical corticosteroids is often useful.

Sarcoidosis

Definition

Sarcoidosis is a chronic multisystem disease characterized by the presence of granulomatous inflammation [337]. The diseases is most common among young adults who typically present with hilar adenopathy, pulmonary infiltrates, as well as skin and ocular lesions [338]. Sarcoidosis is uncommon in children [339]. Most affected children are 13–15 years of age although very young children can also develop the disease [340–342].

Blau syndrome, an autosomal dominant form of the disease is similar to sporadic early onset sarcoidosis (EOS) [343, 344]. Both are characterized by the presence of polyarthritis, rash, and recurrent uveitis. In addition, both are associated with missense mutations of the caspase recruitment domain gene (*NOD2/CARD15*) [345, 346].

The etiology of sarcoidosis is unknown but may involve environmental or infectious risk factors that trigger the abnormal immune response in genetically susceptible patients [347, 348]. Environmental factors such as insecticides, pesticides, mold, and mildew may increase the risk for sarcoidosis [349]. *Mycobacterium tuberculosis* and *Proprionibacterium acnes* have also been suggested as possible infectious etiologies [350].

The characteristic feature in sarcoidosis is the presence of epithelioid granulomas with associated mononuclear cell infiltration. Granulomas develop in response to a persistent poorly soluble antigenic material. Phagocytic cells of the innate immune system surround the antigenic stimulus and initiate an immune response ultimately leading to the formation of a granuloma. Granulomas in sarcoidosis ultimately resolve or heal by fibrosis [349, 350].

History

The first description of sarcoidosis was by Hutchison in 1877 [351]. In 1899 Caesar Boeck described the skin lesions of the disease and was the first to provide histologic confirmation of granulomatous inflammation [352]. Boeck also proposed terminology ultimately leading to the current term of sarcoidosis. The systemic manifestations of the disease were recognized in 1915 [353]. Initial reports of pediatric sarcoidosis appeared during the 1950s [354].

Epidemiology

Childhood sarcoidosis is a rare disease and epidemiologic data are limited. A study of Danish children found an estimated incidence of 0.22–0.27 per 100,000 children per year [355]. The incidence in children 4 years of age or younger was 0.06 per 100,000 person years. The incidence among children 14–15 years of age was 1.02 per 100,000 person years [356].

There is no gender predilection in children with sarcoidosis. In the United States, approximately 81 % of older children with sarcoidosis are African American, however less than 30 % of young children with the disease are African American [340, 342, 357–359]. Most children with Blau syndrome are Caucasian [343, 345, 360]. In other countries, sarcoidosis is more common in the major racial groups of the country.

Systemic Manifestations

Systemic manifestations vary in children with sarcoidosis based upon the presence of or absence of the *NOD2/CARD15* mutation. Children without the *NOD2/CARD15* mutation usually present with fever, malaise, and weight loss [344]. Pulmonary manifestations such as cough, dyspnea, and chest pain occur in virtually all affected children [344, 361–363]. Bilateral hilar adenopathy is the most common finding with chest radiography [350, 355, 364]. Pulmonary parenchymal involvement includes interstitial, nodular, alveolar, and fibrotic patterns [364, 365]. Restrictive lung disease is relatively common in children [366, 367]. Peripheral lymphadenopathy and hepatosplenomegaly are also common. Parotid gland enlargement is another common finding in children [357, 368]. The most common skin manifestation is an erythematous rash seen in up to 77 % of children (Fig. 20.5)

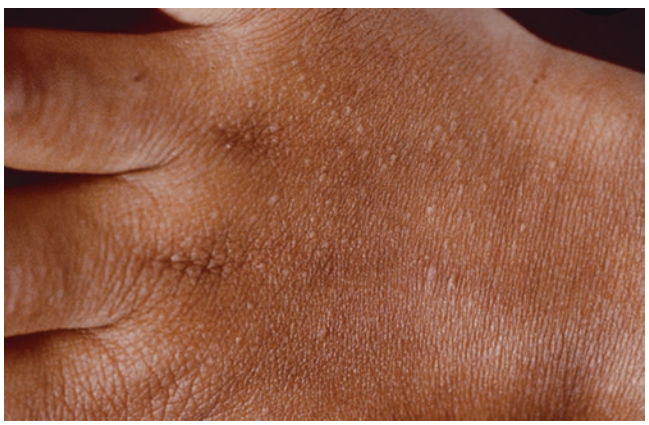

Fig. 20.5 Erythematous papular rash in a child with sarcoidosis (Reprinted from Levin AV and Wilson TW. Hospital for Sick Children's Atlas of Pediatric Ophthalmology and Strabismus. Philadelphia: Lippincott Williams and Wilkins; 2007. With permission from Lippincott Williams and Wilkins/Wolters Kluwer)

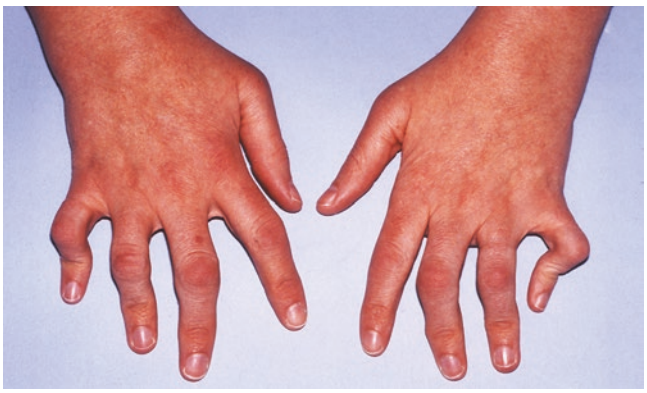

Fig. 20.6 Polyarthritis of the proximal interphalangeal joints of both hands with camptodactyly of both fifth digits in a teenager with Blau syndrome

[355, 358]. Flat papules typically located on the face as well as macules and plaques are also common. Erythema nodosum occurs in approximately one-third of children. Arthritis affects over one-half of children with sarcoidosis. It is typically a boggy tenosynovitis with effusion and good range of motion. Multiple large joints of the upper and lower extremities are most commonly involved [350, 357, 368, 369]. Renal involvement including interstitial and granulomatous nephritis can rarely occur [350]. Neurosarcoidosis is also rare in children [370]. Mass-like lesions may be seen with imaging of the CNS [344]. Other manifestations include seizures, meningitis, and cranial neuropathies, especially involving the facial nerve [365].

Children with the *NOD2/CARD15* mutation include those with Blau syndrome and EOS. Polyarthritis, rash, and recurrent uveitis are the characteristic clinical features among these children [344]. Most patients present with a rash involving the trunk with extension to the face and extremities. Early in the course, the rash my exhibit fine desquamation. Eventually after several years, the rash may appear similar to ichthyosis vulgaris. Subcutaneous nodules similar in appearance to erythema nodosum may also occur. Most children develop polyarthritis within months following the onset of the rash. Large and small peripheral joints are most commonly affected. The proximal interphalangeal joints may exhibit a characteristic flexion contracture known as camptodactyly (Fig. 20.6) [344]. Granulomatous nephritis, small vessel vasculitis, lymphadenitis, pericarditis, and cranial neuropathy have been rarely reported [371–373].

Ophthalmic Manifestations

Ophthalmic manifestations have been reported in up to 80 % of children with sarcoidosis [374–379]. Anterior uveitis is the most common manifestation in both older and younger children occurring in up to 48 % of children [358, 380, 381]. Presenting symptoms in these children were eye pain and loss of vision. Anterior uveitis can be granulomatous or non-granulomatous. Fine or mutton fat keratic precipitates as well as iris nodules may be present (Fig. 20.7). Complications of anterior uveitis are not uncommon including band keratopathy, synechiae, glaucoma, and cataract [382, 383]. Complications are a significant cause of morbidity among children who are inadequately treated [358, 380, 381, 384].

Intermediate, posterior and panuveitis have also been reported. Posterior uveitis is more common in older children [385, 386]. Specific manifestations reported include vitritis, multifocal chorioretinal granulomas, choroiditis, optic disc edema or granuloma, chorioretinal scars, and choroidal neovascularization (Fig. 20.8) [312, 382, 383, 387].

Conjunctival nodules and cysts are not infrequent in children with sarcoidosis (Fig. 20.9) [382, 388–390]. Less common manifestations have been reported in a number of cases reports and limited series such as orbital inflammation with proptosis, small eyelid nodules, sicca syndrome and interstitial keratitis [387, 391–394].

Ocular manifestations of Blau syndrome have been described in a number of families. Manifestations in these children consist of panuveitis with multifocal choroiditis, subretinal exudates, chorioretinal lesions, anterior uveitis, ischemic optic neuropathy and retinal vasculopathy (Fig. 20.10) [395, 396]. Complications associated with uveitis are common including band keratopathy, anterior and posterior synechiae, iris bombé, glaucoma, cataracts, cystoid macular edema, optic disk edema and subretinal fibrosis [395–397].

Diagnosis

The definitive diagnosis of sarcoidosis is established by biopsy of involved tissue demonstrating noncaseating epithelioid cell granulomas and exclusion of other causes of granulomatous inflammation [398–401]. In young children, the skin may be the best site for biopsy while in older children any enlarged lymph nodes may be preferred [382]. No laboratory tests are diagnostic for sarcoidosis. Non-specific laboratory findings include elevated ESR and CRP as well as mild anemia and leukopenia [344]. Hypergammaglobulinemia is relatively common. Angiotensin converting enzyme (ACE) may be elevated in some children, however normal levels vary with age in children [342, 344, 401]. As a result, ACE levels may have limited utility in children with suspected sarcoidosis. Liver function tests are often elevated. Hypercalcemia and or hypercalcuria is found in up to 35 % of children [402].

Chest radiography may reveal bilateral hilar adenopathy especially in older children [342, 380, 381]. These children may have parenchymal involvement as well. Osteopenia and punched out lesions may occur in younger children and visible with radiographs of the hand [357]. Pulmonary function tests are often abnormal in children with sarcoidosis [402].

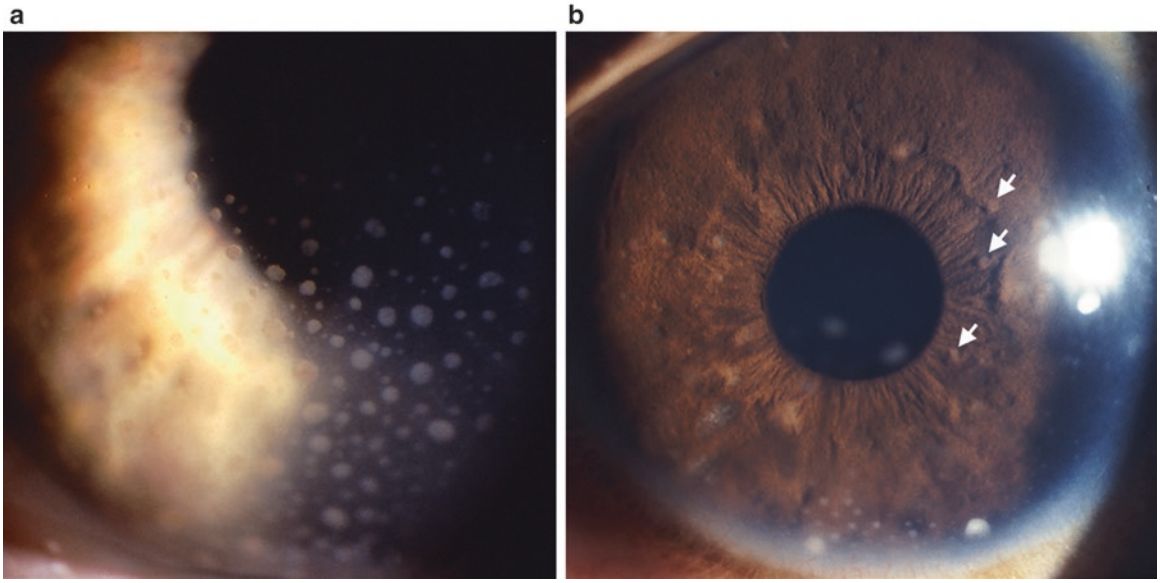

Fig. 20.7 Mutton-fat keratic precipitates (**a**) and multiple iris nodules (*arrows*) (**b**) in a patient with sarcoidosis

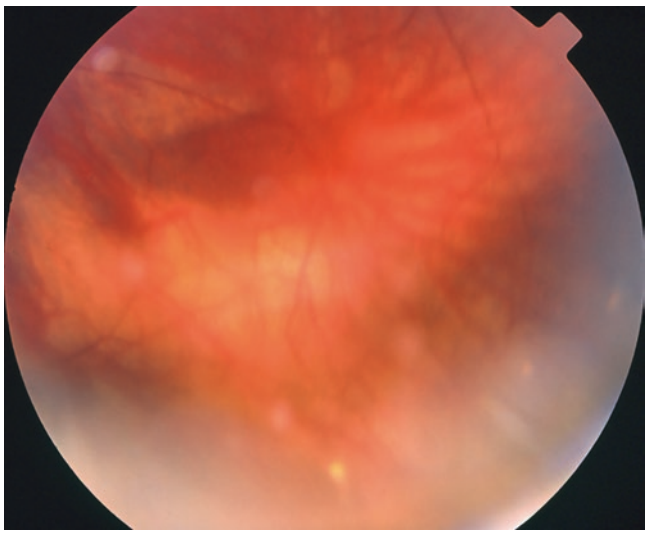

Fig. 20.8 Multifocal choroiditis and mild vitritis in a child with sarcoidosis

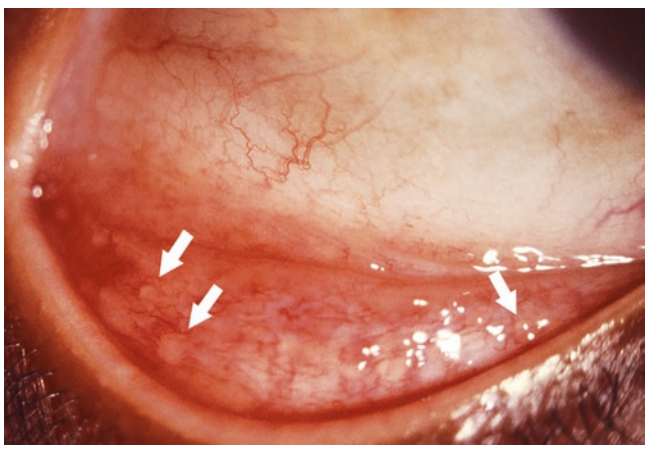

Fig. 20.9 Multiple conjunctival nodules (*arrows*) in sarcoidosis

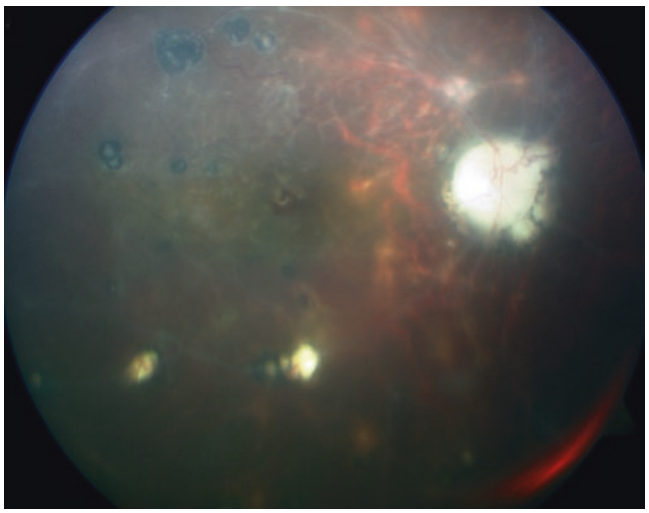

Fig. 20.10 Multifocal chorioretinal scars and perivascular sheathing in a teenager with Blau syndrome. Nodular excrescences are visible adjacent to the optic disc

Management

There are no current guidelines for the treatment of children with sarcoidosis. Treatment should be based upon the severity of the disease as well as the organs involved. Most children with multisystem involvement are initially treated with corticosteroids [337, 344, 366, 403–405]. Methotrexate is an effective steroid sparing agent that has been used to treat a variety a variety of disease manifestations [406–409]. The TNFα antagonists are also useful in the treatment of children with sarcoidosis [410]. Infliximab appears effective in controlling arthritis and visceral manifestations [344, 411].

Management of the ophthalmic manifestations should begin with a comprehensive ophthalmic examination at the time of initial diagnosis and at regular intervals thereafter due to the lack of symptoms in some children. Although no recommendations exist regarding the frequency of ophthalmic examination, it would seem reasonable for older children without uveitis to be followed at 6 month intervals. Younger children may require more frequent follow-up to ensure uveitis or other ocular manifestations are detected and treated early.

Treatment of the ophthalmic manifestations is based upon the specific condition. Children with anterior uveitis are initially treated with topical corticosteroids with or without cycloplegics [382]. Periocular corticosteroids and or systemic corticosteroids may be necessary in severe or recalcitrant cases [341]. Methotrexate may also be considered as a steroid sparing agent in children to avoid serious side effects from prolonged corticosteroid therapy.

Children with intermediate uveitis may be treated with periocular corticosteroids. If the inflammation is not controlled, systemic corticosteroids and or methotrexate may be necessary. Patients with posterior or panuveitis will likely require systemic therapy to control the inflammation [336].

Children with Blau syndrome and panuveitis with multifocal choroiditis or subretinal exudates or chorioretinal lesions will typically require systemic therapy. Initial short-term treatment in most cases consists of oral corticosteroids with or without adjunctive periocular corticosteroids. Long-term treatment should include a steroid-sparing agent such as methotrexate or other immunosuppressive agent [336, 395].

Interstitial keratitis is usually treated with topical corticosteroids [392, 393]. Symptomatic sicca syndrome therapy consists of artificial tear preparations for most cases. Many children with symptomatic band keratopathy treated with EDTA chelation experience improvement in symptoms and visual acuity [412, 413]. Glaucoma is initially treated with topical anti-glaucoma therapy, followed by oral medications. Children with progressive glaucoma may ultimately require glaucoma surgery [382]. Cataract surgery may be necessary in children with visually significant cataracts. To ensure the best possible outcome, the eye should be completely free of inflammation for at least 3 months prior to surgery [382, 414]. There is little data regarding management of cataracts in childhood sarcoidosis compared to other children with uveitic cataracts such as those with JIA. Therefore, it is unclear if an intraocular lens should be implanted in these children.

Juvenile Dermatomyositis

Definition

Juvenile dermatomyositis (JDM) is a rare autoimmune small vessel vasculopathy that primarily affects skin and muscle [415]. It is the most common inflammatory myopathy in children and characterized by proximal muscle weakness as well as characteristic skin rashes [416]. Arthritis as well as gastrointestinal, pulmonary, neurologic, and cardiac manifestations may occur but are much less common. Unlike adult dermatomyositis, JDM results in less functional disability and mortality compared to adults with dermatomyositis. Associated malignancy is also rare in children with JDM [417]. The clinical course is monocyclic in 41 % of children with permanent remission occurring 2–3 years after disease onset. The remaining 59 % of children have a polycyclic chronic course characterized by disease exacerbations and remissions [418–420].

The etiology of JDM remains uncertain although a genetic predisposition is likely in affected children [415]. Environmental triggers, innate and adaptive immune responses, and specific tissue responses are likely involved in the pathogenesis of the disease [415, 416]. Type 1 interferons (IFN-α and IFN-β) and TNFα are important cytokines in the pathogenesis of JDM [421].

The Bohan and Peter criteria are used to classify children with JDM (Table 20.10) [422, 423]. A diagnosis of definite JDM requires the presence of a typical rash and at least three of the other criteria. Children with "probable" JDM have a typical rash and two other criteria while those classified as "possible" JDM have a typical rash with one other criteria [422]. Magnetic resonance imaging of the hip girdle muscles with fat-suppressed T2 weighted or Short Tau Inversion Recovery (STIR) sequences that demonstrate symmetric muscle edema is now often used to confirm the diagnosis of JDM in place of electromyography or muscle biopsy since it is less invasive [424].

Table 20.10 Criteria for the diagnosis of dermatomyositis

Typical cutaneous features
Heliotrope rash
Gottron papules
Symmetric weakness of proximal muscles
Elevation of one or more of the following skeletal muscle enzymes
Creatinine kinase
Aspartate aminotransferase
Lactate dehydrogenase
Aldolase
Electromyography characteristics of myopathy
Short, small, polyphasic motor-unit poetentials; fibrillations, positive sharp waves and insertional irritability; and bizarre, high-frequency repetitive discharges
Muscle biopsy with necrosis, phagocytosis, fiber size variation, degeneration and regeneration, perivascular mononuclear inflammatory infiltrate

Adapted from Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). The New England Journal of Medicine. 1975;292(7): 344–7 [422] with permission from the Massachusetts Medical Society

History

The first clinical descriptions of JDM were reported in 1877 [425–428]. In 1912, the first postmortem examination of a child with JDM was described and noted vascular abnormalities including perivascular infiltrations of small round cells, thickening of vessel walls, and luminal occlusion [429]. Bruce was the first to describe retinitis in JDM [430].

Epidemiology

The incidence of JDM in children is 2–4 children per million per year [431, 432]. It is more common in girls with a female to male ratio of 2.3:1 [431, 433]. The mean age of onset is 7 years with up to 25 % of children developing the disease prior to the age of 4 years [434]. In the United States and United Kingdom, 65–83 % of children with JDM are Caucasian [431, 433].

Systemic Features

Proximal muscle weakness is the usual presenting symptom, often manifested by difficulty climbing stairs or frequent falls [435, 436]. Malaise and easy fatigability usually precede obvious muscle weakness by days to months. Muscle pain is seen in a majority of patients, and back pain may be an early symptom in up to 20 % of cases [435, 436].

The rash of JDM is characteristic and may precede or follow the onset of muscle weakness [417, 435, 436]. The most typical cutaneous manifestations include: heliotrope rash, Gottron's papules, and periungal erythema or nailfold capillary loop abnormalities. The heliotrope rash presents as a violaceous discoloration of the upper eyelids with or without edema (Fig. 20.11). It is erythematous with a varying degree of violaceous or heliotrope tint in most cases [417]. Gottron papules are raised erythematous papules on the extensor surfaces of joints, especially the proximal interphalangeal and metacarpophalangeal joints (Fig. 20.12) [437]. Periungal erythema can be seen by the naked eye. Capillary loop abnormalities surrounding the nail can be seen using an ophthalmoscope for magnification or nailfold capillaroscopy. A photosensitive rash can be seen on sun exposed areas such as the chest and posterior aspect of the neck (V- and shawl sign) and the malar eminences which may be indistinguishable from the malar rash of SLE [438].

Fever is reported in 50–75 % of children [435, 436]. Other constitutional symptoms include anorexia and lymphadenopathy. Calcinosis occurs in up to 70 % of cases, typically at least 2 years following initial diagnosis of the disease [417, 435, 436]. Acquired lipodystrophy has been reported in up to 40 % of children [439–441]. Nondestructive arthritis similar to that in children with SLE can also occur [417, 442].

Gastrointestinal involvement may manifest as dysphagia and dysphonia in severe cases [417]. Gastrointestinal ulceration, perforation, or hemorrhage may occur due to vasculopathy [443, 444]. Malabsorption has also been reported in children with JDM [445].

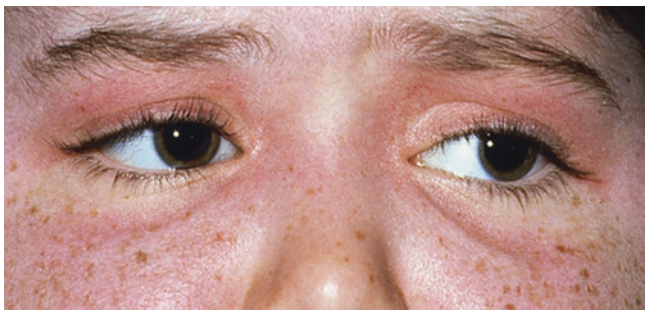

Fig. 20.11 Child with juvenile dermatomyositis and heliotrope rash (Courtesy of Dr. Alex Levin)

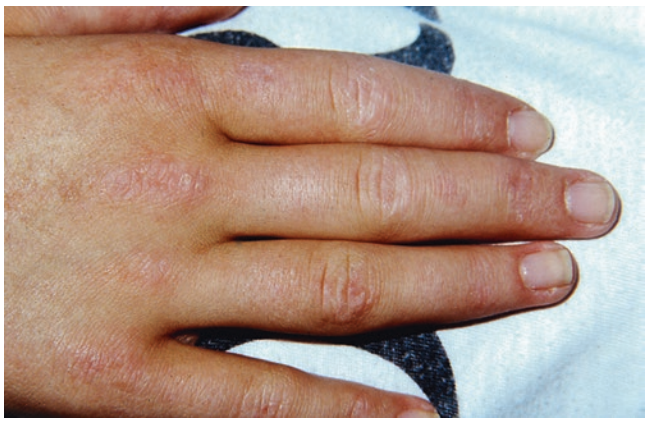

Fig. 20.12 Gottron papules in a patient with dermatomyositis (Courtesy of Dr. Alex Levin)

Up to one-third of children with JDM develop pulmonary manifestations [417]. Respiratory muscle weakness and impaired chest wall compliance may result in reduced ventilatory capacity [446]. Interstitial lung disease may also occur. Some asymptomatic children may have abnormal pulmonary function tests [447].

Central or peripheral nervous system manifestations may occur secondary due to vasculopathy. Seizures, pseudoseizures, and psychosis have been reported. Peripheral polyneuropathy may also occur [417].

Cardiac involvement is very rare in children. Hypertension, pathologic/borderline electrocardiogram, diastolic dysfunction, and pericarditis have been reported but most children have subclinical disease [448].

Ophthalmic Manifestations

One of the most striking features of JDM is the periorbital violaceous or heliotrope rash that may be seen in up to 80 % of cases (Fig. 20.11) [416]. Periorbital edema occurs

in 50–90 % of children [449, 450]. Scaly erythema and edema of the eyelids are also relatively common. Well circumscribed atrophic lid scars likely due to cutaneous vasculopathy have also been described [451]. Eyelid telangiectasias also occur and may persist long after apparent resolution of other symptoms [416]. Extraocular muscle dysfunction and convergent strabismus have been reported [430, 452, 453].

Conjunctival and episcleral vessel tortuosity are relatively common in JDM [453–455]. Avascular areas of conjunctiva have been described in patients with dermatomyositis and may be due to the associated vasculopathy [456]. Additional anterior segment manifestations include episcleritis, scleritis, membranous conjunctivitis, uveitis, and secondary glaucoma [457–459]. Ocular complications of high-dose corticosteroids may develop including glaucoma and posterior subcapsular cataracts [416, 451, 460].

Retinal manifestations are rare in JDM [417, 451]. Children are more likely than adults to develop retinal manifestations because of the systemic vasculitis associated with the childhood form of the disease [423, 453]. The retinal manifestations of JDM may be indistinguishable from those seen in SLE [452]. Most of the retinal manifestations are the result of ischemic retinopathy such as diffuse cotton wool spots, deep and superficial retinal hemorrhages, retinal edema, retinal exudates, and retinal neovascularization [430, 452, 453, 458, 461–464]. The retinopathy may be transient, lasting several weeks or persistent with permanent visual loss. Optic atrophy has been reported following severe cases of retinopathy [453, 465].

Diagnosis

The diagnosis of JDM is based upon clinical features and many clinicians utilize the Bohan and Peter criteria to aid in establishing the diagnosis. Muscle enzymes should be obtained in all children suspicious for JDM including lactate dehydrogenase, creatinine kinase, aldolase, alanine aminotransferase, and aspartate aminotransferase [437]. Up to 75 % of children with JDM will have elevations of at least one of these enzymes. Antinuclear antibodies occur in up to 85 % of patients with JDM [438]. The myositis specific antibodies anti-p155/140 and anti-p140 (MJ) are present in up to 29 and 23 % of children respectively [421].

Magnetic resonance imaging is used to document muscle involvement and myositis [437, 466]. Muscle biopsy is used less often than in the past but should be obtained in atypical cases. Electromyography (EMG) is included in the Bohan and Peter criteria although it is no longer widely used. Baseline chest radiography and pulmonary function studies should be considered in all children with JDM due to the risk of pulmonary involvement [437].

Management

There have been no published clinical trials regarding the treatment of children with JDM. As a result, most treatment recommendations are based upon expert opinion [437]. To assist clinicians with treatment decisions, the Children's Arthritis and Rheumatology Research Alliance (CARRA) has described the typical care of JDM [467, 468]. Initial treatment of moderate disease is oral or intravenous corticosteroids. Most children are treated with corticosteroids for up to 2 years followed by tapering and discontinuation over 12 months. Methotrexate is also recommended as part of the initial therapeutic regimen in addition to corticosteroids [466]. Other medications that may be considered, especially in severe disease are intravenous immunoglobulin, cyclosporine, mycophenolate mofetil, and cyclophosphamide.

Little information exists relating to the treatment of ocular manifestations of JDM. Nevertheless, therapy should be individualized based upon the specific manifestation. Eyelid and periorbital manifestations typically require no therapy. Conjunctivitis and episcleritis are often self-limited conditions but artificial tears may be helpful in children who are symptomatic. Scleritis is usually treated with NSAIDs and occasionally systemic corticosteroids [469]. Children who develop glaucoma are initially treated with topical glaucoma medications although surgery may be required in patients with progressive disease. Cataract surgery may be necessary in some cases if there is a risk of amblyopia or visual impairment.

Most of the retinal manifestations described in the English literature occurred at the time of initial disease presentation [451]. Since the retinal findings are very rare, there are no recommendations regarding their treatment in children. However, since the retinopathy may be associated with the vasculopathy, treatment of the underlying disease may result in resolution of the retinopathy [458].

Juvenile Scleroderma

Definition

Juvenile scleroderma is a rare disease characterized by fibrosis of the involved organs [470–472]. The mechanism of the disease likely involves vascular damage, autoimmunity with immune activation, and excessive deposition of collagen in affected organs [473]. Localized and systemic forms of the disease occur in all age groups but the localized form is most common among children [470, 474]. Manifestations of juvenile localized scleroderma (JLS) are typically limited to the skin while the systemic form known as systemic sclerosis (JSSc) can involve other organs. Juvenile systemic sclerosis can be a life-threatening disease due to cardiac, pulmonary, or renal involvement [470].

Since 1995, localized scleroderma (LS) has been classified into five types: plaque morphea, generalized morphea, bullous morphea, linear morphea, and deep morphea [475, 476]. To develop a more comprehensive system for JLS, this classification has been modified. The revised criteria often referred to as the Padua criteria include circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea, and mixed morphea [477].

In 2007, the Committee on Classification Criteria for JSSc published provisional criteria for the diagnosis of JSSc (Table 20.11). These criteria were developed to enhance and standardize the classification of children for research purposes [478]. To establish a diagnosis of JSSc requires the child to be less than 16 years of age with proximal skin sclerosis or induration (major criterion) and at least two minor criteria.

Table 20.11 Provisional criteria for classification of juvenile systemic sclerosis

Major criteria (required)
Proximal skin sclerosis or induration
Minor criteria (at least 2 required
Cutaneous
Sclerodactyly
Peripheral vascular
Raynaud's phenomenon
Nailfold capillary abnormalities
Digital tip ulcers
Gastrointestinal
Dysphagia
Gastroesophageal reflux
Cardiac
Arrhythmias
Heart failure
Renal
Renal crisis
New-onset arterial hypertension
Respiratory
Pulmonary fibrosis (with high-resolution CT/radiography)
Decreased diffusing capacity for carbon monoxide (DL_{CO})
Pulmonary artery hypertension
Neurologic
Neuropathy
Carpal tunnel syndrome
Musculoskeletal
Tendon friction rubs
Arthritis
Myositis
Serologic
Antinuclear antibodies
SSc-selective autoantibodies
Anticentromere
Antitopoisomerase I
Antifibrillarin
Anti-PM-Scl
Antifibrillin or anti-RNA polymerase I or III

CT computed tomography
Adapted from Zulian F, Woo P, Athreya BH, Laxer RM, Medsger TA, Jr., Lehman TJ, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis and Rheumatism. 2007;57(2):203–12 [478] with permission from John Wiley & Sons

History

The first description of a patient with scleroderma-like manifestations was by Curzio in 1753 [479]. The term scleroderma was subsequently introduced by Giovambattista Fantonetti in 1836 [480]. Numerous early reports of ocular involvement in scleroderma began to appear around 1948 but the first series of patients was reported by Stucchi and Geiser in 1967 [481]. Decreased tear production and conjunctival fornix shortening were described in a number of these patients.

Epidemiology

Both the localized and systemic forms of scleroderma are rare in children [482]. The estimated annual incidence of JLS is 1–3/100,000 while JSSc is 1 per million children [483, 484]. The mean age of onset of juvenile scleroderma is 8–9 years [470, 474]. Females are more commonly affected than males with a female-to-male ratio of 2:1 in JLS and 4:1 in JSSc [482, 485]. Over 90% of affected children are Caucasian. Delays in diagnosis are common ranging from 1.2 to 2.8 years [482, 485–488].

Systemic Manifestations

Juvenile localized scleroderma is a group of conditions affecting the skin and subcutaneous tissues [477]. Circumscribed morphea lesions are round or oval and can involve the epidermis or subcutaneous tissues. Linear scleroderma is the most common type in children; affecting the trunk, limbs or head [489]. Facial or scalp involvement has been termed *en coup de sabre* (ECDS) based upon its similarity to the appearance of someone struck on the head with a sword. The Parry-Romberg syndrome (PRS) is another linear form with progressive hemifacial atrophy below the forehead involving the subcutaneous tissues, muscle, mandible, maxilla, and tongue (Fig. 20.13) [474]. In some cases, there appears to be overlap between ECDS and PRS prompting some authors to suggest they represent a spectrum of disease while others believe they are two distinct disorders [490–493]. Children with ECDS or PRS are at increased risk for central nervous system involvement including seizures,

Fig. 20.13 Parry-Romberg syndrome with hemifacial atrophy (Reprinted from Levin AV and Wilson TW. Hospital for Sick Children's Atlas of Pediatric Ophthalmology and Strabismus. Philadelphia: Lippincott Williams and Wilkins; 2007. With permission from Lippincott Williams and Wilkins/Wolters Kluwer)

chronic headaches, and neuropsychiatric disorders [490, 494]. Generalized morphea is characterized by four or more large plaques at least 3 cm wide affecting at least two anatomic areas. Pansclerotic morphea is a rare form of JLS that manifests as circumferential involvement of the limbs with sparing of the distal fingers and toes. Mixed morphea includes a combination of at least two of the previously described subtypes.

Juvenile systemic sclerosis is a multisystem fibrosing disease that can be divided into three clinical subtypes. Diffuse cutaneous JSSc has extensive rapidly progressive skin thickening with early cardiac, renal and hepatic involvement. Limited cutaneous JSSc has limited nonprogressive skin thickening with late gastrointestinal and pulmonary involvement. The third subtype, overlap JSSc includes diffuse or limited cutaneous JSSc with features of another disease such as SLE or JDM [474, 495].

Children with JSSc often present with Raynaud phenomenon and skin changes involving the hands [485]. Raynaud phenomenon is a reversible vasospasm affecting the fingers and toes characterized by a triphasic color change of white to blue as the tissues become cyanotic and finally red with reperfusion [470]. Numbness and tingling of the digits are common during the cyanotic phase. Skin involvement is typically subtle resulting in delayed diagnosis in many children. Edema of the skin is one of the earliest signs of cutaneous involvement typically affecting the distal extremities. Later, fibrosis leads to increased skin thickness with a shiny appearance and loss of hair follicles [474]. As the skin thickens, the underlying tendons are affected leading to shortening with reduced range of motion. Tightness of the skin of the midface produces the characteristic small mouth, prominent teeth, pinched nose, and expressionless appearance.

Children with JSSc can also develop gastrointestinal, pulmonary, cardiac, musculoskeletal, and renal manifestations. Gastrointestinal involvement affects up to 50 % of children often presenting with dysphagia and gastroesophageal reflux [474]. Pulmonary disease is also common including interstitial lung disease and pulmonary arterial hypertension. Slowly progressive dyspnea with exertion suggests interstitial lung disease while pulmonary hypertension typically presents with rapidly progressive dyspnea [474]. Cardiac involvement is uncommon but a major cause of mortality due to pericarditis, arrhythmia, cardiomyopathy, and heart failure [470, 475]. Up to 40 % of children with JSSc develop inflammatory arthritis as well as synovitis associated with fibrosis of tendons. Tendon friction rubs may be noted with flexion or extension of involved joints [474, 496]. Renal disease is uncommon in children with JSSc. Mild renal dysfunction secondary to vasculopathy may occur but severe scleroderma renal crisis with accelerated arterial hypertension is extremely rare [482, 485].

Ophthalmic Manifestations

Numerous ocular manifestations of scleroderma have been described in adults [497]. The most common ocular manifestation among adults is KCS [498–501]. Eyelid skin changes and telangiectasia are also common especially among patients with extensive skin disease [497]. Fibrosis of the skin can manifest as tightness of the lids, blepharophimosis, or rarely lagophthalmos [499–501]. Superficial punctate keratopathy may occur in patients with KCS or as a result of eyelid fibrosis. Increased central corneal thickness has been described in patients with systemic sclerosis [502]. Iris transillumination defects have been described in many patients and may be due to defects in the iris pigment epithelium [497, 499, 501]. Cataracts may be seen in longstanding disease. Retinopathy has rarely been reported although most patients had advanced disease with renal involvement and hypertension [503, 504]. Several reports have described superior oblique palsy, Brown syndrome, and ophthalmoplegia due to orbital myositis [497]. There also have been suggestions that there may be an increased risk of normal tension glaucoma among patients with scleroderma [505, 506].

Reports describing ocular complications in children are very limited. In a retrospective study of 750 patients with JLS from centers in Europe, North America, South America,

Asia, and Australia, ocular manifestations were noted in 3.2 % of children [487, 507]. Ocular manifestations were more common among children with ECDS compared with the other types of JLS. Overall, the most common manifestations were ocular adnexal disorders in 42 % including eyelid and eyelash abnormalities. Asymptomatic anterior uveitis or episcleritis was noted in 29 % of children. Pupillary mydriasis was noted in two patients; one with pseudotumor cerebri and orbital myositis and the other with epilepsy. One patient had multiple ocular manifestations including enophthalmos, iris atrophy, neuroretinitis, and retinal telangiectasia. Other ocular abnormalities included an abducens palsy and pseudopapilledema. One of these reports also describes additional ocular manifestations such as KCS, keratitis, and acquired glaucoma [487].

A number of case reports have described additional ocular manifestations in children with scleroderma. Among these, the most common are enophthalmos, ptosis, eyelid atrophy, pupil abnormalities, iris heterochromia, uveitis, strabismus, and pigmentary changes in the fundus in children with ECDS or PRS [508, 509]. Orbital myositis, retinal vasculitis, and amblyopia have also been described in single case reports [510–512].

Diagnosis

The diagnosis of juvenile scleroderma is based upon the characteristic clinical manifestations. The provisional criteria for the classification of JSSc may be useful to establish a diagnosis in many children. Biopsy of skin lesions can be considered in cases when the diagnosis is uncertain. No laboratory studies are diagnostic for the disease; however there are a number of autoantibodies that have been associated with juvenile scleroderma. In children with JSSc, autoantibodies have been reported in 81 % of patients. These include ANA, anti-topoisomerase (SCl-70) and anticentromere antibodies [485]. Children with JLS also have positive ANA tests but anti-topoisomerase and anticentromere antibodies are less common [486]. Rheumatoid factor may also be present in 16–17 % of children with JSSc and JLS. Nonspecific acute phase reactants such as ESR and CRP may be also be elevated. Serum immunoglobulin levels, especially IgG may be increased in some children.

Currently there are no guidelines for ongoing diagnostic evaluation of visceral involvement in JSSc. Evaluation of cardiac and pulmonary status with echocardiography and pulmonary function testing should be considered at the time of initial diagnosis for most children [470]. Additional follow-up evaluations should be performed to screen for development of cardiac and or pulmonary disease. MRI of the head and orbits should be considered in children with ECDS or PRS to detect possible CNS or orbital involvement.

Management

There are no current guidelines for the treatment of juvenile scleroderma but therapy should be based upon the specific organ system involvement. In North America, most children with moderate to severe JLS are treated with a combination of methotrexate and systemic corticosteroids [513]. The optimal dosage and duration of this combination has not been established since treatment protocols vary between centers [514–517]. Treatment of children with JSSc is similar to that of adults based upon the specific disease manifestations. Raynaud phenomenon and digital ulcers are typically treated with oral nifedipine or intravenous prostanoids, usually iloprost, if active severe ulceration is present [470, 518]. Methotrexate is recommended for early diffuse skin involvement. Proton pump inhibitors should be used to prevent gastroesophageal reflux, esophageal ulcers and strictures [518]. Rotating antibiotics are recommended for children with malabsorption due to bacterial overgrowth [470]. Endothelin receptor antagonists and phosphodiesterase inhibitors have been recommended for the treatment of pulmonary hypertension including bosentan and sildenafil [518]. Patients with interstitial lung disease are treated with cyclophosphamide with or without low dose corticosteroids [519–521].

Ocular involvement in juvenile scleroderma is rare and at present there are no specific recommendations for the treatment of these conditions. Management should be individualized based upon the specific condition; however a few general principles may be considered for some of these manifestations. Children with KCS are treated with artificial tear preparations and or punctal plugs [497]. Anterior uveitis is typically treated with topical corticosteroids with or without cycloplegics. Periocular or intraocular corticosteroid injections are beneficial in cases of severe uveitis not controlled with topical therapy. Methotrexate may allow reduction or elimination of topical corticosteroids in some patients. Children with symptomatic episcleritis are often treated with artificial tears or mild topical corticosteroids until the symptoms resolve.

Henoch-Schönlein Purpura

Definition

Henoch-Schönlein purpura (HSP) is an acute, self-limited, small vessel leukocytoclastic vasculitis. It is the most common primary vasculitis in children [522]. Characteristic clinical manifestations are palpable purpura, arthritis, colicky abdominal pain, gastrointestinal bleeding and nephritis [523, 524].

The etiology of HSP is unclear although many cases follow an upper respiratory tract infection suggesting infectious agents may be possible triggers. This is further supported by

the seasonal nature of the disease with most cases developing in the winter and spring [525–528]. Group A β-hemolytic streptococcus, *Staphylococcus aureus*, viral infections and *Mycoplasma pneumonia* are the most commonly suspected organisms [529–539]. Several autoimmune disorders may also be risk factors for HSP including complement deficiencies as well as hereditary fever syndromes [540–542].

Since 1990, the ACR criteria for HSP were used to classify children with HSP; however these criteria were developed by analyzing adults with the disease [543]. The most recent proposed EULAR/PRES criteria for HSP are based upon children with vasculitides [544]. The updated criteria requires the presence of purpura or petechiae predominantly affecting the lower extremities plus one of the following manifestations: abdominal pain, arthritis or arthralgias, renal involvement, or histopathology demonstrating immunoglobulin A deposition.

History

In 1802, Heberden first described the disease later termed HSP [545]. Schlönlein in 1837 described the association of purpura, arthritis, and urinary abnormalities [546]. Henoch in 1874 subsequently reported gastrointestinal and renal manifestations of the disease [547].

Epidemiology

Henoch-Schönlein purpura is primarily a disease of childhood and most cases occur in children less than 10 years of age. The mean age at onset of the disease is 7 years with a range of 1–16 years [538, 539, 548]. Boys are more commonly affected with a male to female ratio of 1:5:1 [539, 549]. In children, the estimated annual incidence of HSP is 13.5–20 per 100,000 [522, 549, 550]. The highest reported incidence is among Caucasians while African Americans have the lowest [522].

Systemic Manifestations

The disease onset is acute or subacute with most children presenting with palpable purpura, arthritis and abdominal pain. Low-grade fever and malaise are also common [551]. Some children may have a maculopapular or urticarial rash prior to developing purpura [540]. The purpura may be concentrated in dependent areas such as the lower legs but can also occur on the face and arms. Arthritis occurs in approximately 80 % of children, is typically transient and primarily affects the knees, ankles, and feet [540, 548, 552]. In some children, arthritis may involve the joints of the upper extremities as well. Gastrointestinal involvement occurs in up to 75 % of children. These manifestations typically occur within a week following the onset of the rash although abdominal pain may be the initial manifestation in up to one-third of cases [553–555]. Intermittent colicky abdominal pain, vomiting, hematemesis, and melena are common [548, 556]. Intussusception, pancreatitis, cholecystitis, and bowel perforation may rarely occur [548, 552]. Renal disease occurs in 40–60 % of patients, typically within one to 3 months after onset of the disease [524, 528, 557]. Microscopic hematuria is the most common manifestation although gross hematuria can also occur [538]. Proteinuria is present in over one-half of children with hematuria [558]. Children who develop nephritis are at increased risk for developing hypertension as well as renal impairment [559]. Orchitis has been reported in up to 38 % of boys. Scrotal pain and swelling are also common in HSP [560, 561].

Ophthalmic Manifestations

Ocular manifestations are uncommon in HSP [538, 562]. Episcleritis, scleritis, anterior uveitis, keratitis, and central retinal vein occlusion have been described in children with HSP [548, 562–564]. Cortical blindness has been reported in 5 % of HSP patients with neurologic manifestations [565]. A case of transient conjugate eye deviation associated with cortical blindness has also been described in HSP [566]. Orbital subperiostial hematomas presenting with bilateral exophthalmos and eyelid ecchymoses has been described in a 5-year-old boy [567]. Bilateral central retinal artery occlusion was reported in a 6-year-old girl who subsequently developed cerebral vasculitis [568].

Diagnosis

Diagnosis of HSP is based upon clinical manifestations. Acute phase reactants ESR and CRP may be elevated, especially during the active phase of the disease. Serum IgA and IgM are elevated during the acute phase in approximately one-half of children with HSP [569]. Anemia and leukocytosis may also be present [570]. Platelet counts are normal or elevated [556]. Urinalysis may reveal microscopic hematuria and or proteinuria in patients with renal involvement [570]. Weekly urinalysis is recommended during the active phase of the disease and then monthly for the subsequent 3 months [523].

Conventional radiography is useful in children with gastrointestinal involvement. Abdominal ultrasound or computed tomography may also be useful in children with possible cholecystitis, pancreatitis, or intussusception [523].

Management

Treatment of mild HSP is mainly supportive typically with analgesics and NSAIDs [523, 556]. Corticosteroids are useful for management of gastrointestinal symptoms, arthritis, and renal disease. In severe cases, intravenous corticosteroids are commonly used [530, 540, 571–575]. Patients with acute renal failure or life-threatening manifestations may require plasmapheresis followed by azathioprine, cyclophosphamide, or cyclosporine [540]. Rituximab has been used in a small number of patients with severe disease refractory to traditional immunosuppressive therapies [576].

With few reports describing ocular manifestations in children with HSP, recommendations for the treatment of these disorders is based upon the treatment of children with other rheumatic diseases. Children with episcleritis may require no therapy but symptomatic patients are usually treated with artificial tears or systemic NSAIDs if symptoms are severe [185]. Scleritis often responds to treatment with systemic NSAIDs but short-term systemic corticosteroids may be necessary if NSAIDs are ineffective [336]. Keratitis and anterior uveitis are both treated with topical corticosteroids. Cycloplegics may be considered in children with severe anterior uveitis or those with photophobia.

Granulomatosis with Polyangiitis (Wegener)

Definition

Granulomatosis with polyangiitis (Wegener, GPA) is a chronic necrotizing primary systemic vasculitis involving small and medium sized arteries [577, 578]. The classic triad of inflammation of the upper and lower respiratory tract and glomerulonephritis is characteristic of GPA [579]. Most patients present with upper and lower respiratory tract involvement such as sinusitis, epistaxis, oral and nasal ulcers, otitis media, pulmonary hemorrhage, and pulmonary nodules [578]. Renal involvement occurs in up to three-quarters of children.

In 2010, the term granulomatosis with polyangiitis (Wegener, GPA) was introduced as a replacement for the eponym Wegener granulomatosis [580–582]. This change was based upon recommendations by the American College of Rheumatology, American Society of Nephrology, and European League Against Rheumatism to progressively shift from honorific eponyms to disease-descriptive or etiology-based terminology [581, 582].

There is no single widely accepted classification of childhood GPA. The 1990 American College of Rheumatology (ACR) criteria are based on adult data and therefore may not be ideal for use in children [577, 583, 584]. In 2006, the European League Against Rheumatism and the Pediatric Rheumatology European Society (EULAR/PRES) proposed modified criteria in an effort to improve the classification of GPA in children (Table 20.12) [585]. However, in the cohort described by Cabral, the EULAR/PRES classification did not demonstrate a significant improvement compared with the ACR criteria [586]. At this time, both sets of criteria are used in the classification of children with GPA.

Table 20.12 ACR and EULAR/PRES criteria for childhood onset granulomatosis with polyangiitis (Wegener)

ACR	EULAR/PRES
Diagnosis requires at least two of the four criteria below:	Diagnosis requires at least three of the six criteria below:
Nasal or oral inflammation	Nasal, oral, or sinus inflammation
Abnormal chest radiograph	Abnormal chest radiograph or CT scan
Abnormal urinalysis	Abnormal urinalysis including hematuria and or significant proteinuria
Granulomatous inflammation on biopsy	Granulomatous inflammation or necrotizing pauci-immune glomerulonephritis on biopsy
	Sub-glottic, tracheal, or endobronchial stenosis
	Anti-PR3 ANCA or cANCA staining

Anti-PR3-anti-proteinase 3, *ANCA*-antineutrophil cytoplasmic antibody, *cANCA*-cytoplasmic antineutrophil cytoplasmic antibody
Adapted from Cabral DA, Uribe AG, Benseler S, O'Neil KM, Hashkes PJ, Higgins G, et al. Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. Arthritis and Rheumatism. 2009;60(11):3413–24 [586] with permission from John Wiley & Sons

History

McBride was the first to describe a patient with the midfacial granuloma syndrome in 1896 [587]. In 1931, a medical student, Heintz Klinger first described the disorder ultimately known as GPA [588, 589]. The diffuse systemic form of the disease was described in detail by Wegener in 1936 and 1939 [589–591]. The term Wegener granulomatosis first appeared in the English literature in 1954 [592].

Epidemiology

Childhood GPA is a rare disease but one of the most common primary systemic vasculitides seen in children [586]. The incidence in children ranges from 0.03 to 3.2 per 100,000 children per year [38, 522]. Two single center studies describing forty children with GPA found that females were more commonly affected than males [584, 593]. A larger study of 65 children with GPA from the United States and Canada reported 63 % of patients were females and over two-thirds were Caucasian [586]. Among these children, the median age at diagnosis was 14.2 years (range 4–17 years).

Systemic Manifestations

In children with GPA, multiple organ involvement is common [577]. The most common features at presentation are constitutional symptoms such as fatigue, malaise, fever, and weight loss [586, 594]. Pulmonary and ear, nose and throat involvement occurs in 80 % of children at presentation [578, 586]. Pulmonary manifestations including hemorrhage, nodules, infiltrates, pleurisy, and abnormal pulmonary function studies are relatively common. Upper airway involvement is also common such as sinusitis, nasal septal perforation, saddle nose deformity, otitis, mastoiditis, hearing loss, and subglottic stenosis. Renal involvement occurs in 75–88 % of children at presentation with most having abnormal urinalysis or glomerulonephritis [578, 586]. Up to 24 % of children ultimately develop renal failure requiring dialysis. Arthritis or arthralgias may be present at the time of initial diagnosis or develop later in 20–54 % of children [578, 586]. Petechiae and palpable purpura are also common in childhood GPA.

Ophthalmic Manifestations

Ophthalmic manifestations are common in patients with GPA. Numerous reports have noted that 50–60 % of patients have ophthalmic involvement [595–600]. Most of these studies consist of adults with GPA although a few children are included in some series. Nonetheless, the most common ocular manifestations in these reports are orbital disease and scleritis. Orbital disease may represent focal inflammation or extension of adjacent disease of the paranasal sinuses or nasopharynx [595]. Other common manifestations include episcleritis, interstitial and peripheral ulcerative keratitis, and optic neuropathy [589]. Uveitis is uncommon and retinochoroidal involvement is rare in patients with GPA [601–604].

There are limited reports describing the ophthalmic manifestations of GPA in children. In the cohort described by Akikusa, one-half of the children had ocular manifestations; mostly conjunctivitis [578]. Scleritis, episcleritis, and proptosis were also noted in this group of children. In a larger study of 65 children, 37 % of patients had ocular involvement [586]. Non-specific red eye was most the most common finding followed by conjunctivitis and scleritis. Among six patients from various institutions, ocular findings included proptosis, eyelid edema and erythema, limited extraocular muscle motility, dacryoadenitis, conjunctivitis, scleritis with limbal infiltrates, iritis, and disc edema [605]. Numerous case reports and smaller series have also described proptosis, orbital inflammation, orbital tumor, lacrimal mass, nasolacrimal duct obstruction and motility disturbances [600, 606–610]. Additional manifestations from these reports include conjunctivitis, episcleritis, scleritis, uveitis, papillitis, and vasculitis affecting the retina, choroid and optic nerve [605, 611, 612].

Diagnosis

The diagnosis of childhood GPA is based upon characteristic clinical manifestations, serologic markers, and histopathologic features [577]. Elevated ESR and anemia are common in childhood GPA [578]. Antineutrophil cytoplasmic antibodies are found in up to 90 % of children with GPA. Of these, 86 % have cytoplasmic antineutrophil cytoplasmic antibody (cANCA) and 13 % have perinuclear antineutrophil cytoplasmic antibody (pANCA) [577]. In addition, anti-proteinase-3 (PR-3) is found in 68 % of children [586]. Rheumatoid factors are present in 50 % while antinuclear antibodies are present in up to 36 % of children [586]. Anticardiolipin antibodies or lupus anticoagulants are found in approximately one-half of children. Antiphospholipid antibodies are rarely present but may increase the risk for thrombosis [578].

Urinalysis is frequently abnormal in childhood GPA. Proteinuria, hematuria, and red cell casts are commonly found in patients with glomerulonephritis [599]. Elevated serum creatinine and BUN are present in patients with renal disease.

Abnormal chest radiographs are common in children with GPA. Pulmonary nodules and infiltrates are the most common findings [578, 586]. High resolution CT may be useful for detecting additional pulmonary manifestations. Conventional sinus radiographs of CT are useful to detect sinus inflammation. Magnetic resonance imaging may be more sensitive for demonstrating sinusitis as well as soft tissue changes involving the upper airways [613, 614]. Computed tomography and MRI are useful for evaluation and management of orbital disease [613, 615, 616].

In some children, orbital biopsy may be necessary to exclude other diseases and to guide therapy, however orbital biopsy has a low sensitivity and should not be used to exclude GPA if the classic histopathologic features are not present [600, 617, 618].

Management

With no controlled trials in childhood GPA, most of the treatment recommendations are based on studies of adults with GPA [597, 599]. In a study of 23 children, treatment with cyclophosphamide and corticosteroids achieved remission in 89 % of patients [593]. In a larger cohort of 65 children, 83 % of children were treated with combination cyclophosphamide and corticosteroids but no follow-up data was reported [586]. Methotrexate has also been used as an alternative to cyclophosphamide in children with GPA [578, 619]. The anti-CD20 monoclonal antibody rituximab may also have a role in the treatment of patients with GPA. The RAVE trial compared rituximab with cyclophosphamide for remission induction in adults with ANCA positive GPA or microscopic polyangiitis. The results of this trial demonstrated that rituximab was not inferior to cyclophosphamide and may be

superior in patients with relapsing disease [620]. Treatment options for maintenance therapy in adults include azathioprine, leflunomide, and mycophenolate mofetil [577, 621, 622]. The TNFα antagonist infliximab has also been shown to be effective in adults [623].

Initial therapy of the ophthalmic manifestations of GPA is based upon treatment of the underlying disease. Although isolated ocular disease may be the initial manifestation of GPA, most patients will have multiple organ involvement requiring systemic therapy. Combination therapy with cyclophosphamide and corticosteroids should be considered as initial therapy for most children. Rituximab is an alternative therapy in patients with refractory orbital disease [624–626]. Maintenance therapy is ultimately required and the choice is often dependent upon other systemic manifestations. Adjunctive topical corticosteroid therapy may be needed in children with uveitis or inflammatory keratitis [596].

Dacryocystorhinostomy is recommended for patients with nasolacrimal duct obstruction [627]. Dacryocystectomy may be required in refractory cases [627, 628]. Orbital decompression may be necessary in some patients with optic nerve compression, severe pain or proptosis who do not respond to typical medical therapy [600, 629].

Treatment of retinal vasculitis is combination systemic therapy for the underlying disease. Some patients may benefit from periocular corticosteroids. Panretinal photocoagulation may be necessary if retinal neovascularization develops [593, 630].

Kawasaki Disease

Definition

Kawasaki disease (KD) is an acute febrile illness of childhood typically affecting young children less than 5 years of age. It is the second most common childhood vasculitis; primarily affecting medium-sized arteries. The disease is characterized by fever, rash, conjunctivitis, oropharyngeal changes, extremity changes and lymphadenopathy [540, 631]. Previously termed mucocutaneous lymph node syndrome, KD is the leading cause of acquired heart disease in children from Japan and North America [632, 633].

The cause of KD is unknown but the disease may be associated with an infectious trigger in a genetically predisposed child [631, 634]. This suspicion is based upon the clinical manifestations, epidemiology, and increased risk in certain ethnic groups as well as children with a parent with a history of KD [635–640]. It has been suggested that the vasculitis may be caused by conventional antigens or superantigens that initiate an immune response directed against endothelial cells [641].

Several classification criteria have been developed to aid in the diagnosis of KD [585, 634]. All of these classifications require the presence of fever for at least 5 days with additional manifestations. The American Heart Association criterion categorizes KD as classic/complete, incomplete, or atypical (Table 20.13). However, in some cases there may not be a clear distinction between incomplete and atypical KD [642]. On the other hand the 2006 EULAR/PRES classification has similar criteria but does not use these three categories [585]. At present, there is no consensus as to which classification performs best when categorizing these children.

Table 20.13 American Heart Association criteria for Kawasaki disease [634]

Classic/complete Kawasaki disease
Fever for at least 5 days duration and four or more of the following:
Bilateral nonexudative conjunctivitis
Oropharyngeal changes such as strawberry tongue, erythema of the oropharyngeal mucosa, or erythema/cracking of the lips
Cervical lymphadenopathy
Polymorphous rash
Peripheral extremity changes with erythema/edema of the palms and soles or periungal desquamation
Incomplete Kawasaki disease
Fever for at least 5 days duration with two or three of the above criteria
Atypical Kawasaki disease
Used for patients who meet criteria for KD but have a clinical feature not typically seen with KD

History

Kawasaki disease was first described in the Japanese medical literature in 1967 by Kawasaki and in the American literature by Melish and colleagues in 1977 [643, 644]. In 1974, Kawasaki described bilateral congestion of the ocular conjunctivae as a prominent manifestation of the disease [645]. The first reports of uveitis associated with KD were in 1980 by Germain [646].

Epidemiology

Kawasaki disease is more common in eastern Asia [647]. In 2008, the incidence in Japan was 218.6 per 100,000 children; an increase when compared to previously reported epidemics [648]. In 2006, the estimated incidence of KD in the United States was 20.8 per 100,000 children [649]. In American populations, KD is most common among children with Asian and Pacific Island ancestry. Most patients are less than 5 years of age, but KD occurs most commonly in children from age 6 to 11 months. Cases in children over 5 years of age are much less common [649–651]. It is more common in boys with a male to female ratio of 1.62:1 [648, 649, 652]. Disease recurrence occurs in 3.5 % of children [648].

Systemic Manifestations

Kawasaki disease is characterized by three clinical phases. The acute febrile period typically lasts up to 2 weeks. Resolution of fever signals the beginning of the subacute phase which ends when all of the clinical features resolve. In most children, this phase lasts 2–4 weeks. Following the end of the subacute phase, the convalescent phase begins and can last for months to years. The convalescent phase ends when the platelet count and ESR return to normal [540, 653].

The fever in KD is high, spiking in character, poorly responsive to antipyretics and lasts up to 14 days [540, 653]. Rash, oropharyngeal changes, and conjunctivitis are the most common manifestations during the acute phase. The rash may resemble measles, scarlet fever, or erythema multiforme, although most frequently described as diffuse, erythematous and maculopapular [631, 634]. It may be prominent in the perianal region and desquamation is frequent during the acute phase [654]. Diffuse erythema of the oropharynx is common as well as erythema, fissuring, cracking and bleeding of the lips. A "strawberry tongue" similar to that of scarlet fever may be present.

Edema and or erythema of the hands and feet sometimes with induration, usually occurs during the acute phase. Periungal lifting or detachment of the skin below the nail plate may also develop during the acute phase [631]. Periungal desquamation usually begins during the second week of the illness.

Some children may have cervical adenopathy; typically unilateral with nodes exceeding 1.5 cm in diameter. Fever and cervical adenopathy may be the initial manifestations of KD in a small number of children and may be confused with a bacterial infection [655].

Additional manifestations that are not included in the diagnostic criteria may also occur. Severe irritability is a common finding in children. This is probably due to aseptic meningitis Oligoarticular and polyarticular arthritis as well as arthralgias are present in up to 8 % of children [656]. Abdominal pain, vomiting, and diarrhea are also common. Cholecystitis or gallbladder hydrops can be seen. Upper respiratory symptoms occur in approximately one-third of children [657]. Urethritis and meatitis are also common findings and may be associated with white blood cells in the urine [631, 653].

Cardiac manifestations may develop during the acute phase. Myocarditis may occur in up to one-half of children [658]. Pericarditis may also develop in children with KD. Coronary artery aneurysms develop in up to 25 % of children without treatment and are a leading cause of morbidity and mortality [659]. Treatment with intravenous immune globulin (IVIG) markedly decreases the risk for developing coronary aneurysms [634, 660]. Although less common, peripheral arterial complications may also occur [631].

Ophthalmic Manifestations

Ocular manifestations are common in children with KD. Bilateral bulbar conjunctivitis (Fig. 20.14) is the most common manifestation with almost all children affected during the acute phase of the disease [661–663]. Onset usually occurs within a day or two after the onset of fever and may last for several months [664]. The conjunctivitis primarily involves the bulbar conjunctiva; frequently with sparing of the limbus [644, 645, 665]. Chemosis and purulent discharge are not characteristic features. However, palpebral conjunctival scarring has been rarely reported [666].

Anterior uveitis is seen in over 75 % of cases of KD [662, 665]. These children may complain of photophobia; especially during the first week of the illness. Similar to the conjunctivitis, most cases are bilateral. Anterior chamber cells and flare as well as keratic precipitates are common. The uveitis is usually mild and resolves with the other manifestations of disease without sequelae or recurrence [646, 661, 667, 668]. Complications of uveitis such as posterior synechiae, cataract and glaucoma have not been reported [661]. Significant correlation has been reported between uveitis and the ESR and CRP [662].

Less common manifestations include superficial punctate keratitis, vitreous opacities, optic disc swelling, and subconjunctival hemorrhage [662, 669]. In addition, isolated cases of disciform keratitis and periorbital vasculitis have been reported [670, 671]. A single child has been reported with choroidal, retinal and vitreous changes resulting in severe visual impairment [661]. In addition, postmortem findings in a child with KD noted multiple areas of thrombotic occlusion of ophthalmic artery branches due to vasculitis resulting in bilateral retinal ischemia [672].

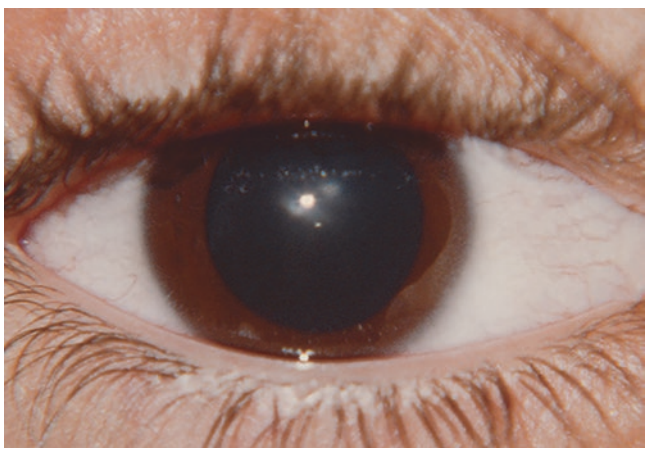

Fig. 20.14 Bulbar conjunctivitis in Kawaski disease (Reprinted from Levin AV and Wilson TW. Hospital for Sick Children's Atlas of Pediatric Ophthalmology and Strabismus. Philadelphia: Lippincott Williams and Wilkins; 2007. With permission from Lippincott Williams and Wilkins/Wolters Kluwer)

Diagnosis

The diagnosis of KD is based upon clinical manifestations. Initial laboratory evaluation should include baseline complete blood count with differential, platelet count, ESR, and CRP. In addition, serum electrolytes, BUN, creatinine, serum transaminases, serum albumin, bilirubin and urinalysis are obtained. During the acute phase of the disease, increased ESR, CRP and white blood cell count are common. Anemia and thrombocytosis may be seen, especially following the acute phase. Elevated serum transaminase levels and decreased albumin are also common [631, 634].

Initial evaluation of children with KD or suspected KD should also include a baseline electrocardiogram and echocardiogram [631]. A repeat echocardiogram should be performed after 6–8 weeks.

Management

Based upon recommendations by the American Heart Association, all children with suspected KD should be treated within the first 7–10 days of the disease with IVIG and high dose aspirin (80–100 mg/kg daily) [634]. Some clinicians reduce the aspirin dosage after the child is afebrile for at least 48 h while others continue the original dose of aspirin through day 14 of the illness and at least 48 h following resolution of the fever. Low dose aspirin (3 to 5 mg/kg per day) is typically continued until there is no evidence of coronary changes 6–8 weeks after disease onset [634]. Up to 38 % of children have persistent or recurrent fever after treatment with IVIG. These children are at increased risk for development of coronary artery aneurysms and should be retreated with IVIG [634]. Less than 5 % of children fail to respond to two courses of IVIG and these patients are typically treated with intravenous methylprednisolone. Infliximab has also been shown to be effective in treating KD unresponsive to IVIG [673–675].

Children with coronary artery abnormalities are usually treated with antithrombotic agents until the lesions resolve. Anticoagulation with warfarin is necessary for children with large aneurysms. Thrombolytic agents may also be used in patients with coronary or peripheral arterial obstructions [634].

Most of the ocular manifestations of KD are self-limited and resolve as the underlying disease improves [667]. Thus, specific treatment of these conditions is not required in most children. Children with symptomatic conjunctivitis may be treated with artificial tear preparations or topical corticosteroids in cases with significant symptoms. The treatment of anterior uveitis consists of short-term topical corticosteroids in most cases.

Polyarteritis Nodosa

Definition

Polyarteritis nodosa (PAN) is a necrotizing vasculitis affecting medium and small arteries. It is the third most common vasculitis in children although it is very uncommon in this age group [540]. Characteristic manifestations are fever, weight loss, livedo reticularis, painful cutaneous nodules or ulcers, myalgias, leukocytosis and elevated ESR [676].

Polyarteritis nodosa is characterized by focal necrosis of the walls of small and medium-sized arteries [677]. The etiology of PAN is unknown although association with hepatitis B or other viruses including parvovirus B19 and cytomegalovirus has been described. These associations are much less common in children with PAN [678]. Isolated cases of PAN associated with familial Mediterranean fever have also been described [679–681]. In some cases, superantigens may be involved in the pathogenesis of PAN [682].

The diagnosis of PAN is often difficult and several classification criteria have been proposed for children. The most recent EULAR/PRES classification for childhood PAN has been validated in children with vasculitis (Table 20.14) [544]. In this classification, histopathologic confirmation of necrotizing vasculitis involving medium or small arteries or angiographic demonstration of aneurysm, stenosis, or occlusion of these arteries is required plus one other criterion to establish the diagnosis of PAN.

History

Polyarteritis nodosa was originally described in 1866 by Kussmaul and Maier [683]. Although the original designation was periarteritis nodosa, descriptions of involvement of the entire wall of the vessel led to widespread use of the preferred term polyarteritis nodosa.

Table 20.14 EULAR/PRES classification criteria for childhood polyarteritis nodosa [544]

Criteria	Description
Histopathology or angiographic abnormalities	Histopathology demonstrating necrotizing vasculitis in medium/small arteries.
	Angiography showing aneurysms, stenosis, or occlusion of medium/small arteries
Plus one of the following:	
Skin manifestations	Livedo reticularis, tender skin nodules, superficial skin infarctions or deep skin infarctions
Myalgias/muscle tenderness	
Hypertension	
Peripheral neuropathy	
Renal involvement	

Epidemiology

There are no reports describing the epidemiology of childhood PAN while the incidence in adults from Europe and the United States is estimated to be 2.0–9.0/1,000,000 per year [684]. In children, the disease typically develops between 7–11 years of age with a mean age of 9 years [676, 684]. Some authors describe a greater frequency of boys with PAN, similar to adults, while others report a similar incidence among boys and girls [676, 677, 685, 686].

Systemic Features

The clinical manifestations of PAN are diverse and vary depending on the regions of vascular involvement. The skin, musculoskeletal system, kidneys, and gastrointestinal system are most commonly affected [678]. Neurologic, pulmonary, and cardiac involvement occurs less commonly [676, 684, 687, 688].

The key features of PAN are fever, malaise, weight loss, abdominal pain, rash, myalgia, and arthropathy [677, 684, 685, 688–692]. Skin lesions are highly variable and may appear similar to those in HSP. Livedo reticularis is a characteristic finding in children with PAN. Tender subcutaneous nodules may be present overlying the affected arteries. Myalgias and arthropathy are seen in approximately one-third of children [676]. Neurologic manifestations include hemiplegia, focal defects, mononeuritis multiplex, and psychosis [693, 694]. Children with renal involvement may have proteinuria, hematuria, and hypertension [688, 695, 696]. Testicular pain has also been described in boys with PAN. Peritoneal hemorrhage may result from rupture of arterial aneurysms [697]. Pulmonary symptoms such as asthma, rhinitis, or pulmonary infiltrates are uncommon [677].

Common manifestations in infants are transient prolonged fever, macular exanthum, cardiomegaly, congestive heart failure, electrocardiogram changes and an abnormal urinalysis [698]. Hypertension and gangrene of the extremities is not uncommon in infants with PAN [698, 699]. Coronary arteritis has been noted in 90 % of all fatal cases of infantile PAN at autopsy.

Ophthalmic Manifestations

Ophthalmic manifestations occur in up to 20 % of patients with PAN [700, 701]. Most studies describing ocular findings consist of adults with PAN. In these reports, manifestations include episcleritis, scleritis, interstitial keratitis, peripheral ulcerative keratitis, anterior uveitis, retinal vasculitis, cotton-wool spots, retinal exudates and hemorrhages, retinal edema, serous retinal detachment, retinal arterial occlusion and papilledema or papillitis [700–702]. The retinal findings can occur with or without hypertension [703]. Exophthalmos may also occur due to inflammation of the orbital vasculature [700]. Extraocular muscle palsies, amaurosis, nystagmus, and visual field defects have also been reported [700, 704]. Central retinal vein occlusion has been described in a single patient with marked thrombocytosis [705]. Approximately one-half of infants with PAN have transient conjunctivitis [698].

Diagnosis

The EULAR/PRES criteria for childhood PAN requires histopathologic evidence of necrotizing vasculitis or angiography demonstrating aneurysm, stenosis, or occlusion of medium or small arteries [544]. Additional clinical manifestations are necessary to establish the diagnosis. The acute phase reactants including ESR and CRP are frequently elevated. In addition, leukocytosis, thrombocytosis, and mild anemia are relatively common [678]. Children with renal involvement may have proteinuria, hematuria, and decreased glomerular filtration rate. Conventional angiography remains the best vascular imaging technique however magnetic resonance angiography may be useful in selected cases [678]. Fluorescein angiography is used for patients with suspected retinal vasculitis.

Management

There are no widely accepted recommendations for the treatment of childhood PAN. In general, treatment is based on the severity of the disease. Patients with mild PAN may be treated with corticosteroids while those with more severe disease are typically treated with cyclophosphamide and corticosteroids to induce a remission [540, 684, 706, 707]. Plasmapheresis has been used in cases of organ or life-threatening disease [540]. Maintenance therapy for most children is a traditional immunosuppressive agent such as azathioprine, methotrexate, mycophenolate mofetil, or IVIG. Biologic agents may be considered for children who fail to respond to these traditional therapies [708].

Systemic corticosteroids with or without immunosuppressive agents are typically required for the treatment of the ocular manifestations of PAN. With few reports describing ocular manifestations in children, recommendations regarding additional therapy are based upon experience in adults with PAN. Children with anterior uveitis and interstitial keratitis may benefit from topical corticosteroids. Cycloplegics are useful for children with photophobia or severe uveitis. Periocular corticosteroids may be considered in children with severe uveitis or retinal vasculitis. Patients with retinal vein occlusion should be monitored closely for the development of macular edema and secondary glaucoma.

Takayasu Arteritis

Definition

Takayasu arteritis (TA) is a rare, relapsing vasculitis of unknown etiology affecting large arteries, particularly the aorta, its main branches and the pulmonary arteries. Any portion of the aorta may be involved although the renal, subclavian and carotid arteries are most commonly affected in children [709]. Early reports suggested that TA was primarily a disease of East Asian females, although it is now evident that the disease occurs throughout the world and affects both males and females [710]. The clinical manifestations of TA vary depending on the specific arteries involved. Fatigue, fever, weight loss, hypertension, arthritis/arthralgias, abdominal pain and ischemic strokes are common [577].

Criteria for the classification of childhood TA were developed by the EULAR/PRES [544]. The diagnosis of TA in children requires angiographic evidence of aneurysm/dilation of the aorta or it branches plus at least one of the following: decreased peripheral pulses or claudication, blood pressure discrepancy of greater than 10 mm Hg in any extremity, bruits of large arteries, hypertension, or elevated acute phase reactants. Unfortunately, the diagnosis of TA is often delayed by months to years in many children [711–714].

The disease is characterized by granulomatous periarteritis with adventitial thickening, leukocyte infiltration of the tunica media, as well as intimal hyperplasia [713, 715]. Fibrosis of the media and intima ultimately leads to fixed stenosis or arterial occlusion [716]. Most patients have stenotic lesions while aneurysms occur in up to 25 % of cases [714, 717–721]. The etiology of TA is unknown but exposure to *Mycobacterium tuberculosis* may be associated with the development of TA [722–724].

Epidemiology

There are currently no studies describing the incidence of TA in children. However, 20–30 % of patients with TA may be less than 20 years of age [725–728]. The median age in studies including only children was 8–14 years [729]. The youngest patient reported was 2.4 years old [730]. The incidence in adults ranges from 0.8–2.9 per 1,000,000 per year [728, 729, 731, 732]. Females are more commonly affected with a female to male ratio of 1.2:1 to 6.9:1 [731, 733, 734].

History

The first description of pulseless disease was in 1908 by the Japanese ophthalmologist Takayasu [735, 736]. He noted ocular changes in a 21 year old woman which consisted of a peculiar capillary flush in the ocular fundi, wreath-like arteriovenous anastomosis around the optic disk, and blindness due to cataracts. The first report of corticosteroid therapy in Takayasu arteritis was in 1954 by Ask-Upmark [737].

Systemic Manifestations

In children, the onset of TA is characterized by headache, fever, anorexia, weight loss, abdominal pain, arthralgias, myalgias, and hypertension [709, 730, 738–740]. Hypertension is the most common presenting symptom in children [741]. Without treatment, additional manifestations develop as a result of reduced blood supply to affected areas [741]. Diminished or absent pulses and claudication are characteristic in involved areas [738–740]. Cardiac involvement such as cardiomyopathy, congestive heart failure, as well as valvular disease is relatively common affecting approximately 20 % of children with TA [540, 741]. Neurologic manifestations are also common including headache in approximately one-third of children as well as dizziness, seizures and ischemic stroke [540, 738]. Abdominal pain, hypertension, and claudication of the lower extremities are common manifestations of mid-aorta involvement [540].

Ophthalmic Manifestations

Ocular manifestations have been reported in up to 68 % of patients with TA and may be the reason the patient initially seeks medical attention [742–744]. Many of the ocular manifestations are the result of occlusion or stenosis of the carotid arteries. The most notable findings are retinal manifestations such as venous dilation, arteriovenous anastomoses, microaneurysms, retinal hemorrhages, cotton-wool spots, capillary non-perfusion, retinal neovascularization, vitreous hemorrhage, macular edema, and tractional retinal detachment [742, 745, 746]. Uyama and Asayama established the classification of TA retinopathy to categorize these retinal manifestations [747]. The four stages are: Stage1—dilation of small vessels, Stage 2—microaneursym formation, Stage 3—arteriovenous anastomosis, and Stage 4—further ocular complications such as cataract, iris neovascularization, and retinal neovascularization. Patients with retinopathy also exhibit delayed arm-to-retina circulation time [746]. Delayed arteriovenous filling is often noted in cases of moderate to severe retinopathy.

Anterior segment abnormalities can also occur including conjunctival and episcleral vascular dilation, uveitis, iris neovascularization, glaucoma and cataract [730, 748–750]. Additional common manifestations include ischemic optic neuropathy, amaurosis fugax, ocular ischemic syndrome, central retinal artery occlusion [751]. Uncommon manifestations are enophthalmos, mydriasis, iris atrophy, corneal involvement with Krukenberg's spindles and pigmented

deposits in Descemet's membrane, unequal pupils, paralysis of accommodation, optic atrophy, obliteration of the peripheral retinal arterioles, exudative retinal detachment and occlusion of the central retinal artery [742, 752].

Diagnosis

Vascular imaging is essential to the diagnosis and monitoring of children with TA [753, 754]. In most cases, initial diagnosis requires angiographic demonstration of abnormalities of the aorta and its main branches. Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) is used to monitor the activity of the vasculitis.

Laboratory testing often reveals an increased ESR, CRP, white blood cell count, and platelet count. Anemia may present in some children. Other laboratory abnormalities include elevated levels of C3 complement and von-Willebrand-Factor antigen [709, 729, 731, 732, 755–757].

Management

Management of children with TA is challenging. Active vasculitis is typically treated with combination corticosteroids and immunosuppressive therapy. For induction, children are often treated with corticosteroids and methotrexate or cyclophosphamide depending on the extent of the disease [758]. After remission occurs, most children receive methotrexate as maintenance therapy. TNFα antagonists have also been used to induce remission in a small number of children [759]. Despite treatment, up to one-quarter of children do not achieve remission [760]. TNFα antagonists may be useful in these patients based upon limited early reports [761]. Recent studies have shown tocilizumab may be an effective initial treatment for TA as well as cases resistant to TNFα antagonists [762–764]. Anticoagulation is also required to reduce the risk of stroke. Endovascular revascularization procedures may be considered in children with inactive TA. Percutaneous transluminal angioplasty (PCTA) is the most common procedure used in patients with stenosis with reported success rates up to 80 % [714, 741]. Endovascular revascularization procedures may provide temporary benefit; however high failure rates are common [765–767].

Management of the ocular manifestations of TA is based on increasing the perfusion to the central retinal artery. Surgical procedures to relieve stenosis or occlusion of the carotid arteries may allow increased blood flow to the retinal circulation and likely prevent secondary complications such as neovascular glaucoma, retinal neovascularization, and vitreous hemorrhage [746]. Patients with retinal ischemia and or vitreous hemorrhage may benefit from panretinal photocoagulation. Treatment of neovascular glaucoma includes panretinal photocoagulation, topical glaucoma therapy, and in most cases drainage tube implants to control the intraocular pressure. Intravitreal anti-vascular endothelial growth factor therapy may also have a role in the initial management of neovascular glaucoma [768–770]. There are no current recommendations concerning the management of cataracts in children with TA but a single report described a 14-year-old child who developed phthisis following cataract surgery [752].

Behçet Disease

Definition

Behçet disease (BD) is a chronic relapsing multisystem vasculitis characterized by recurrent aphthous oral ulcers, genital ulcers, skin lesions and ocular lesions [771]. Neurologic, gastrointestinal, vascular and articular manifestations may also occur but are less common. Many of the clinical manifestations of BD are likely due to vasculitis. The disease is most common in the Middle East, Mediterranean basin and the Far East. It is much less common in northern Europe, the United Kingdom, and the United States [771, 772].

The etiology of BD is unknown although microbial infection may serve as a trigger in genetically susceptible patients [771]. Several viruses and bacteria have been implicated in the pathogenesis but none have been proven to cause the disease [773]. However, ubiquitous antigens from microorganisms such as heat shock proteins may activate innate and adaptive immune responses in predisposed patients [771, 774]. Neutrophil hyperactivation is a major feature of the immune response in BD [775, 776]. Patients with the HLA-B51 allele who are from regions where BD is highly prevalent are at higher risk of developing the disease [777].

Several diagnostic criteria for BD have been proposed but none are universally accepted or specific for children [778]. Currently, the International Study Group (ISG) criteria are the most frequently used (Table 20.15) [779]. Recurrent oral ulceration must be present with at least two other criteria for diagnosis of the complete form of the disease. Incomplete or partial BD is the term used in patients with oral ulceration and only one additional criterion.

History

Behçet disease may have been described in the writings of Hippocrates in ancient times [780]. In 1930, the Greek ophthalmologist, Benediktos Adamantiades presented in a lecture a case of recurrent iritis with hypopyon in a 20 year-old

Table 20.15 International Study Group criteria for diagnosis of Behçet disease [779]

Criterion	Description
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration; occurring at least three times over a 12 month period
Plus any two of the following criteria:	
Recurrent genital ulceration	Genital aphthous ulceration or scarring
Ocular lesions	Anterior uveitis, posterior uveitis, vitreous cells, or retinal vasculitis
Skin lesions	Erythema nodosum-like lesions, pseudo-folliculitis, papulopustular lesions, or acneform nodules observed by a physician in post-adolescent patients not receiving corticosteroids
Positive pathergy test	Observed after 24–48 h by a physician

Reprinted from Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990;335(8697):1078–80 [779] with permission from BJM Publishing Group

man resulting in bilateral blindness [781, 782]. The patient later developed arthritis with recurrent genital and oral aphthous ulcers and Adamantiades proposed these manifestations represent a single disease. Several years later, the Turkish dermatologist, Hulusi Behçet, described a female with recurrent oral aphthous ulcers, genital ulcers, and ocular lesions [783]. Jensen was the first to use the term "Behçet's syndrome" in 1941 although he was not aware of Adamantiades previous reports [783–785].

Epidemiology

Behçet disease typically occurs in adults 20–40 years of age. Childhood onset BD is much less common although few studies have described the epidemiology in children. Furthermore, estimates of incidence and prevalence of childhood BD is complicated by the lack of established diagnostic criteria for children. Among existing reports, 3–24 % of patients with BD developed symptoms prior to the age of 16 years [786–789]. A study of 55 children in France found a mean age of onset of 7.5 years. The mean age when these children met the criteria for BD was 11.6 years [790]. Most cases of childhood BD are diagnosed between 10 and 15 years of age [791, 792]. In some patients, symptoms may develop during early childhood with subsequent delays in diagnosis ranging up to years [793]. Familial aggregation has been reported in up to 10 % of children with BD [794–797]. In most studies of children, males and females are equally affected [792, 794].

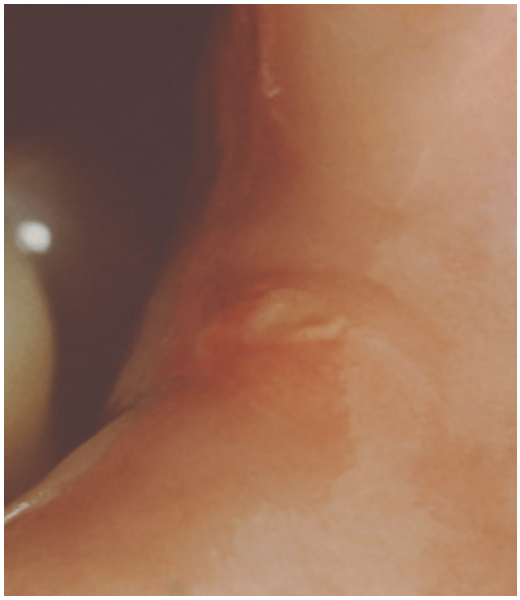

Fig. 20.15 Oral mucosal aphthous ulcer in a patient with Behçet disease

Systemic Manifestations

The systemic manifestations of BD are similar in children and adults with a few exceptions. Recurrent oral ulcers are the most common manifestation in children and adults with BD (Fig. 20.15). Crops of painful ulcers are typical and virtually indistinguishable from common canker sores [798]. The most commonly affected areas are the mucous membranes of the lips, gingiva, buccal mucosa and tongue; while the palate, tonsils, and pharynx are rarely involved [799]. The lesions typically heal within 2 weeks without scarring [771]. Recurrent painful genital ulcers are less common among children but increase with age [793]. Lesions may develop on the scrotum as well as the glans penis, prepuce, vulva, vagina, and perianal area [800].

Skin involvement occurs in over 90 % of children [792]. Erythema nodosum, folliculitis, papulopustular lesions, and purpura have been reported typically on the face, neck, breast and back [788, 799, 801]. The "pathergy" phenomenon may be seen in up to 70 % of patients although it is not specific for BD. This reaction is characterized by development of a pustular reaction within 1–2 days following minor trauma to the skin. The pathergy test utilizes a sterile 20 gauge needle to induce trauma and is read 24–48 h later. Arthritis is also common in children with BD. Most children have oligoarticular or polyarticular disease affecting the knees, ankles, wrist, and elbows [792, 794, 801].

Gastrointestinal involvement also occurs in children. Up to 40 % of children may develop gastrointestinal involvement although the frequency varies widely among different series [788, 793, 802, 803]. Colicky abdominal pain and

diarrhea, sometimes bloody, are the most common manifestations [793, 803, 804]. Central nervous system involvement has been reported in up to 25 % of children with BD [792, 793, 805]. This is the most serious manifestation in children with BD and can result in death. Manifestations include meningoencephalitis, encephalomyelitis, benign intracranial hypertension (pseudotumor cerebri), and psychiatric disorders [806, 807]. Vascular involvement is rare in children but can result in significant morbidity. Superficial or deep venous thrombosis, vena cava thrombosis, and aneurysms have been described [792, 793].

Ophthalmic Manifestations

Ocular involvement occurs in up to 80 % of children with BD [793, 808, 809]. In most patients, ocular involvement develops within 4 years following onset of the disease [810]. Ophthalmic manifestations are more common in older children with BD although children as young as 6 months may develop ocular lesions [811]. Panuveitis is the most common ocular manifestation in children followed by posterior uveitis, isolated anterior uveitis and intermediate uveitis [792, 809, 812–814]. In most series, uveitis is more common in boys [792, 813, 814]. Bilateral involvement is typical occurring in up to 80 % of children [815]. The uveitis tends to be recurrent with hyperacute onset. Recurrent anterior uveitis may present with a hypopyon in some cases [816, 817]. Multiple ocular attacks involving the posterior segment of the eye results in severe visual impairment, whereas attacks of the anterior segment alone generally do not result in visual loss [818].

Other common ophthalmic manifestations in children are retinal vasculitis, retinal infiltrates, and optic neuropathy (Fig. 20.16) [793, 817]. Neuro-ophthalmologic manifestations of BD include nystagmus, diplopia, ptosis, facial nerve palsy, retrobulbar neuritis, and papilledema [799, 800, 815]. Less common findings include scleritis, corneal ulceration, retinal vascular occlusion, retinal and or optic disc neovascularization and retinal detachment (Fig. 20.17) [800].

Complications develop as a result of the recurrent attacks of inflammation or the use of corticosteroids. Common complications in children with BD are cataracts, posterior synechiae, glaucoma, epiretinal membrane, and macular edema [810, 812, 817]. Patients with end-stage disease may have marked visual impairment, optic atrophy, retinal vascular attenuation, diffuse retinal atrophy and phthisis (Fig. 20.17) [810, 812].

Diagnosis

The diagnosis of BD is based on the clinical manifestations outlined in the ISG criteria. During active disease, acute phase reactants are elevated. Patients with active disease and vasculitis may have elevated von Willebrand factor and decreased thrombomodulin levels [800]. Angiography and MRI are useful for evaluation of CNS lesions. Fluorescein angiography is often used to evaluate changes in the retina and retinal vasculature.

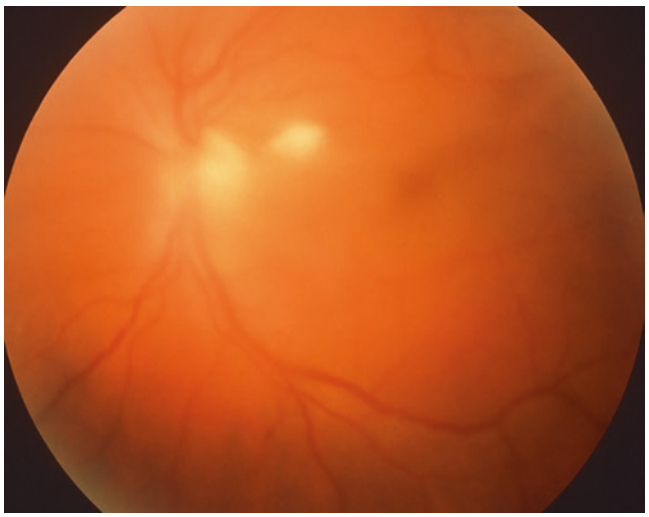

Fig. 20.16 Recurrent panuveitis in Behçet disease. A single retinal infiltrate is present near the optic disc

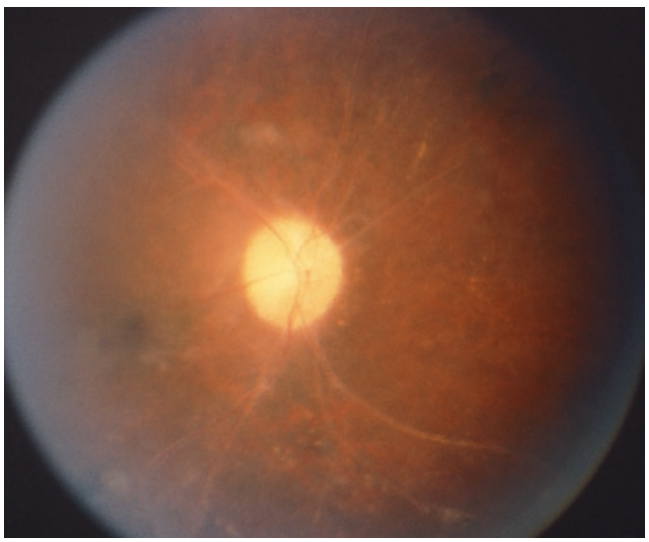

Fig. 20.17 End-stage Behçet disease following multiple recurrences with optic atrophy, sheathed and attenuated retinal vessels, and retinal atrophy

Management

The European League Against Rheumatism have published recommendations for the management of BD [819]. Treatment of skin and mucosal involvement is based upon severity. Topical corticosteroids are typically used as initial

therapy for oral and genital ulcers. Colchicine is recommended for patients with erythema nodosum. Persistent cases may be treated with azathioprine, IFNα, or TNFα antagonists [810]. Gastrointestinal involvement may be treated with several agents including sulfasalazine, corticosteroids, azathioprine, TNFα antagonists, or thalidomide [819, 820]. Arthritis is usually managed with colchicine. Treatment of neurologic manifestations is based upon limited reports and clinical experience. For patients with parenchymal disease, treatment options are corticosteroids, IFNα, azathioprine, cyclophosphamide, methotrexate, and TNFα antagonists. Corticosteroids are recommended for dural sinus thrombosis. Treatment options for patients with deep vein thrombosis include corticosteroids, azathioprine, or cyclophosphamide. Pulmonary or peripheral artery aneurysms are treated with cyclophosphamide and corticosteroids [819].

Treatment of the ocular manifestations of BD is based upon the location of the inflammation. Initial treatment of anterior uveitis is typically topical corticosteroids with or without cycloplegics to prevent posterior synechiae formation [336, 811, 816]. Severe episodes of anterior uveitis may require treatment with periocular or systemic corticosteroids. Immunosuppressive agents may be necessary in cases of recalcitrant anterior uveitis or as a steroid sparing therapy [810, 816, 821].

Initial therapy for patients with panuveitis, posterior uveitis, or retinal vasculitis is azathioprine and systemic corticosteroids [819]. Other immunosuppressive agents have also been used including cyclosporine, cyclophosphamide, chlorambucil, and methotrexate [816]. Despite the use of immunosuppressive agents, some patients experience relapses of uveitis. Therapeutic options in this group of patients are limited but treatment with IFNα-2a has shown promising early results [822–825]. However, the optimal dose and duration of IFNα-2a has not been established. Another option in patients who fail traditional immunosuppressive therapy is the TNFα antagonist infliximab. Numerous reports have described improvement of refractory posterior segment inflammation with infliximab therapy [117, 826–831]. In addition, infliximab has a more rapid onset compared to traditional immunosuppressive agents and may prevent irreversible retinal damage [832].

Relapsing Polychondritis

Definition

Relapsing polychondritis is a multisystem disease characterized by episodic and progressive inflammation and destruction of cartilaginous tissues, especially auricular, nasal, laryngotracheal and peripheral joint cartilage [833, 834]. Ocular, cutaneous, cardiovascular, and renal involvement may also occur [835]. Up to 37% of patients have an associated connective tissue disease, vasculitis, or other autoimmune disease [833]. Relapsing polychondritis is very rare in children and delays in diagnosis are common. Unlike adults, a family history of autoimmunity is not uncommon in children [836].

Table 20.16 Criteria for the diagnosis of relapsing polychondritis [834]

Recurrent, bilateral auricular chondritis
Nonerosive, seronegative inflammatory polyarthritis
Nasal chondritis
Ocular inflammation
Conjunctivitis, keratitis, scleritis, episcleritis, or uveitis
Respiratory tract chondritis
Cochlear and/or vestibular dysfunction
Neurosensory hearing loss, tinnitus, and/or vertigo

The etiology of relapsing polychondritis is unknown. It is likely an autoimmune mediated disease with a possible genetic predisposition [837, 838]. This hypothesis is based upon the increased association of other autoimmune diseases, history of familial autoimmunity, presence of antibodies to several collagens, and increased frequency of HLA-DR4 in some patients with relapsing polychondritis [834, 839].

Diagnostic criteria for relapsing polychondritis were proposed by McAdam in 1976 (Table 20.16). These criteria were subsequently revised and represent the most widely used classification [840, 841]. Using these modified criteria, diagnosis requires at least three of the original McAdam's criteria, or at least one of these criteria with positive histopathology from a cartilage biopsy, or the presence of chondritis in at least two different locations with response to treatment with corticosteroids and or dapsone.

History

The first recognizable case of relapsing polychondritis was reported by Jaksch-Wartenhorst in 1923 [842]. Little attention was given to relapsing polychondritis until 1960 when Pearson and colleagues reported four additional patients and suggested the name relapsing polychondritis [843]. The first case presenting with ocular manifestations was described by Rucker and Ferguson in 1965 [844].

Epidemiology

Relapsing polychondritis is a very rare disease in children and thus there are no epidemiologic studies in this population. Most reports describing children are small case series or single case reports. Nevertheless, it has been estimated that children with relapsing polychondritis represent less

than 5 % of all patients with the disease [836]. The onset of disease is typically between 40 and 60 years of age. The disease predominantly affects Caucasians but all races can be affected [835, 841]. In addition, there is no gender predilection in patients with relapsing polychondritis. Mortality in relapsing polychondritis appears to be related to age at onset. The death rate in patients less than 50 years with severe disease ranges from 28–50 % [840, 845]. Trentham and Le reported a 94 % survival in their series of 66 patients followed for a mean of 8 years [846]. Mortality primarily results from airway collapse, pneumonia, aneurysmal rupture, vasculitis or valvular heart disease.

Systemic Manifestations

The most common presenting manifestation of patients with relapsing polychondritis is relapsing-remitting pain, redness and swelling of one or both ears with sparing of the lobule [835, 847]. Inflammation of the external auditory canal can lead to narrowing and conductive hearing loss. Attacks often vary in severity and typically last days to weeks before resolving spontaneously.

Arthritis and arthralgias are the second most common presenting feature affecting up to 80 % of patients [847]. Oligoarthritis or polyarthritis affects the large and small peripheral joints and is typically episodic, asymmetric, and migratory [848].

Painful nasal chondritis affecting the distal portion of the septum is common. Recurrent episodes with resultant cartilage destruction may lead to the classic saddle nose appearance. Laryngotracheal and bronchial involvement occurs in over one-half of patients. The clinical manifestations vary by severity and extent of airway involvement. Common symptoms are hoarseness, cough, wheezing, or shortness of breath [835]. Laryngeal stricture has been reported in children with relapsing polychondritis.

Renal involvement occurs in up to 23 % of patients [849]. Urinalysis may reveal hematuria and or proteinuria. Neurologic manifestations may also occur in patient with relapsing polychondritis. The most common manifestations are cranial neuropathies; primarily affecting the second sixth, seventh, and eighth nerves [850]. Aortic and or mitral valvular disease affects up to 10 % of patients. Additional cardiac manifestations include aortic aneurysm, atrioventricular conduction disturbances, pericarditis, and myocardial infarction [851].

Ophthalmic Manifestations

Ophthalmic manifestations have been described as the initial feature in up to 18 % of patients with relapsing polychondritis [852]. Ocular symptoms occur in up to 70 % of patients at some time during the course of the disease [853]. The frequency of ocular manifestations in children is probably similar to that seen in adults [854]. Ocular involvement like other disease manifestations is often episodic. The most common ophthalmic manifestations are scleritis, episcleritis, uveitis, and peripheral keratitis [833, 847, 853, 855]. Additional manifestations include proptosis, extraocular muscle palsy, KCS, and ischemic optic neuropathy [844, 856, 857]. Although rare, peripheral corneal thinning, central corneal ulceration, cotton-wool spots, chorioretinitis, panophthalmitis, exudative retinal detachment and retinal vein occlusion have also been reported [840, 853, 858–861]. Cataracts may also occur and are associated with uveitis and or corticosteroid treatment. Additional ocular complications include scleromalacia perforans, corneal ulceration and visual impairment.

Diagnosis

The diagnosis of relapsing polychondritis is typically made based on characteristic clinical manifestations [834]. No laboratory findings are specific for relapsing polychondritis but during disease exacerbations, elevated ESR and CRP are common as well as leukocytosis and thrombocytosis. Anemia of chronic disease is also a common finding. Up to 60 % of patients have antinuclear antibodies [839]. Autoantibodies to several types of collagen and other cartilage proteins have also been found in patients with relapsing polychondritis [834]. Specific organ involvement should be evaluated in all patients. Chest radiography, CT, MRI and pulmonary function studies are typically utilized in patients with pulmonary involvement. Baseline electrocardiogram and echocardiography is also recommended.

Management

Most treatment recommendations are based upon small case series and clinical experience. Patients with less severe manifestations such as auricular or nasal chondritis and arthritis may be managed with NSAIDs only [839, 840, 847]. Treatment options for patients who fail to respond to NSAID therapy include dapsone or corticosteroids [840, 862, 863].

Patients with laryngotracheal, bronchial, cardiovascular, renal, ocular or neurologic manifestations should be treated aggressively. The goal of initial therapy is to achieve a rapid clinical response. Corticosteroids are the mainstay of initial therapy in these patients. Early studies noted that up to 30 % of patients will require chronic low-dose ($\leq$10 mg per day) corticosteroids [841]. Immunomodulatory therapy is often used as an adjunct to corticosteroids or as a steroid sparing therapy. Cyclophosphamide is the preferred agent based upon its success in the treatment of other systemic vasculitides

[849, 864]. Alternative immunosuppressive agents include methotrexate, azathioprine, and cyclosporine. A number of case reports have also described the use of biologic therapies including infliximab, etanercept, adalimumab, rituximab, anakinra, and tocilizumab [865]. However, the results of treatment with these agents have been variable.

Many of the ophthalmic manifestations are treated with systemic therapy as outlined above for the systemic features of the disease. Patients with isolated scleritis may be treated with NSAIDs. If NSAIDs fail to control the scleritis, systemic corticosteroids may be used but only as short-term therapy in children to avoid serious side effects. As such, children requiring prolonged therapy should be treated with immunomodulatory therapy. Systemic therapy is often supplemented with topical corticosteroids for uveitis and some cases of keratitis [860]. Artificial tear preparations and or punctal occlusion are recommended in patients with KCS.

Sjögren Syndrome

Definition

Sjögren syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands. The salivary and lacrimal glands are predominantly affected leading to the classical symptoms of dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca) [866]. Pulmonary, renal, articular, skin, and neurologic involvement can also occur. Sjögren syndrome is very rare in children and the clinical features differ somewhat compared to adults [867–869]. Patients with SS are at increased risk for development of lymphoma, however this has not been reported in children with SS [870].

Sjögren syndrome can be a primary isolated disease or secondarily associated with other autoimmune diseases such as SLE. Primary Sjögren syndrome is rare in children. Similar to other autoimmune diseases, the pathogenesis likely involves environmental factors such as infectious agents that trigger an autoimmune response in genetically susceptible individuals [871, 872].

Several classification criteria have been developed for SS in adults although none have been widely accepted [873]. In 1999, Bartunkova and co-workers proposed criteria for the diagnosis of primary SS in children [868]. These criteria were subsequently compared with previously published criteria for adults [874]. Neither the proposed criteria for the diagnosis of SS in children or adults performed well in children. Therefore, clinical diagnosis by a pediatric rheumatologist remains the best method for diagnosing SS in children.

History

Filamentary keratitis was described by Leber in 1882, xerostomia by Hadden in 1888 and lacrimal and salivary gland enlargement without KCS or xerostomia by Mikulicz [875]. Additional features of SS were described between 1883 and 1933, but it was not until 1933 that a full description was given by the Swedish ophthalmologist, Henrik Sjogren [876, 877].

Epidemiology

At present, there are no epidemiologic studies of SS in children. In adults, there are a limited number of studies and few reports describing the incidence of the disease. These studies differ in criteria used to establish the diagnosis if SS as well as the age groups included. Despite these limitations, adult incidence rates of 4–5.3 per 100,000 population have been reported [878, 879]. The mean prevalence is approximately 0.6 % [16]. The disease can affect all age groups but is most common during the fourth and fifth decades. Childhood SS has been reported rarely and prolonged delays in diagnosis are common [880]. Sjögren syndrome is much more common in females with a female to male ratio of 7–9:1.

Systemic Manifestations

In children, early systemic manifestations often differ compared to adults with SS. Unilateral or bilateral parotid swelling occurs in up to 77 % of children and is the most common presenting manifestation of SS in this age group [867, 869, 881]. Parotid swelling may be painful in some children. Compared to adults, sicca symptoms are uncommon and typically mild [882]. Xerostomia may be present in some children although symptoms may be difficult to elicit in this age group.

Dryness of the oropharynx and upper respiratory tract can also occur. Typical symptoms are hoarseness, chronic bronchitis, and recurrent pneumonitis [883]. Renal tubular acidosis (RTA) can be an acute life-threatening complication and is likely under diagnosed in children with SS [884]. RTA should be suspected in children who develop fatigue, weakness, or growth failure. Overall, RTA has a good long-term prognosis in most children with SS.

Less common systemic manifestations in children include rashes, arthralgias or arthritis, Raynaud phenomenon, headache, cerebellar ataxia, neuromyelitis optica, peripheral neuropathy, vasculitis, and meningoencephalitis [867, 881].

Ophthalmic Manifestations

Children typically have less ophthalmic manifestations at the time of diagnosis compared to adults. Keratoconjunctivitis sicca is the most common manifestation in both adults and children. Symptoms suggestive of KCS are persistent foreign body sensation, excess secretions often forming ropy strands at the inner canthus of the eye, burning, and inability to produce tears in response to irritants or emotion [885]. Although foreign body sensation is the most common symptom in adults, lack of tears was a more specific symptom. Schirmer testing with topical anesthetic typically reveals wetting less than 5.5 mm after 5 min in patients with SS. Slit-lamp examination following installation of fluorescein dye is used to assess tear film break-up time and corneal epitheliopathy. Reduced tear film break-up time is commonly seen in patients with SS. Superficial punctate keratopathy is also seen with fluorescein staining. Rose bengal and lissamine green are other dyes that stain devitalized epithelium and may reveal staining of the conjunctiva in patients with SS. Additional manifestations are conjunctival hyperemia, mucus debris, corneal epithelial defects and filamentary keratitis [886].

Ocular complications of KCS may also occur. There is an increased incidence of bacterial and viral infections of the eye due to impairment of the conjunctival defense mechanisms which depend on antibacterial components found in tears. Gram-positive bacteria are the most common cause of microbial keratitis and may be associated with complications such as perforation [887]. Other complications include symblepharon, pannus formation, marginal corneal ulceration, and sterile corneal ulceration with perforation.

Diagnosis

Patients with SS often have markedly elevated ESR and hypergammaglobulinemia [868, 874]. Antinuclear antibodies, RF, anti-Ro/SSA and anti-La/SSB autoantibodies are common [881]. Antifodrin antibodies have also been found in children with SS [888]. Serum electrolytes, BUN, creatinine and urine pH are recommended to screen children for renal tubular acidosis.

Schirmer testing is used to measure tear secretion, however younger children may not be able to cooperate with testing. In these children, staining of the ocular surface with vital dyes such as fluorescein, rose bengal or lissamine green may reveal damaged corneal and conjunctival epithelium. Salivary gland ultrasound can reveal abnormalities although no studies of children have been reported [889]. Additionally, salivary gland scintigraphy is useful to assess salivary gland function [883].

Biopsy may be considered in selected patients. The minor salivary glands and parotid gland are the most frequent sites for biopsy. In children, biopsy of the parotid gland may be the preferred procedure; especially in cases with parotid swelling [890, 891]. Biopsy of the minor salivary glands of the lower lip may be an alternative approach.

Management

Treatment of SS can be divided into the treatment of the sicca components and treatment of the associated disorders. Dry mouth is uncommon in children yet difficult to treat. Frequent sipping of water or other sugar-free liquids may be sufficient in some cases. Additional methods to increase salivary flow such as sugar free chewing gum or lozenges provide temporary relief [883, 892]. Oral pilocarpine or civemeline can also stimulate salivary flow in some patients with residual salivary function [892, 893]. Side effects of both of these agents include headache, flushing, excessive sweating and frequent urination. Frequent dental evaluations may prevent or delay the onset of rapidly progressive caries.

Hydroxychloroquine is used frequently in patients with SS for arthritis, fatigue, and other constitutional symptoms although no clear benefit has been demonstrated in controlled studies [894]. Corticosteroids, immunosuppressive agents, and biologic therapies have been used for extraglandular manifestations of SS although most reports describing their use are small case series. Patients with severe life-threatening manifestations such as systemic vasculitis, myelitis or central nervous system disease are typically treated with intravenous corticosteroids combined with cyclophosphamide and possibly plasmapheresis [892, 894].

Initial treatment of dry eyes is preservative-free artificial tear preparations since most children will require long-term therapy [79, 886]. In many patients with KCS, instillation of 0.5–1.0 % carboxymethylcellulose eye drops is sufficient to ameliorate symptoms and prevent any local complications [895]. Ocular lubricating ointments are often used at bedtime. Avoidance of ocular irritants such as cigarette smoke, windy environments and dust are also recommended. Oral pilocarpine or civemeline may also improve symptoms of dry eye. If artificial tears fail to control symptoms, topical cyclosporine emulsion may be an option although there are limited reports of its use in children [136–139]. Short pulse therapy with topical corticosteroids may be beneficial in selected cases [896]. In severe cases, autologous serum tears may be considered but this requires periodic blood collection and thus may prove difficult in young children. Punctal occlusion may be necessary if artificial tears do not provide relief of symptoms or resolution of keratopathy. Silicone plugs are the preferred method but extrusion of the plug is not uncommon. In addition, punctal plug insertion may require general anesthesia, especially in younger children. Permanent occlusion is another option but is not frequently used in children.

Ocular complications such as corneal ulceration, bacterial keratitis, and eyelid infections require topical antibiotic therapy. Blepharitis is a frequent complication and is typically treated with lid hygiene, warm compresses, and topical antibiotics in some cases.

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Ocular Manifestations of Systemic Syndromes

21

Arcot Sadagopan Karthikeyan and Adele S. Schneider

Introduction

A syndrome is defined by a group of signs that consistently occur together usually due to a common genetic cause. Syndromes may also be described in response to environmental exposures (e.g. valproate embryopathy) but this chapter focuses only on those with a genetic etiology. The eye is the second most common individual organ to be involved in genetic disorders after brain [1]. Ophthalmic examination is integral in the evaluation of many syndromes. Some ocular manifestations are very specific for a syndrome and greatly assist in making the right diagnosis, as in the chorioretinal lacunae in Aicardi syndrome. Some ocular findings are non-specific such as myopia, strabismus and nasolacrimal duct obstruction. Some syndromes develop ocular manifestations years before systemic signs develop and may have major implications in modifying patient care.

This chapter discusses the ocular and systemic manifestations of syndromes not otherwise covered in chapters on metabolic disorders, chromosomal aberrations, neurologic and mitochondrial disease, craniosynostosis, and phakomatoses or those syndrome with a single predominate systemic manifestation that would cause them to be covered in the chapter related specifically to that system. At the end of the chapter we provide a list of other important texts; atlases and dedicated websites which will assist the reader in making a correct diagnosis and also in recognition and understanding the multitude of syndromes now known.

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Adams-Oliver Syndrome (AOS) (MIM 100300)

Definition

Adams-Oliver syndrome (AOS), (MIM 100300) is characterized by congenital absence of skin usually limited to the scalp (Aplasia Cutis Congenita [ACC]) and variable degrees of terminal transverse limb defects. The clinical features are highly variable. Five subtypes (AOS1, AOS2, AOS3, AOS4 and AOS5) have been recognized based on inheritance pattern and the genes involved. Variability in clinical expression has been described with some of the patients with AOS having only ACC and heart defects without associated limb defects [2, 3].

Autosomal dominant and recessive inheritance patterns have been recognized. AOS1 is caused by heterozygous mutations in Rho GTPase activating protein 31 (*ARHGAP31* [MIM 61091]), AOS3 is caused due to heterozygous mutations in recombination signal binding protein for immunoglobulin kappa J region (*RBPJ* [MIM 147183]), homozygous or biallelic mutations in either dedicator of cytokinesis 6 (*DOCK6* causes AOS2 [MIM 614194]). Mutations in EGF-domain-specific O-linked N-acetylglucosamine transferase (*EOGT*) cause AOS4. Mutations in *NOTCH1* (190198) cause AOS5, were identified recently in patients with AOS and may be the most common cause of AOS [4]. Several theories have been postulated to explain the pathogenesis of the observed defects seen in AOS. Early embryonic vascular disruption or insufficiency is considered to the most plausible mechanism [5]. AOS is considered to result from ischemia, necrosis, and resorption of structures after an intrauterine vascular event affecting the brachial artery. This is further

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supported by the occurrence of several vascular malformations and clinical features.

History

In 1945, Adams and Oliver described eight members of one family in three generations with variable defects involving the limb, scalp and skull [6]. Whitley and Gorlin (1991) later reported that another member in the fourth generation was also affected [7].

Epidemiology

Adams-Oliver syndrome is seen in all ethnicities. It is very rare.

Systemic Manifestations

Aplasia Cutis Congenita

The cutaneous defects are usually limited to scalp, mostly midline, sometimes in the occipital or parieto-occipitial area, and can vary in size. Superficial lesions involving only the epidermis are shallow and usually heal over with scarring before the child is born. Deeper lesions usually involve the dermis, subcutaneous tissue or, rarely can involve the skull [8, 9]. In acrania, the flat bones of the cranial vault are absent, whereas the bones at the base of the skull are intact and normal. In some older children, patchy areas of scalp without hair might be the only findings. Dilated scalp veins are frequently an associated finding [10]. Cutaneous defects may also occur on other areas including the face, trunk or limbs. Cutis marmorata might be seen in some of the patients [11, 12]. In some cases maternal serum AFP will be elevated if enough skin is exposed.

Limb Defects

The lower limbs are generally more commonly and also more severely affected [13]. Asymmetrical limb defects are characteristic and seen in approximately 80–85 % of patients with AOS [14]. Hypoplastic or absent distal phalanges are the most commonly reported limb anomalies (see Fig. 21.1). The severity of the spectrum might vary from hypoplastic nails to absence of entire hands or lower legs. Brachydactyly, ectrodactyly, syndactylies are other abnormalities that have been reported [15].

Neurological Manifestations

Neurological abnormalities include encephalocele (uncommon), intellectual disability (uncommon), seizures, hypotonia, developmental delay, enlarged ventricles, periventricular calcifications, cerebral hemorrhage and/or periventricular leukomalacia (PVL). PVL may be due to vascular disruption and decreased perfusion during critical periods of fetal brain development [16]. Neuronal migration abnormalities such as cortical dysplasia, pachygyria and polymicrogyria have also been reported [17]. Hypoplasia of the corpus callosum has been reported [18]. Absence of the superior sagittal sinus also supports the theory of embryonic vascular disruption in the pathogenesis of this syndrome [19–22].

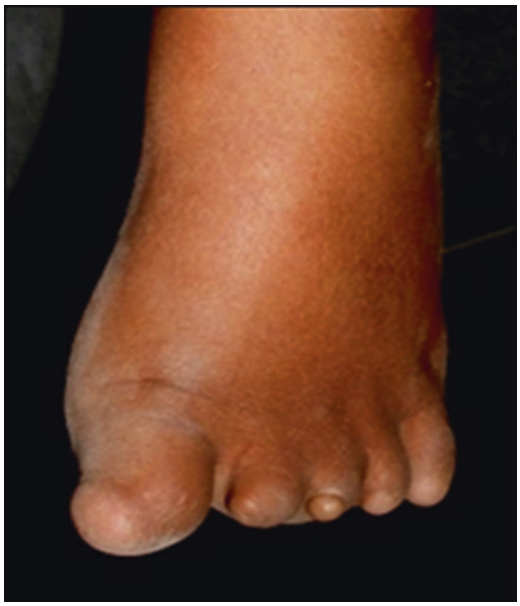

Fig. 21.1 Adams-Oliver syndrome. Terminal transverse limb defect in AOS: The toes are reduced to stubs (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Cardiac Abnormalities

Santos et al. first suggested that cardiac abnormalities could be a part of this syndrome [23]. Approximately 10–20 % individuals with this syndrome might have congenital heart anomalies, mostly involving obstructive lesions on the left side of the heart [24]. Other cardiovascular malformations such as bicuspid aortic valve,[24] atrial septal defect, Shone's complex, aortic valve stenosis, hypoplastic left heart syndrome, double outlet right ventricle, coarctation of aorta [23], ventricular septal defect [25, 26] and tetralogy of Fallot have been reported [3]. Portal hypertension and pulmonary hypertension may occur [2, 27].

Other Abnormalities

The following less consistent abnormalities have also been reported: oligohydramnios, upper limb micromelia, palatal or auricular malformations, anatomic bronchial anomalies, renal anomalies and craniofacial anomalies with frontonasal cysts [28].

Other findings include cutis marmorata telangiectasia congenita (CMTC), abnormal pulmonary and portal vasculature, and necrosis of the abdominal skin and gangrene of digits and optic disc drusen. Several theories have been postulated to explain the pathogenesis of the observed defects seen in AOS. Early embryonic vascular disruption or insuf-

ficiency is considered to the most plausible mechanism [5]. AOS is considered to result from ischemia, necrosis, and resorption of structures after an intrauterine vascular event affecting the brachial artery. This is further supported by the occurrence of several vascular malformations and clinical features.

Ophthalmic Manifestations

Hypertelorism, narrow palpebral fissures, blue sclera, strabismus, microphthalmia, nuclear and anterior polar congenital cataract, retinal dystrophy, congenital vitreoretinal abnormalities, optic disc drusen and congenital optic atrophy have been reported uncommonly [29, 30]. Peripheral avascular retina with capillary dropout, arteriovenous anastomosis, and telangiectasia has been observed [31]. Microphthalmia, microcornea and partial scleralization of the cornea were reported in the other eye. Congenital retinal non-attachment and falciform fold have also been reported [18]. Eyes with optic disc drusen often tend to show abnormal angiogram patterns such as abnormal branching pattern on the disk, increased capillarity and relatively large blood vessels connecting the superficial and deep disk circulations.

Further literature and postmortem examination findings [32] demonstrating abnormalities in the vascular smooth muscle cells and pericyte coverage of the vasculature associated with vessel dilatation (pericyte absence) or stenosis (pericyte hyper proliferation) have been observed [32].

Diagnosis

There are no specific clinical diagnostic criteria due to the heterogeneity in clinical presentation. Some of the important differential diagnoses include the syndrome of scalp defect and split-hand defect, amniotic band sequence and focal dermal hypoplasia (Goltz suyndrome) and [19] Genetic testing offers the definitive diagnosis, although it is expected that other genes are yet to be identified.

Management

Systemic

The main concerns depend on the severity of the scalp defect. The major concern is an open scalp lesion especially when associated with absent of parts of the skull. The risk for developing sepsis and/or meningitis in such patients is high. If the scalp defect is small, recovery occurs with gradual epithelialization and formation of a hairless atrophic scar [33]. Small bony defects tend to close spontaneously during infancy. Large or multiple scalp defects may require surgical intervention.

Ophthalmological

The management of ophthalmological problems in AOS does not differ significantly from those who do not have this syndrome, except for the increased risk for procedures under anesthesia due to the systemic abnormalities. The role of laser ablation of the avascular peripheral retina is unknown.

Aicardi Syndrome (MIM 304050)

Definition

Aicardi syndrome is characterized by the classic triad of, agenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms. Aicardi Syndrome is an X-Linked dominant disorder. Invariably it occurs sporadically. It is seen only in females with *in utero* lethality in males. The severity of the clinical features appears to be related to the degree of X inactivation. Mosaic mutations have been suggested as possible cause for the rare phenotype of Aicardi that is seen in males. It may also be seen in males with 47 XXY Karyotype [34, 35]. A possibility that Aicardi syndrome is caused by new mutations on an autosome with gender-limited expression in females is currently being considered.

Major Criteria

The presence of all three classic features is diagnostic for Aicardi syndrome. Some patients may not have all three characteristic features. The presence of at least two major features or additional features strongly suggests the possibility of Aicardi syndrome.

Major Features

- Agenesis of the corpus callosum,
- Distinctive chorioretinal lacunae,
- Infantile spasms

Other main features include

- Cortical malformations (usually polymicrogyria)
- Periventricular and subcortical heterotopia
- Cysts around third ventricle and/or choroid plexus (typically not communicating with the ventricles)
- Optic disc/nerve coloboma or hypoplasia

Supporting Features Include

- Skeletal anomalies: vertebral and rib abnormalities
- Microphthalmia
- EEG which has characteristic asynchronous multifocal epileptiform abnormalities with burst suppression

and dissociation between the two hemispheres ("Split-brain" EEG)
- Gross asymmetry of the cerebral hemispheres
- Vascular malformations or vascular malignancy

History

The syndrome was first described by Aicardi et al. [36], as a neurodevelopmental disorder that affects primarily females [37–39].

Epidemiology

Aicardi syndrome incidence has been estimated to be 1:105,000 to 1:167,000 in the United States and slightly more common in some European countries [40].

Systemic Manifestations

The clinical picture is often dominated by neurological symptoms and signs. Other clinical findings include craniofacial, skeletal, gastrointestinal and dermatological manifestations. Some of these patients are at increased risk for certain tumors and cutaneous malignancies. Patients usually have significant neurologic compromise and developmental delay.

Neurological

Aicardi suggested microcephaly, axial hypotonia, and appendicular hypertonia, hemiparesis and unilateral spasticity, global developmental delay and intellectual disability of varying severity as the main features of the syndrome [41–43]. Seizures dominate the neurological presentation. Seizures tend to develop in the first year of life and most by 3 months old. The seizures initially present as infantile spasms but with time present in different forms, often severe and refractory to medical management. Several neuroimaging findings have been reported. Corpus callosum agenesis is the most consistent and is one of the diagnostic criteria. The next consistent finding is polymicrogyria and cortical heterotopias. Polymicrogyria often involves the frontal and perisylvian regions. The heterotopias are almost always bilateral, asymmetric and most often involve the periventricular area [44, 45]. Opercular abnormalities include widening of the operculum and less commonly under development of the operculum. Intracranial cysts that typically do not communicate with the ventricular cavity are seen. The cyst walls show contrast enhancement on MRI. Posterior fossa abnormalities include superior foliar prominence of the vermis, inferior vermian hypoplasia, dysplastic or hypoplastic cerebellar hemispheres, cerebellar subcortical and/or periventricular heterotopias, enlarged cisterna magna and cerebellar cysts.

Dysmorphic Facial Features

Patients with Aicardi syndrome have characteristic craniofacial features which include posterior plagiocephaly, facial asymmetry, sparse eyebrows, large ears, prominent premaxilla, short philtrum and upturned nasal tip. Some of the patients have cleft lip and palate.

Costovertebral Anomalies

Costovertebral abnormalities are common including hemi-, block, and fused vertebrae. Missing ribs are common. Scoliosis is seen in almost one third of the affected individuals [46].

Gastrointestinal

Diarrhea, constipation, Gastroesophageal refluxes are commonly reported symptoms.

Ophthalmic Manifestations

Chorioretinal lacunae are required for the diagnosis of Aicardi syndrome. This clinical finding is highly specific but not pathognomonic. They are usually found in the peripapillary retina or macula. The lesions are white or yellow-white colored, well-circumscribed, round, depigmented areas of the retinal pigment epithelium and underlying choroid. The borders of the lesion often have variable pigmentation. Donnenfeld et al. reported several ophthalmic manifestations including microphthalmia, optic nerve coloboma often usually without co-existent iris coloboma, nystagmus and retinal detachment [46]. Within lacunae, the RPE is typically absent, and the choroid and sclera are thin [47]. The reported eye findings can be unilateral or bilateral and can be grossly asymmetric. Other optic nerve abnormalities include optic nerve aplasia and hypoplasia [47]. Patients also often have cortical visual impairment.

Diagnosis

Diagnosis is based on the diagnostic criteria. Any female infant with seizures early in life needs to have an eye examination to rule-out Aicardi syndrome. Currently there is no specific laboratory, DNA test or diagnostic imaging test to establish a definitive diagnosis. Some of the findings that occur in Aicardi syndrome can also occur in isolation such as agenesis of the corpus callosum and infantile spasm. Parenchymal abnormalities may also be seen in neuronal migration disorders. Some features may share overap with Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR) (OMIM 152950).

Presence of features like agenesis of the corpus callosum with intracranial cysts and other brain abnormalities in a female infant during prenatal ultrasound examination should raise the suspicion for possible Aicardi syndrome. Early ophthalmic fundus examination is critical in all female children with medically refractory seizures to make the correct diagnosis and differentiate it from other causes of seizures in female children and infants.

Management

Systemic

Infantile spasms are often difficult to manage and may be most responsive to vigabatrin. To monitor the side effects of vigabatrin, electroretinogram especially the 30-Hz flicker ERG provides assessment of retinal damage and Ocular Coherence tomography is often required [48].

Ophthalmological

No specific treatment is possible for the chorio-retinal lacunae.

Alagille Syndrome (AGS; MIM 118450)

Definition

Alagille syndrome (AGS; OMIM 118450) is a complex multisystem disorder involving predominantly the liver, heart, eyes, face, and skeleton [49]. It is inherited as an autosomal dominant condition. It is also referred to as Arterohepatic dysplasia.

The diagnosis of AGS is based on clinical criteria initially set forth by Alagille et al. [50]. Which include the histological finding of bile duct paucity on liver biopsy in association with three out of five major clinical features (cholestasis, cardiac defects, vertebral anomalies, ophthalmologic findings, and facial features) and is referred as the classic clinical criteria. Since the association of butterfly vertebrae and cardiac anomalies can be seen in other conditions like chromosome 22q deletion [51], a revised diagnostic criterion has been recently proposed by Kamath et al. [52]. They included presence of typical renal anomaly (renal dysplasia, acidosis, vesico-ureteric reflux and urinary obstruction) as the sixth disease defining criteria.

The majority of cases (97 %) are caused by haploinsufficiency of *JAG1* at 20p11.2-20p12 which encodes the protein (JAGGED1). *JAG1* gene has not been implicated in any other phenotype. It consists of 26 exons, and encodes the JAGGED1 cell surface protein that functions as a ligand for the Notch receptors. There are four receptors Notch 1, 2, 3, and 4. These receptors act as transmembrane proteins, and interaction with their ligands triggers a cascade of intracellular downstream effects that result in transcription of genes. These subsequently help determine cell fate and differentiation. Most of the mutations that involve *JAG1* are protein-truncating. No specific hotspots have been identified, and any part of the entire coding region may be involved. Gene deletions are found in less than 10 % cases. Larger deletions are likely to be associated with additional problems such as learning difficulties. New mutations occur commonly (60 %), and the rate of germline mosaicism may also be relatively high. A small percentage (1 %) is caused by mutations in *NOTCH2*, in which group renal malformations may be more common. Both genes are components of the Notch signaling pathway. *NOTCH2* gene comprises of 34 exons and encodes the *NOTCH2* transmembrane protein. *De novo* mutations contribute to approximately 60 %. Germline mosaicism may occur at a frequency up to 8 % [53]. The current consensus is that AGS is possibly due to a vasculopathy. This is supported by the spectrum of vascular anomalies seen in AGS. There is also evidence that the formation of mature tubular bile ducts follows on from the initial development of the intrahepatic arterial network accounting for the biliary duct atresia.

History

The clinical condition was first reported by Alagille et al. in 1969 [50]. It was subsequently reported by Watson and Miller in 1973 [54], and again by Alagille et al. in 1975. Hence it is sometimes also referred to as Alagille–Watson syndrome.

Epidemiology

The incidence of Alagille syndrome ALGS is estimated to be approximately 1 in 30,000–50,000 live births [55, 56].

Systemic Manifestations

A characteristic inverted triangular face (broad, prominent forehead; pointed chin; bulbous tip of the nose; and deep set, hypertelloric eyes), posterior embryotoxon, cardiovascular defects (particularly peripheral pulmonary artery hypoplasia), and skeletal abnormalities (butterfly vertebrae, shortened ulna and distal phalanges) constitute the main clinical features [57–59].

Facial Features

Recognizing the dysmorphic facial features is critical and one of the major criteria for making a diagnosis [57]. Alagille et al. determined the facial phenotype to be present in 95 % of cases in his series [57]. This was supported in a subsequent

study by Emerick et al. who found the characteristic facial phenotype in 96 % of 92 patients [58]. The characteristic facial features include a prominent forehead, deep-set eyes that may be hyperteloric, straight nose with a flattened tip, and prominent pointed chin.

Sokol et al. suggested that the facial dysmorphism seen in AGS was nonspecific and was secondary to a variety of causes resulting in congenital intrahepatic cholestasis [60]. They referred it to as "cholestasis facies" They suggested that a common structural effect involving several disease genes or the effect of the multiple biochemical aberrations caused by the cholestasis resulted in the facial phenotype. Kamath et al. in their series found that the facial phenotype had 76 % sensitivity and 85 % specificity in making a diagnosis of Alagille syndrome suggesting that the facies seen in Alagille syndrome was very specific to this condition [61]. Hence recognition of the facial features is considered a significant clinical finding and is frequently integral to making the correct diagnosis.

The facial features are more difficult to recognize in adult patients, although recognition of this phenotype in adults has major clinical implications. Individuals might have been followed for apparently isolated congenital heart disease but may be at risk for having severely affected children with full clinical manifestations. The recurrence risk of congenital cardiac abnormalities in children of adults with truly isolated cardiac defects is generally less than 5 % but this risk rises to 50 % in Alagille syndrome [62].

Paucity of bile ducts, which is a histological diagnosis from liver biopsy, occurs in a diverse group of conditions, which, apart from AGS, include Down syndrome, cystic fibrosis, congenital infections, alpha-1-antitrypsin deficiency, and Zellweger and Ivemark syndromes. Screening for characteristic ocular findings may allow early diagnosis and differentiate Alagille syndrome from other causes of intrahepatic cholestasis thus avoiding the need for the extensive and invasive systemic investigations.

Liver

Chronic cholestasis occurs in a very high proportion (95 %) of patients [58]. It often manifests in the first 3 months of life, with jaundice due to conjugated hyperbilirubinaemia. Progressive liver disease eventually resulting in cirrhosis and liver failure require a liver transplantation in approximately 15 % of cases. However a very small proportion of patients do not develop liver disease [49].

Cardiac

More than 90 % have a cardiac abnormality. Involvement of the pulmonary outflow tract in the form of peripheral pulmonic stenosis is the most common finding. Tetralogy of Fallot (TOF) is the most common complex structural anomaly. Congenital heart disease may sometimes be the only manifestation of a mutation in *JAG1*.

Skeletal

A characteristic form of segmentation anomaly known as 'butterfly' vertebrae occurs due to failure of fusion of the anterior vertebral arches. This finding is seen in at least 80 % of cases. These do not have any functional significance but help in making a diagnosis of Alagille syndrome in a child with cardiac disease. Craniosynostosis and radioulnar synostosis have also been reported [63]. Other vertebral anomalies including spina bifida occulta and fusion of adjacent vertebrae, hemi vertebrae, and absence of the 12th rib has been reported. Digits may have shortening of the distal phalanges resulting in fusiform appearance of fingers.

Vascular

Several vascular abnormalities have been reported. Neurovascular accidents, [64], renovascular anomalies, aortic syndrome, and moyamoya syndrome [65, 66] have been reported. Anomalies of the major intracranial blood vessels involving the basilar, carotid, and middle cerebral arteries have also been reported [64, 67]. Intracranial bleeding may occur following trivial head trauma.

They contribute to a significant cause of mortality.

Renal

Structural renal abnormalities include renal dysplasia, small kidneys, renal cysts, and ureter pelvic obstructions. Renal tubular acidosis is the most common functional abnormality reported [52]. Cardiac disease, when severe, accounts for early mortality, whereas hepatic complications account for a significant proportion of later deaths.

Others

Growth retardation and learning difficulties have been reported.

Ophthalmic Manifestations

The most consistent ocular finding is posterior embryotoxon. Other reported anterior segment abnormalities include microcornea, nanophthalmos, keratoconus, band keratopathy, corneal pannus, iris hypoplasia, corectopia, and cataract [68–74, 76, 77]. Refractive errors and strabismus have also been reported [69, 70]. Posterior segment abnormalities include disc and retinal vascular abnormalities [75, 76]. Several optic disc anomalies including tilting, hypoplasia, elevation, atrophy, temporal crescent, peripapillary depigmentation may occur. Optic disc drusen are extremely common and ocular ultrasound has been suggested as a possible noninvasive, simple, and safe method for diagnosis in infants with cholestatic jaundice [78]. Retinal vascular and pigmentary changes, with macular pigment clumping, speckling and chorioretinal folds can occur [70].

Ophthalmic findings are usually mild and most are non-progressive. Hence most patients tend to have reasonably good vision.

Diagnosis

Molecular genetic testing is currently available, although, mutations may not be detected either in *JAG1* and *NOTCH2* in a proportion of the patients.

Alagille must be differentiated from other causes of intrahepatic cholestasis such as cystic fibrosis, congenital infections, alpha-1-antitrypsin deficiency, Zellweger syndrome and Ivemark syndromes. Alagille has a relatively better prognosis for liver disease. The characteristic dysmorphic features, classic ocular findings and specific cardiac abnormalities are not seen in the remaining clinical conditions. Hence it is imperative to look for these findings in any child with neonatal cholestatic jaundice. Several reports suggest examination of the parents alone might provide the diagnosis in at least 36–43 % of cases, and simple ocular examination of the child could reveal a characteristic abnormality in most patients. However posterior embryotoxon is present in 8–15 % of normal persons [79].

Management

Systemic

Multiple specialty services are usually involved. The Kasai procedure, an direct intestine-hepatic anastomosis, is the most common surgical approach to the live malfunction.

Ocular

The retinal pigmentary changes usually do not affect vision.

Alstrom Syndrome (ALMS MIM 203800)

Definition

Alström syndrome is an autosomal recessive genetic disorder characterized by cone-rod dystrophy, hearing loss, childhood truncal obesity, insulin resistance and hyperinsulinemia, type 2 diabetes, hypertriglyceridemia, short stature in adulthood, cardiomyopathy, and progressive pulmonary, hepatic, and renal dysfunction. Symptoms begin to appear even during early infancy and the progressive development of multiorgan pathology results in reduced life expectancy. Though this disorder is unusually frequent among French Acadians, it also occurs in other ethnic groups.

Alström syndrome is caused by bilalellic mutations in the *ALMS1* gene OMIM 203800, located on chromosome 2p13. *ALMS1* is expressed in the organ of Corti, retinal photoreceptors, renal tubules, liver, and pancreatic islets [80, 81]. Several splice variants of *ALMS1* have been described encoding isoforms of the protein accounting for high variability in severity of tissue involvement. Onset of retinal degeneration before age 1 year and occurrence of urologic dysfunction have been linked with disease-causing variants in exon 16 [82]. A more significant association was also found between alterations in exon 8 and absent, mild, or delayed renal disease. There is great variability in age of onset and severity of clinical symptoms, even within family members bearing identical mutations.

The Marshall criteria describe eight major and eight minor clinical features [83]. The recent revised criteria are shown in Table 21.1 [84]. The disorder appears to segregate into three groups: Less than 2 years old, 3–14 years and above 15 years. Presence of two major features is sufficient to make the diagnosis in the first two groups. If only one major criterion is present, the number of additional minor criteria required to make the diagnosis increases with each subsequent age group (2 in group 1, 3 in group 2 and 4 in group 3). The major criteria remain the same for the three age groups. The minor criteria differ in each age group as more systems tend to get affected with disease progression.

Table 21.1 Alstrom syndrome: diagnostic criteria and clincial features

Major criteria (same for all age groups)	
Presence of *ALMS1* mutation in one allele and/or	
Family History of Alstrom Syndrome	
Vision related issues (photophobia/nystagmus/reduced visual acuity/cone dystrophy confirmed by an ERG/legal blindness in adults)	
Minor criteria	
Birth to 2 years	Obesity:
	Dilated Cardiomyopathy/Congestive Heart failure
3 years–14 years	Obesity and/or insulin resistance and/or T2 DM
	History of dilated cardio myopathy/congestive heart failure
	Hearing loss
	Hepatic dysfunction and renal failure
	Advanced bone age
15 years and above	Findings under minor criteria mentioned for age group 3–14 years
	Additional findings include:
	Short stature
	Males: hypogonadism
	Females: irregular menses and/or hyperandrogenism
Supportive findings (common to all age groups)	Recurrent pulmonary and urinary tract infections.
	Developmental delay
	Normal digits
Other findings	Hyperlipidemia, scoliosis, flat feet, hypertension, hypothyroidism, recurrent UTI and alopecia (15 years and above)

History

It was first described by Alström in 1959.

Epidemiology

Alström syndrome appears to have a prevalence of less than one per million in the general population [83]. Patients usually have worsening of all symptoms and signs by second/third decade resulting in reduced life expectancy due to progressive multisystem involvement.

Systemic Manifestations

Obesity

Obesity is one of the early and consistent findings observed in most children with Alström syndrome. They have apparently normal birth weight but gain weight rapidly within the first or second year of life. Decreased levels of physical activity, often exacerbated by dual neurosensory losses and childhood hyperphagia contribute.

Sensorineural Hearing Loss

Hearing loss may be detected in early infancy. It is bilateral and progressive. Most patients have moderate to severe hearing impairment by the second decade [85]. The age of onset and severity is highly variable. Chronic and acute otitis media often exacerbate the sensorineural deficits with a component of conductive hearing loss [83].

Cardiomyopathy

Both dilated cardiomyopathy and restrictive cardiomyopathy has been observed [83, 86]. Dilated cardiomyopathy is more common in early infancy and childhood. It may be the presenting sign of the syndrome. Most children recover but can have a recurrence in later childhood when it presents as restrictive cardiomyopathy. Sixty percent of children with cardiomyopathy develop congestive cardiac failure.

Lung

Chronic bronchitis, asthma, and chronic rhinosinusitis are common. Pulmonary hypertension, Chronic Obstructive Pulmonary Disease and Adult Respiratory Distress Syndrome also occur. History of recurrent hospitalizations for breathlessness is common as some individuals are unable to maintain adequate oxygen saturation.

Type II Diabetes Mellitus

Severe insulin resistance, hyperinsulinemia, and impaired glucose tolerance are often observed from very early childhood. Acanthosis nigricans, a marker of insulin resistance, may occur. The onset of Type II Diabetes Mellitus has been shown to be unrelated to the degree of obesity, unlike the general population [87].

Liver

Elevation of transaminases is common and is often the initial finding. In patients with severe involvement, cirrhosis, portal hypertension, esophageal varices, encephalopathy, with upper gastrointestinal hemorrhage may result in death. End stage liver disease is the cause of death in approximately 10% of individuals [83].

Renal

Renal abnormalities include reduced urine concentrating ability, renal tubular acidosis, polyuria and polydipsia. Secondary hypertencion may occur. Lower urinary tract dysfunction, vesicoureteral reflux, urethral stenosis, and detrusor instability due to abnormal bladder and sphincter function have also been reported [88].

Endocrine

Though there is an initial rapid growth most adolescents and adults have a final short stature. Hypothyroidism and growth hormone deficiency has been reported [89, 90].

Hypogonadism

Hyper- or hypogonadotropic hypogonadism is seen in both males and females. It is more common in males. Secondary sex characteristics are normal. Affected females tend to have hyperandrogenism, hirsutism, and alopecia. No individuals with Alström syndrome are known to have reproduced.

Others

Mild delay in developmental milestones, autistic spectrum behaviors, seizures, and cerebellar anomalies can occur.

Ophthalmic

Progressive cone-rod dystrophy is the main clinical feature. It usually begins in early infancy with parents noticing photophobia, visual impairment and high frequency small amplitude symmetric nystagmus due to early involvement of cones. Full Field-ERG is required to confirm the diagnosis to demonstrate the early cone involvement. When rods get subsequently involved, there is progressive deterioration of vision, constriction of visual fields and eventual blindness usually by third decade. Posterior subcapsular cataracts have been reported. Retinal findings include attenuation of retinal vessels, optic disc pallor, optic nerve drusen and increasingly significant retinal pigmentary epithelial (RPE) atrophy. Histological studies have demonstrated other findings including asteroid hyalosis [91, 92]. The retina may eventually

appear as advanced retinitis puigmentosa. Reports have showed thinning of the macula and an early arrest of macular development with immature retinal structural organization in one of the patients [93]. The severity and age of onset of the retinal degeneration vary among affected individuals [94].

Diagnosis

Molecular genetic testing is available and is one of the major criteria for making a diagnosis.

Since Alström syndrome causes a severe retinal dystrophy with reduced vision and photophobia, it could be confused with several early onset pediatric retinal dystrophies. These include Leber congenital amaurosis (LCA), cone dystrophy and achromatopsia. Often an initial diagnosis of achromatopsia is revised as further characteristic systemic findings emerge. The absence of obesity and other systemic abnormalities, presence of oculodigital sign, enophthalmos and an extinguished ERG response are seen in LCA.

The phenotypic characteristics of Alström syndrome also resemble Bardet-Beidl syndrome (BBS) BBS has polydactyly which is not seen in Alström syndrome. Hearing impairment is less common with BBS. Obesity, insulin resistance and diabetes are common findings in both disorders tend to present slightly at a later age than Alstrom syndrome. Intellectual disability and hypogonadism are more common in BBS.

Other differential diagnoses include Wolfram, Cohen, Biemond II and Usher syndromes. Cohen syndrome has long tapering fingers, a classic facial appearance and high myopia. The presence of diabetes insipidus in addition to diabetes mellitus suggests Wolfram syndrome (also known as DIDMOAD syndrome). The macula is normal in DIDMOAD syndrome. The presence of iris coloboma suggests Biemond syndrome. Obesity is not a feature of Usher syndrome and most of the systemic findings seen in Alstrom syndrome are absent in Usher syndrome. Vestibular abnormalities, as seen in Type 2 Usher syndrome but do not occur in Alström.

Management

Correction of refractive error and vision rehabilitation is required. Given the poor prognosis for vision, early intervention is required. Patients should be screened periodically by echocardiogram to result out emerging cardiomyopathy. Prescription of tinted glasses to avoid photophobia can be attempted. Recommended health care guidelines include

1. Height, weight and BMI
2. Hearing assessment
3. Fasting Blood sugar
4. Serum lipid profile
5. Renal function tests
6. Liver function tests
7. Pediatrician consult
8. Cardiac evaluation by pediatric cardiologist
9. Systemic geneticist consult
10. Endocrinologist consult

Axenfeld-Reiger Spectrum (ARS MIM 180500)

Definition

Axenfeld–Rieger syndrome (ARS) is an autosomal dominant disorder, characterized by anterior segment dysgenesis, dysmorphic facial features and systemic developmental abnormalities. ARS is most often caused by mutations of either *FOXC1* (601090) and *PITX2* (601540). Other genes that have been implicated to have a possible role include *GJA1* [95]. These encode transcription factors which play a critical role in the development of the anterior segment of the eye. The timing of expression and dosage of these transcription factors is critical [96]. Gain of function or haploinsufficiency can result in similar phenotypes [87, 97, 98]. Patients with mutations in *PITX2* are more likely to have systemic abnormalities. An anirdicphenotype can result from 6p25 dosage abnormalities.

History

The clinical condition had been described earlier as several forms initially separated as Axenfeld anomaly, Axenfeld syndrome, Rieger anomaly and Rieger syndrome. It has since been recognized that these phenotypes all fall in a continuum, currently referred as Axenfeld-Rieger spectrum. Axenfeld described posterior embryotoxon with attached iris strands in 1920 [99]. Rieger anomaly was first described by Austrian ophthalmologist, Herweh Rieger, in 1935 [100, 101].

Epidemiology

Axenfeld-Rieger spectrum has an estimated prevalence of 1 in 200,000 people [102].

Systemic Manifestations

Dysmorphic Facial Features

The facies is characterized by subtle craniofacial dysmorphism which includes prominent forehead, broad and flat nasal bridge, mid-facial abnormalities maxillary hypoplasia, hypertelorism and telecanthus.

Dental
Absent teeth, microdontia, delayed eruption, cone shaped teeth and increased spacing between teeth may be seen.

Redundant Periumbilical Skin
Failure of involution of the periumbilical skin in the abdominal region leads to the typical "elephant trunk" umbilicus. Patients also have an increased incidence of umbilical hernia.

Others
Hypospadias in males, pituitary abnormalities, growth retardation and anal stenosis may be observed [103].

Ophthalmic Manifestations

Posterior Embryotoxon
Prominent anteriorly displaced Schwalbe line (the peripheral termination of Descemet's membrane and the anterior limit of the trabeculum) is referred to as posterior embryotoxon [104]. It is seen in 15 % of normal population [105]. It is one of the most consistent findings but not essential to make the diagnosis of ARS. However in the presence of posterior embryotoxon in a child with anterior segment dysgenesis and glaucoma, one should first consider ARS.

Abnormalities of the Iris
Several iris abnormalities can be observed including iris hypoplasia, correctopia and polycoria and most uncommonly, anirdia [106, 107]. Iris processes to the posterior embryotoxonmay or may not be present. Patients with aniridia phenotype do not have the other panocular features of aniridia due to *PAX6* mutation and are not at risk for Wilms tumor.

Glaucoma
Approximately 50 % of the patients develop glaucoma primarily due to the anterior segment dysgenesis [108, 109]. Glaucoma can develop in infancy, but usually tends to occur in adolescence or early adulthood.

Diagnosis

There are no specific diagnostic criteria. If systemic features apart from those discussed above occur, a chromosomal abnormality involving these genes should be suspected or alternative diagnosis considered. Peters anomaly, ICE (Iridocorneal-Endothelial) syndrome, aniridia, congenital ectropion uveae and ectopia lentis etpupillae may mimic ARS. Peter's anomaly is characterized by corneal opacification and variable degrees of irido- or lenticulo-corneal touch. ICE is unilateral and not found in early childhood. True anirdia is associated with foveal hypoplasia, corneal pannus, nystagmus and cataract. Congenital ectropion uveae is unilateral and characterized by prominent ectriopian uvea and a whitish tissue on the iris surface. Ectopia lentis etpupillae has no posterior embryotoxon but also has ectopia lentis in a direction opposite of the corectopia. It may be seen by slit lamp biomicroscopy but gonioscopy is required to detect it in subtle cases [107]. Clinical genetic testing is available. Chromosomal microarray can be useful in identifying the etiology of anirdia like phenotype in such patients in addition to the clinical differentiation discussed.

Management: Recommendations

Systemic
Hearing assessment, systemic genetics consult, dentist consult are required.

Ophthalmic
Patients with ARS have a life time risk of glaucoma and should be monitored. If glaucoma requires surgery, the angle anatomy may make trabeculotomy or goniotomy difficult if not impossible. Periodic monitoring of IOP and disc is critical in all patients with ARS as they have a life time risk of developing glaucoma.

Bardet-Beidl Syndrome (BBS)

Definition

Bardet-Biedl syndrome is an autosomal recessive genetically heterogeneous ciliopathy characterized by retinitis pigmentosa, obesity, renal dysfunction, polydactyly, developmental delay, and hypogonadism. It is one of the more common forms of syndromic RP. It shows very high interfamily and intrafamilial variability. Like most other autosomal recessive disorders, it is more common in highly consanguinous population. It is the first clinical condition where triallelic inheritance characterized by the requirement of 3 mutations in 2 genes to manifest the disease, has been demonstrated.

Bardet-Biedl syndrome can result from mutations in at least 14 different genes. These genes play a critical role in the structure and normal functioning of cilia. *BBS1* accounts for most cases of BBS. *BBS10* is the second most common gene involved. The product of eight genes implicated in the disorder, assemble to form a stable complex called the BBSome. This plays a critical role in signalling receptor trafficking to and from the cilia. Defects in any of the BBS genes eventually affects this complex resulting in ciliopathy and hence BBS. Patient with mutations in *BBS1* tend to be taller [110]. Heterozygous carriers have been shown to have increased risk of obesity, hypertension, diabetes mellitus, renal disease and adenocarcinoma [111, 112].

History

The disorder was previously grouped as one entity along with Lawrence-Moon syndrome as Lawrence-Moon-Bardet-Beidl Syndrome [113]. The first case was reported by Laurence and Moon in 1866. Laurence–Moon syndrome is usually considered a separate entity. Laurence-Moon syndrome is a distinct disorder characterized by the presence of paraplegia and absence of obesity and polydactyly [114].

Epidemiology

The estimated incidence is approximately 1:160,000 in northern European populations and 1:13,500 in some Arab populations [115].

Systemic Manifestations

Dysmorphic Facial Features

The facial features are often subtle and inconsistent: deeply set eyes, hypertelorism, down-slanting palpebral fissures, depressed nasal bridge, small mouth, malar flattening, and retrognathia. Minimal cranial dysmorphic features include brachycephaly, macrocephaly and male frontal balding.

Polydactyly

Polydactyly is seen in approximately 60–80 % of patients [115, 116]. Polydactyly is post-axial and can be seen in upper and/or lower limbs (see Fig. 21.2a–c). It might vary in severity from a small bump to a large complete finger. Other digital anomalies include syndactyly, brachydactyly, and clinodactyly and "sandal-gap" in toes.

Obesity

Patients with BBS usually have normal birth weight [112]. The obesity is truncal in nature and acquired over time. Most patients are obese and often also have associated endocrinological abnormalities. Insulin resistance can be observed and acanthosis nigricans might be seen. Factors contributing to obesity include increased food intake, decreased energy expenditure, reduced physical activity and increased peripheral leptin resistance [117].

Hypogonadism

Hypogonadotropic gonadism is more common in males than in females.

Urogenital

Cryptorchidism and micropenis may also occur. Complex structural urogenital abnormalities can occur in females including partial and complete vaginal atresia, septate vagina, duplication of the uterus, hematocolpos, persistent urogenital sinus, vesico-vaginal fistula, absent vaginal orifice, and absent urethral orifice [118–120]. Hypoplastic fallopian tubes, uterus and ovaries can also occur.

Renal

Both structural and functional abnormalities can occur. Renal manifestations include tubular disease, rare glomerular disease and cystic renal dysplasia [121]. End stage renal failure is one of the causes of morbidity and mortality [121, 122].

Other Features

Developmental delay, speech delay, behavioral abnormalities, brachydactyly, syndactyly, ataxia, diabetes, cardiovascular anomalies, hepatic fibrosis, Hirschsprung disease and anosmia have been reported [123].

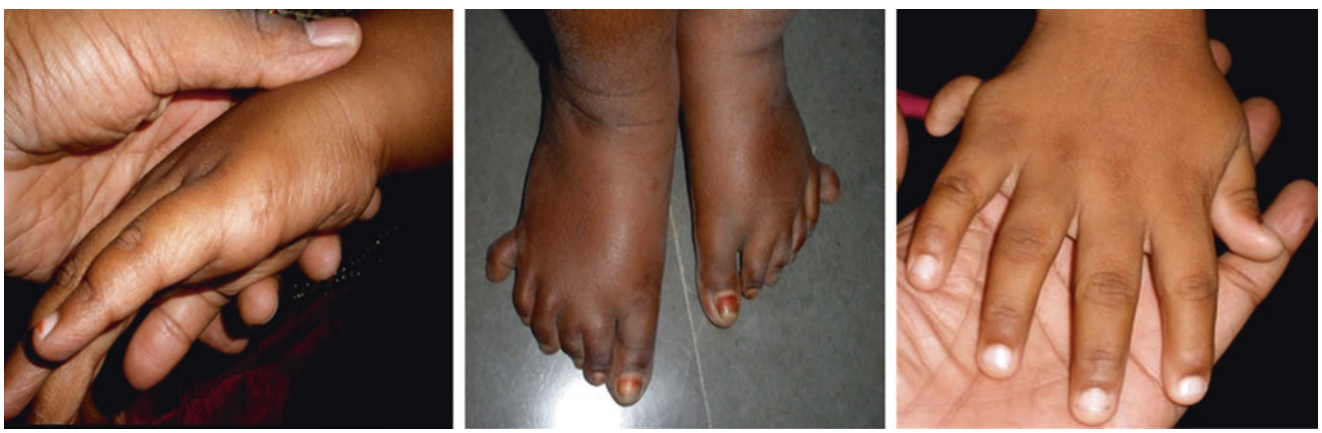

Fig. 21.2 (**a**) Surgical scars following removal of supernumerary post axial polydactyly. (**b**) Photograph of another patient with polydactyly of the foot. (**c**) Photograph of another child with polydactyly (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madura)

Ophthalmic Manifestations

The primary feature is retinal dystrophy. Although it is usually rod-cone, cone-rod phenotypes have also been reported and macular lesions are not uncommon [124]. Retinal dystrophy is observed in 90 % of patients. It usually begins in late childhood and shows typical features of retinitis pigmentosa, but may initially only manifest as internal limiting membrane irregularity and attenuated vessels. Night blindness is the earliest symptom, beginning usually at 7–8 years of age. It is followed by slowly progressive visual field loss. The maculopathy may or may not be associated with peripheral retinal degeneration. There is high inter-familial variability in the onset and severity of symptoms. Other ophthalmic findings include secondary nystagmus, cataract and strabismus as well as primary refractive errors, mainly myopia and astigmatism. Glaucoma is rarely seen.

Diagnosis

A diagnosis can be made based on the presence of four primary clinical features or a combination of three primary features and two secondary features [112].

The primary features include rod-cone dystrophy, polydactyly, truncal obesity, learning disability, hypogonadism and renal anomalies.

The secondary features include developmental delay, speech delay, behavioral abnormalities, and ocular manifestations other than retinal dystrophy like cataract, strabismus and refractive errors, ataxia, hypertonia, endocrine abnormalities like diabetes, cardiac, orodental anomalies and hepatic disease. Hirschsprung disease and anosmia are other secondary features.

Molecular genetic testing can confirm the diagnosis and microarray panel technology for genes known to be involved in BBS is available. There are several clinical conditions which resemble BBS. It is important to carefully observe for surgical scars as many patients would have had a surgical excision at a very young age for cosmetic reasons (see Fig. 21.2a). In the absence of polydactyly it is often difficult to differentiate BBS from many other clinical conditions. However onset of ocular features assists in distinguishing from other clinical conditions. Many patients reported in the literature who were initially diagnosed to have McKusick Kaufmann syndrome were later diagnosed to have BBS when retinal dystrophy became evident. It is currently recommended that all children with a possible diagnosis of McKusick-Kaufman syndrome made during infancy should be re-evaluated for ophthalmological findings and other signs of BBS during follow-up [125].

Differential Diagnosis

McKusick-Kauffman Syndrome (MKS)

It is characterized by the triad of hydrometrocolpos, postaxial polydactyly, and congenital heart disease. It is caused by mutation of *MKKS*, which can also cause BBS accounting for the similar clinical features. MKS is also inherited in an autosomal recessive manner. The main differentiating feature is the absence of retinal dystrophy in MKS.

Meckel-Gruber Syndrome

Meckel-Gruber syndrome, another autosomal recessive condition is usually lethal. It consists of the triad of occipital encephalocele, large polycystic kidneys, and postaxial polydactyly. It is associated with other anomalies that include genital anomalies, central nervous system malformations, and fibrosis of the liver. Pulmonary hypoplasia is the most common cause of death. Mutations in *MKS1* and *TMEM67* can also cause Bardet-Biedl syndrome, thereby demonstrating phenotypic overlap between these two conditions [126, 127].

Alström Syndrome (See Above)

Biemond Syndrome

The presence of ocular coloboma in a child with features with BBS should alert the clinician to this diagnosis. Hydrocephalus and facial dyostosis are additional features.

Cohen Syndrome

This autosomal recessive inherited disorder is characteristised by facial dysmorphism, truncal obesity and retinal dystrophy. There is no polydactyly but the fingers are long and tapering. Some patients also have hyperextensibility of joints. Cerebellar involvement is common and revealed by neuro-imaging. The retinal dystrophy is also different from BBS, and more characterized by pathologic myopia. Transient neutropenia is seen. Intellectual disability tends to be less severe than in BBS. Microcephaly is also a feature.

Management: Recommendations

Systemic

Renal function tests including blood urea and serum creatinine, ultrasound abdomen and pelvis to detect renal and urogenital anomalies is advised. Blood pressure and periodic weight measurement and monitoring should be performed. Developmental assessment, endocrinological evaluation and hearing assessment should be performed. Polydactyly might also cause not only cosmetic concerns but can also cause significant functional limitations in some patients including writing. Pre-axial polydactyly can occur as an isolated genetic disorder or can be seen in other genetic syndromes but is not seen in BBS.

Ophthalmic

Although there is currently no specific treatment for the retinal dystrophy in BBS, a gene therapy trial for one genotype is expected in the near future.

Blepharophimosis Syndrome (BPES MIM 110100)

Definition

Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES; OMIM 110100) is an autosomal dominant syndrome characterized by the presence of four adnexal features: shortened horizontal palpebral fissure length, ptosis, epicanthus inversus, and telecanthus [128]. It has two subtypes. Type I is characterized by the additional finding of primary ovarian failure in affected females. Type 2 does not have ovarian failure. Mutations in the fork head transcription factor gene *FOXL2* have been found to be responsible for BPES. There has been only one report of autosomal recessive transmission in an Indian family [129]. Penetrance appears to be 100 % in BPES1 and 96.5 % in BPES2 [130]. In BPES1 there is transmission by males only as females are infertile. In BPES2, transmission occurs through both sexes. Fifty percent of cases are due to *de novo* mutations. *FOXL2* is the only gene currently known to be associated with BPES. A patient with BPES and genital malformations was reported to have a deletion del(7)(q34) [131]. *FOXL2* gene has a single exon and the encoded protein has an alanine-rich domain. Mutations predicted to result in proteins truncated before the polyalanine tract preferentially lead to BPES1.

Polyalanine expansions preferentially lead to BPES2. Positive correlation between the size of the polyalanine expansion and the penetrance of the BPES phenotype has been reported [129].

Occasionally individuals with BPES may have cytogenetic rearrangements, including interstitial deletions or translocations involving locus interface between 3q22.3 and 3q23 [132] Waardenburg [133] suggested that the ocular defects seen in this syndrome possibly occurred during the third month of intrauterine life as this timing coincides with the critical period in the development of the ovary and the beginning of formation of the uterus by fusion of the Mullerian ducts. It has been shown in mice that the *Foxl2* gene is expressed in the mesenchyme of developing mouse eyelids and adult ovarian follicles [134].

History

Von Ammon' first used the term blepharophimosis in 1841 [135]. However it was Vignes in 1889 that first associated blepharophimosis with ptosis and epicanthus inversus [136].

Epidemiology

The exact frequency of BPES is unknown [137].

Systemic Manifestations

Apart from the primary ovarian failure seen in females affected with BPES1, there are no systemic findings. Secondary sexual characteristics in BPES1 are normal. Intellectual development is usually normal although mild intellectual disability has occasionally been reported and is usually present when a microdeletion is the cause. Large deletions often can cause other associated features like microcephaly, intellectual disability, and growth delay [138–141]. (Balanced translocations involving 3q23 lead to classic BPES without these additional findings.)

Ophthalmic Manifestations

See Fig. 21.3.

Shortened Horizontal Palpebral Fissure Length

The horizontal palpebral fissure length in individuals with BPES usually measures less than 20 mm.

Ptosis

Ptosis is usually severe with poor levator function and present at birth. Patients might use their frontalis muscle in an attempt lift the drooping lid or adopt a compensatory chin up posture. Though the ptosis can cause stimulus deprivation amblyopia or uncorrected refractive error and anisometropia may also contribute.

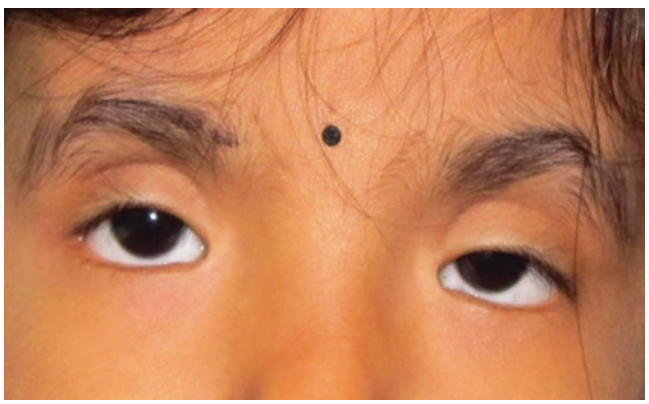

Fig. 21.3 This female child has ptosis, epicanthus inversus, telecanthus and blepharophimosis, the characteristic features of BPES (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Telecanthus

Telecanthus has been reported as the most consistent finding of the syndrome [137]. It is characterized by lateral displacement of the inner canthi with normal interpupillary distance. It may or may not be associated with hypertelorism.

Epicanthus Inversus

BPES is characterized by the presence of epicanthus inversus, where the lower lid contributes to most of the epicanthus and the epicanthal fold extends onto the lower lid below the lashes. Unlike other types of epicanthus, epicanthus inversus does not improve much with age.

Other Eye Abnormalities

Congenital nasolacrimal duct obstruction and strabismus also have a higher incidence in BPES [142]. Hypoplastic supraorbital rims, bushy eyebrows, low set ears and broad nasal bridge are other reported findings particularly in patients with deletions. There is often lateral displacement of the upper and lower lacrimal puncta, more than what would be expected from the lateral displacement of the inner canthi alone.

Diagnosis

BPES is a clinical diagnosis. Molecular genetic testing is currently available.

Chromosomal microarray may be indicated when non ocular features, in particular developmental delay, other than ovarian failure are present. In girls, a positive family history of BPES and infertility can indicate the type of BPES. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation in the family has been identified. There are many syndromes which have either ptosis or blepharophimosis as a feature. In particular, Ohdo syndrome is an X-linked recessive disorder with blepharophimosis, developmental delay and a characteristic facies. Say-Barber syndrome has blepharophimosis, developmental delay, thyroid dysfunction and dental anomalies.,

Management

There is no specific treatment for the primary ovarian failure and infertility in BPES1. Hormone replacement therapy and other reproductive assisted options are available.

Systemic

Females with BPES should be evaluated for primary ovarian failure.

Ophthalmological

The usual approach to this condition is surgical. Medial canthoplasty, for example the Roveda procedure, is often done first at which time correction of the epicanthus may also be accomplished. Ptosis surgery is sometimes performed as the last procedur unless earlier intervention for amblyopia is needed. Levator sling operations tend to be the procedure of choice. The last phase of the correction is usually the extension of the lateral canthus.

CHARGE Syndrome (MIM 214800)

Definition

CHARGE syndrome is the mnemonic for *C*oloboma, *H*eart anomaly, Choanal *A*tresia, *R*etardation of growth and/or development, *G*enital and/or urinary anomalies and *E*ar Anomalies and deafness. Not all features need to be present [143].

The diagnostic criteria as described by Blake et al. (1998), which was modified by Amiel et al. (2001) and subsequently by Verloes (2005) is shown in Table 21.2 [144–146]. The major diagnostic characteristics of CHARGE syndrome are the following.

The presence of four major criteria or a combination of three major and three minor criteria is required. The major features are specific to this syndrome while the minor features are not specific and can be observed in other clinical conditions.

CHARGE syndrome is most often caused by heterozygous mutations in the *CDH7* gene [147]. Most patients have *denovo* mutations. Increased paternal age appears to be risk factor [148]. Genetic testing is available on a clinical basis. The gene encodes the chromodomain helicase DNA-binding protein which is essential for the formation of multipotent migratory neural crest cells which subsequently undergo a major transcriptional reprogramming and acquire a broad differentiation potential. These then migrate throughout the body, giving rise to various important structures that include craniofacial bones and cartilages, the peripheral nervous system and cardiac structures.

History

Hall (1979) and Hittner et al. (1979) provided the first descriptions of this syndrome and hence the eponym Hall-Hittner syndrome was suggested, though the simplicity of the acronym CHARGE has withstood the test of time [149, 150].

Table 21.2 CHARGE syndrome: diagnostic criteria and clincial features

Major criteria	
Coloboma	Coloboma of the iris, retina, choroid, disc; microphthalmia
Cranial nerve dysfunction or anomaly	I: hyposmia or anosmia
	VII: facial palsy (unilateral or bilateral)
	VIII: hypoplasia of auditory nerve
	IX/X: swallowing problems with aspiration
Choanal atresia or stenosis	Unilateral/bilateral: bony or membranous atresia/stenosis
CHARGE syndrome ear	External ear anomalies including "snipped off" helix, prominent antihelix that is usually discontinuous with tragus, triangular concha, decreased cartilage.
	Middle ear: ossicular malformations
	Mondini defect of the cochlea
	Temporal bone abnormalities, absent or hypoplastic semicircular canals
Minor criteria	
Dysmorphic facial features	Square face with broad prominent forehead, prominent nasal bridge and columella and a flat midface
Genital hypoplasia	Micropenis, cryptorchidism in Males
	Hypoplastic labia
	Males and females: delayed puberty secondary to hypogonadotropic hypogonadism
Growth retardation	Short stature, with or without growth hormone deficiency
Developmental delay	Delayed milestones, hypotonia
Cardiovascular malformation	Tetralogy of Fallot, AV canal defects, and aortic arch anomalies
Orofacial cleft	Cleft lip and/or palate
Tracheoesophageal fistula	TE Fistula
Occasional Findings	DiGeorge sequence, Omphalocele or umbilical hernia, bony scoliosis or Hemivertebrae, Renal anomalies including dysgenesis, horseshoe/ectopic kidney, hand anomalies including polydactyly, altered palmar flexion creases, atypical split hand/split foot deformity, short webbed neck, sloping shoulders, and nipple anomalies
Typical CHARGE syndrome	4 Major criteria or 3 Major + 3 Minor
Probable/possible CHARGE syndrome	One or two major + several minor features

Epidemiology

CHARGE syndrome occurs in approximately 1 in 8500 to 10,000 individuals [151].

Systemic Manifestations

Dysmorphic Facial Features

CHARGE syndrome is characterized by a square face, flat midface, broad prominent forehead, and prominent nasal bridge and columella.

Heart Defects

Congenital malformations of the heart are seen in 75–85 % of patients. Many forms of congenital cardiac anomalies can occur.

Choanal Atresia

Observed in up to 60 % of patients, the choanal atresia may be membranous or bony, unilateral or bilateral. Bilateral choanal atresia presents as an emergency at birth with acute respiratory distress. Unilateral atresia may present as unilateral rhinorrhea. Choanal stenosis may also be an incomplete manifestation.

Retarded Growth and Development

Growth retardation and developmental delays commonly occur. Feeding difficulties due to coexistent congenital malformations such as orofacial clefts and tracheoesophageal fistula contribute to growth retardation. Both pre- and postnatal growth deficiency is observed, but patients usually have normal birth weight and length.

Genitourinary Anomalies

Cryptorchidism is seen in males and hypogonadotropic hypogonadism occurs in both males and females. Solitary kidney, hydronephrosis, and renal hypoplasia are some of the renal anomalies. They occur in approximately 25–40 % of children [144].

Ear Anomalies and Hearing

At least 80 % of patients have some form of ear anomaly. The abnormalities can involve the inner ear, middle ear and/or outer ear. The external ear is usually short and wide. The ear lobe may be absent. There is a prominent antihelix that is often discontinuous with the tragus, truncated helix and triangular concha. The middle ear may show ossicular malformations. The semicircular canals may be hypoplastic or absent. Mondini defect of the cochlea is a characteristic finding. The hearing loss can be sensorineural, conductive or

mixed and can vary from a mild to profound hearing loss. The presence of facial palsy suggests the presence of hearing impairment [152].

Vestibular Dysfunction

Absence or hypoplasia of the semicircular canals can impair vestibular balance, especially when combined with visual loss.

Cranial Nerve Dysfunction

Hyposmia, unilateral or bilateral facial palsy, hypoplasia of the auditory nerve and problems with swallowing resulting in aspiration are the most common cranial nerve anomalies observed in CHARGE syndrome.

Behaviour Abnormalities

Obsessive-compulsive, aggressive, and self-abusive behavior may be seen [153]. These abnormal behavior patterns are considered as aberrant attempts at communication about pain, unease, or frustration [154].

Hands

The hands may have a characteristic shape with broad palms and with a "hockey-stick" palmar crease, short fingers and small malformed thumbs.

Others

Skeletal anomalies including scoliosis, rib, vertebral anomalies and limb anomalies, dental anomalies, global developmental delay, and gastro-esophageal reflux may be seen in these patients. Prognosis for life is guarded in the presence of bilateral choanal atresia, cardiac abnormalities and teacheo-oesophageal fistula or esophageal atresia [155]. Male gender and central nervous system malformation appear to have adverse prognosis [143].

Ophthalmic Manifestations

Coloboma may be unilateral or bilateral and seen in 80–90 % of the patients. There is often asymmetric involvement. Macular involvement results in poor visual prognosis. The coloboma may also involve the optic nerve or the optic nerve may be dysplastic. Eyes with coloboma are also prone to retinal detachment. The coloboma may involve only the iris or in some patients there might be a fundus coloboma in the absence of an iris coloboma. Microphthalmia when present further reduces the visual prognosis. Isolated iris coloboma does not affect visual acuity.

Diagnosis

The diagnosis is said to be definitive if the patient has all four major criteria or three major and minor criteria each. The diagnosis is probable if the patient has one or two major and many minor criteria.

Differential Diagnosis

22q11.2 Deletion Syndrome

These children have a distinct facial dysmorphism very different from CHARGE syndrome. They also do not have the ear anomalies seen in CHARGE syndrome. Cleft palate in the absence of cleft lip is more common.

VACTERL association (*V*ertebral anomalies, *A*nal atresia, *C*ardiac anomalies, *T*racheoEsophageal fistula or esophageal atresia, *R*enal abnormalities and *L*imb anomalies) shares many minor features of CHARGE syndrome but lack the major clinical findings of CHARGE syndrome. Coloboma is absent.

Other differentials include Kabuki syndrome (distinct dysmorphic face, cleft palate,, persistent fetal fingertip pads) and renal-coloboma syndrome (also known as papillorenal syndrome, with its characteristic vacant optic disc) which has none of the other major features of CHARGE syndrome. The optic nerve "coloboma" seen in this syndrome is not due to failure of closure of the fetal fissure [156]. Burn-McKeown syndrome (oculo-oto-facial dysplasia) is characterized by choanal atresia, hearing loss, cleft lip/palate, cardiac malformation and protruding ears but also has nasal deformity and lower lid coloboma rather than intraocular coloboma [157].

Management

Systemic

The extensive involvement of several systems requires a team management. Anesthesia considerations include the presence of choanal atresia, cleft lip and palate, and possibility of tracheomalacia.

Ophthalmologic

A full dilated ophthalmologic examination by a pediatric ophthalmologist is required to determine the type and extent of the coloboma and to detect and treat refractive errors, strabismus and amblyopia. Cortical vision impairment (CVI) may contribute to the reduced visual acuity. Periodic follow-up examination to screen for retinal detachment is recommended.

Conradi Hünermann-Happle Syndrome: X Linked Dominant Chondrodysplasia Punctata (MIM 302960)

Definition

Chondrodysplasia punctata (CDP) MIM 302960 is a clinically rare and genetically heterogeneous disorder which encompassesa group of several skeletal disorders character-

ized by the presence of abnormal foci of calcification at the epiphyseal plates, causing radiographic stippling. Cutaneous and ocular findings also occur.

The X-linked recessive from of CDP, known as CPDX1 is caused by mutations in the *CPDX1* gene [158]. Autosomal dominant and recessive forms also occur [2]. Maternal vitamin K deficiency especially during early pregnancy and warfarin teratogenicity can cause CDP.

CPDX2 is inherited as an X-linked dominant disorder known as Conradi-Hünermann Happle syndrome and is the most well characterized form. Mutations in the gene encoding the emopamil-binding protein, encoded by the gene CPDX2 have been identified as an underlying cause. The syndrome occurs due to disturbances in the pathway of cholesterol biosynthesis. Increased levels of 8-dehydrocholesterol and 8[9]-cholestenol are found in these patients. These metabolites appear to have a role on the hedgehog proteins and sonic hedgehog pathway. The Hedgehog proteins play a critical role in the development of limb buds and their correct orientation and also in regulating the embryonic patterning [159], Cartilage formation and enchondral growth.

Affected males usually die in-utero. Rarely males with a milder phenotype can be seen they have an additional X chromosome (e.g. XXY) [160]. The gene is located at Xp11.22-p11.23. Variable inactivation of the X chromosome accounts for the variability in the ocular and systemic findings. Therefore, the phenotypic effect of a given mutation cannot be fully predicted. The hallmark of the condition is the punctate stippling of the epiphysis seen in radiographs in children [161, 162]. These findings tend to disappear after normal epiphyseal ossification in children. Hence early diagnosis is critical. Many clinical features resemble other X-linked dominantly inherited conditions.

History

The clinical features of CDPX2 were first described by Happle and hence referred to as Conradi-Hünermann-Happle (CHH) syndrome [163].

Epidemiology

Malou et al. suggested that the incidence could be 1 in 5, 00,000 [164].

Systemic Manifestations

Dysmorphic Facial Features

Mild dysmorphic facial features including frontal bossing, saddle nose and hypertelorism are often observed. The scalp hair, eyebrows and eye lashes are scanty. Patches of cicatricial alopecia and twisted hairs also occur. The scalp hair also appears coarse and dry.

Skeletal

The most characteristic finding is calcific stippling of the epiphyses, particularly seen in the knees. It is most consistent in the first year of life and later disappears. Asymmetric shortening of limbs and bowing of the legs are prominent features. Scoliosis is frequent and can occur even in early infancy. Growth retardation and short stature are often present.

Skin

Icthysoiform eythroderma and collodion membrane formation can sometimes occur. During infancy, scaling and eythroderma in swirls and linear patterns develop along the lines of Blaschko. The ichthyosis tends to improve with age and might be so subtle in adulthood that it can be easily missed.

Other Manifestations

Hearing loss, congenital cardiac defects, cleft palate, brain anomalies and renal anomalies have been reported [165]. The prognosis is generally good if the child survives infancy. Intellect is typically normal and combined with growth retardation gives a false impression that the child is smarter for the age as lay people easily underestimate the age of the affected patient.

Ophthalmic Manifestations

Nearly two-thirds of patients have cataracts at birth [166] (see Fig. 21.4). They are often asymmetric or even unilateral reflecting the variable X inactivation. Other eye abnormalities that have been reported include microphthalmia, nystagmus, glaucoma and optic nerve atrophy [167, 168]. Vitreoretinal abnormalities in the form of unusual vitreoretinal tractional complexes with underlying retinal pigment epithelium disturbance have been reported [169].

Diagnosis

There are no specific diagnostic criteria. It is a clinical diagnosis based on the constellation of clinical findings involving skeletal, ophthalmological and dermatological findings. The radiographic appearance of punctate stippling is highly suggestive of the diagnosis. Plasma sterol analysis of scales from skin lesions, or cultured lymphoblasts or fibroblasts showing increased concentration of 8[9]-cholestenol and 8-dehydrocholesterol strongly support the diagnosis. DNA testing is available.

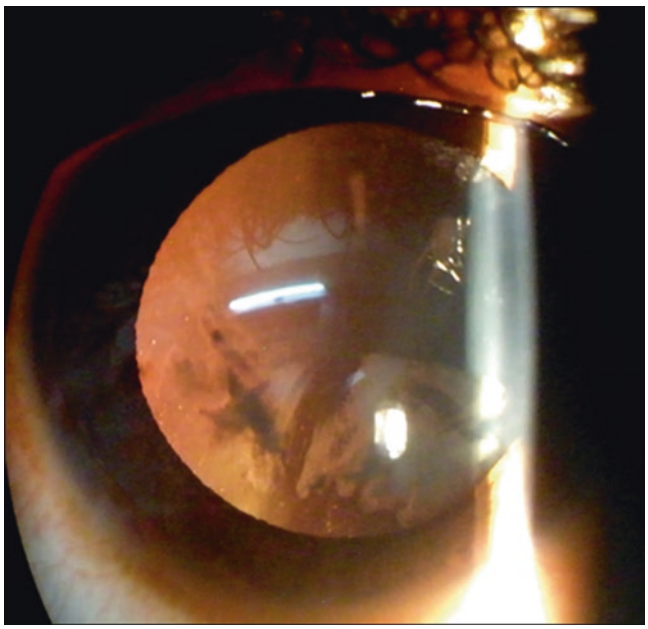

Fig. 21.4 Chondrodysplasia punctata. Partial cataract in a child with X linked Chondrodysplasia punctate (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Management

Systemic

Standard interventions are required for systemic abnormalities like hearing loss, cardiac and renal abnormalities. Orthopedic and dermatological consults should be arranged.

Ophthalmologic

Standard interventions are required for Ophthalmologic abnormalities.

Cockayne Syndrome

Definition

Cockayne syndrome is an autosomal recessive syndrome of premature aging characterized by growth failure, developmental delay, characteristic facies, behavioral and intellectual decline with early mortality and ocular manifestations. There are three subtypes [170]. Type 1 is the classic form and more common than the other subtypes. Type II is the most severe form and manifests prenatally. Type III is a milder form with late onset. The phenotypic spectrum of Cockayne syndrome also includes a fourth condition with overlapping features of Xeroderma pigmentosa and Cockayne syndrome (see Fig. 21.5c). Type I alone has diagnostic criteria. The presence of two major and three minor criteria in an older child is required for making the diagnosis. The presence of two major criteria alone in an infant is sufficient for a diagnosis.

Two major genes are currently known, bilallelic mutations of which cause Cockayne syndrome: excision repair cross-complementation group 6 and Group 8 (*ERCC6* and *ERCC8*). Mutations in other genes *ERCC1* cause Cockayne syndrome type 2 and COFS. Mutations in *ERCC4* cause Type 1. These genes are responsible for making proteins CSB and CSA respectively which actively play a role in repairing defective DNA. *ERCC8* is located at 5q12.1 and *ERCC6* at 10q11.23. There is no specific genotype-phenotype correlation. Mutations in *ERCC6* account for 65% and *ERCC8* account for 35% of the cases with Cockayne syndrome [171, 172]. A mild UV-sensitive syndrome has been reported due to a null mutation of *ERCC6* [173].

DNA is susceptible to damage by ultraviolet rays from the sun and by toxic chemicals, radiation, and free radicals. However normal DNA has the ability to rectify these errors by several repair mechanisms. Mutations in these two genes result in proteins that are unable to participate in some of the repair mechanisms of defective DNA resulting in progressive cumulative errors finally resulting in premature cell death [174]. There appears to be a preferential loss of function to repair active genes [175].

History

Edward Alfred Cockayne first described most of the features of Cockayne syndrome in 1933 [176].

Epidemiology

The incidence of Cockayne syndrome is approximately 2.7 per million births in Western Europe. This disease is probably under diagnosed and under reported [177].

Systemic Manifestations

The systemic features include neurological, dermatological, skeletal, dental and hearing abnormalities. Postnatal severe growth failure and neurological deterioration are the hallmark features. Signs of growth failure occur within the first 2 years of birth in the classic form and are evident at birth in type 2. The neurological findings include hypertonia, hypo or hyper-reflexia, tremor, ataxia and hearing loss. Neuroimaging often shows hypomyelination, supratentorial white matter loss, cerebellar atrophy or hypoplasia. Bilateral putaminal calcifications often occur in classic and

late onset Cockayne syndrome. In addition to these findings cortical calcifications occur more often in earlyonset Cockayne syndrome [178]. A typical stooped posture develops giving the appearance of horse riding stance due to contractures involving the knee joints. Contractures also develop in fingers and toes (see Fig. 21.5b). Dermatological findings include thinning of hair and skin. Cutaneous photosensitivity occurs and is especially more prominent in the variant that has overlapping features of Xeroderma pigmentosa. Dental abnormalities and caries are seen in later childhood. Other manifestations include endocrine abnormalities, renal abnormalities and hepato-splenomegaly [179]. Unlike other disorders that occur due to defective DNA repair, cancers are not common in Cockayne syndrome [180]. The mean age of death is 12 years but survival into the second or third decade has been reported [181]. In the variant with overlapping features with Xeroderma pigmentosa (see Fig. 21.5c), ocular surface neoplasms occur. The prognosis for life is poor with mortality within the first two decades.

Newborns with Type 2 present with severe prenatal growth retardation and then show minimal or no postnatal neurological development. Extensive contractures of the spine and other joints commonly occur. These findings contribute to mortality within the first decade.

Ophthalmic Manifestations

Enophthalmos, microphthalmia, congenital cataract, and miosis often occur [182] (see Fig. 21.5a). Pigmentary retinopathy associated with abnormal electroretinogram is the most consistent and common finding although the retinal exam is limited by miosis [182]. Refractive errors, mainly hyperopia, strabismus and nystagmus also occur [182]. Optic atrophy may occur in isolation or subsequent to pigmentary retinopathy [183]. Corneal opacity and reduced lacrimation have been reported [184]. Corneal perforation has also been reported [183].

Diagnosis

Diagnosis is based on the diagnostic criteria in Type 1. The diagnosis becomes more evident with progression of the condition. The main differential diagnoses include cerebro-oculo-facial syndrome (COFS) is considered as an allelic form of CS, and has overlapping features especially with CS type II and the most severe cases of the CS phenotypic spectrum [185]. Type II shares features with Cerebro-oculo-facial syndrome COFS. DNA testing is available. Other conditions that cause microcephaly and cataract can be differentiated by the sunken eye appearance and retinal dystrophy seen in Cockayne. Congenital infections can simulate Cockayne syndrome due to intracranial calcification. Other disorders due to defective DNA repair such as Blooms syndrome and Xeroderma Pigmentosa and syndromes with premature aging share some clinical features with Cockayne syndrome. Molecular genetic testing is available to confirm the diagnosis (Table 21.3).

Table 21.3 Cockayne syndrome: Diagnostic Criteria and Clinical Features

Major criteria
Postnatal growth failure
Progressive microcephaly and neurologic dysfunction
Minor criteria
Cutaneous photosensitivity with or without thin or dry skin or hair
Demyelinating peripheral neuropathy diagnosed by electromyography, nerve conduction testing, and/or nerve biopsy
Pigmentary retinopathy and/or cataracts
Sensorineural hearing loss
Dental anomalies, including dental caries, enamel hypoplasia, anomalies of tooth number, tooth size and shape
Cachectic dwarfism with thinning of the skin and hair, sunken eyes, and a stooped standing posture
Characteristic radiographic findings of thickening of the calvarium, sclerotic epiphyses, vertebral and pelvic abnormalities
Infants: 2 Major alone is sufficient for diagnosis
In Older children, 2 Major + 3 minor criteria is required for making a diagnosis

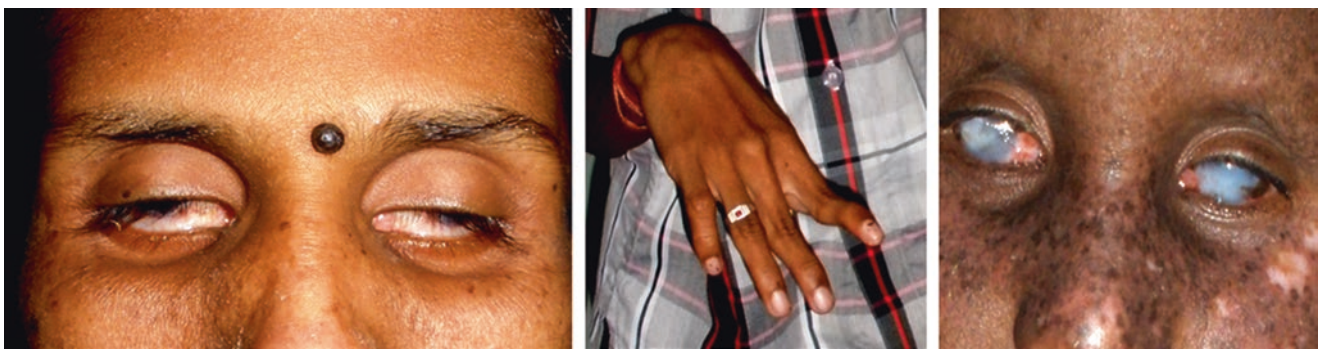

Fig. 21.5 Cockayne syndrome. (**a**) This patient with Cockayne syndrome has deep set eyes (enophthalmos), lagophthalmos and small pupils. She also has cataract. She had retinal dystrophy. (**b**) Contractures are shown in the hand of her sibling, who also was affected with Cockayne syndrome. (**c**) This child has Xeroderma pigmentosa and Cockayne syndrome (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Management

Ophthalmological

Perhaps the most difficult aspect of ophthalmic management is the limitations imposed by the miosis. This may artifactually reduce electroretinogram responsiveness and complicate cataract surgery. Appropriate surgical techniques are required for the latter. Viusal prognosis is poor due to the retinal dystrophy.

Systemic

Monitoring of growth and developmental assessment is necessary. The prognosis for life is poor due to progressive nature of the condition and failure to thrive. Children are at higher risk for anesthesia due to difficulties in airway management and higher risk of gastric aspiration. Laryngeal mask airway appears to be safer than intubation [186, 187].

Cornelia De Lange Syndrome

Definition

Cornelia de Lange Syndrome (CdLS) is a developmental malformation syndrome characterized by short stature, intellectual disability, characteristic dysmorphic facial features, hirsutism, and limb abnormalities. Lifespan may be reduced particularly in more severely affected persons with major malformations but more mildly affected individuals have lived well into their 40s and 50s.

A diagnosis of CdLS is made based on any one of the criteria.

- A disease causing mutation of the genes *NIPBL*, *SMC1A* or *SMC3* by mutation analysis.
- Criteria for facial features + 2 of (growth/development/behavior)
- Criteria for facial features + 3 other criteria (growth/development/behavior + 2 from other category)

The diagnostic criteria is shown in Tables 21.4 and 21.5

Muatations in one of six genes can cause CdLS. All five genes, *NIPBL*, *SMC1A*, *SMC3*, *HDAC8*, *EP300* and *RAD21*, encode components of the cohesion complex. A milder phenotype with characteristic facial features but with less severe cognitive and limb involvement is seen in individuals with mutations in *SMC1A* and *SMC3 NIPBL*, *EP300* and *SMC3*-related CdLS have an autosomal dominant pattern of inheritance. HADC8 and *SMC1A*-related CdLS are X-linked recessive. The *EP300* phenotype tends to be milder. Patients with mutations in HDAC8 have some atypical features including large anterior fontanel, broader nasal root, hooded eyelids and a pleasant personality [188]. Patients with mutations in RAD21 show growth retardation, minor skeletal anomalies and facial features that overlap with typical CdLS. The phenotype is milder [189].

Table 21.4 Cornelia de Lange syndrome: diagnostic criteria and clincial features

CdLS: diagnostic criteria[a]	
A disease causing mutation of the genes *NIPBL*, *SMC1A* or *SMC3* by mutation analysis **OR**	
Criteria for facial features + 2 of (growth/development/behavior) **OR**	
Criteria for facial features + 3 other criteria (growth/development/behavior + 2 from other category)	
Facial features	Eyebrows that meet at the midline and > three or more of the following:
	Long eyelashes
	Short nose, anteverted nostrils
	Long, prominent area between upper lip and nose
	Broad or depressed nasal bridge
	Small or square chin
	Thin lips, downturned corners
	High palate
	Widely spaced or absent teeth
Growth	**(> two or more of the following)**
	Weight below fifth percentile for age
	Height/length below fifth percentile for age
	Head circumference below fifth percentile for age
Development	**(> one or more of the following)**
	Developmental delays or intellectual disability, with speech more affected than motor skills
	Learning disabilities
Behavior	(> two or more of the following)
	Attention deficit disorder plus hyperactivity
	Obsessive-compulsive characteristics
	Anxiety
	Constant roaming
	Aggression
	Self-injurious behavior
	Extreme shyness or withdrawal
	Autistic-like features

[a]Diagnostic criteria for Cornelia de Lange Syndrome (*CdLS*) were created by the CdLS Foundation's Medical Director Antonie Kline, M.D., in collaboration with members of the Clinical Advisory Board of the CdLS Foundation and the Scientific Advisory Committee of the World CdLS Federation

The protein products of the genes appear to play an important role in regulating the structure and organization of chromosomes and are also involved in the repair of damaged DNA. They influence the activity of other genes in the developing limbs, face, and other parts of the body.

History

A German physician Brachmann first described an autopsy of an affected child, but it was Dutch pediatrician Cornelia de Lange who described two surviving children with features

Table 21.5 Cornelia de Lange syndrome: diagnostic criteria and clincial features

Minor criteria
Musculoskeletal (> one or more of the following)
Absent arms or forearms
Three or more of the following or small hands and feet and/or missing digits with two or more of the following
Fifth finger Clinodactyly
Abnormal palmar crease
Dislocated elbow/abnormal elbow extension
Short first knuckle/proximally placed thumb
Bunion
Partial webbing between second and third toes
Scoliosis
Chest or sternum deformity
Hip dislocation or dysplasia
Neurosensory/skin (three or more of the following)
Droopy eyelid(s)
Tear duct malformation or inflammation of eyelid
Nearsightedness
Major eye malformation or peripapillary
Deafness or hearing loss
Seizures
Mottled appearance to skin
Excessive body hair
Small nipples and/or belly button
Other major systems (three or more of the following)
Gastrointestinal malformation/malrotation
Diaphragmatic hernia
Gastroesophageal reflux
Cleft palate or submucous cleft palate
Congenital heart disease
Micropenis
Abnormally placed opening of urethra on penis
Undescended testes
Renal or urinary tract malformation

of this syndrome. The syndrome is sometimes referred to as Brachmann-de Lange syndrome.

Epidemiology

The approximate incidence of this syndrome is 0.6–10 in 100,000.

Systemic Manifestations

Dysmorphism

The dysmorphic features include small or depressed nasal bridge with anteverted nares, small or square chin, long philtrum, thin vermilion border of upper lip, down turned corners of the mouth ("carp shaped"), high arched palate (or cleft palate), micrognathia and small, widely spaced teeth or oligodontia. Patient may show hirsutism as well. Other possible findings include small nipples, small umbilicus and cutis marmorata.

Growth

Weight, head circumference and height are all usually less than fifth percentile both prenatally and after birth. Proportionate short stature occurs. There appears to be a genotype-phenotype correlation between the degree of growth, developmental delay and limb defects [190].

Development and Behavior

A wide range of developmental delays and intellectual disability is seen. There is also a wide spectrum of behavioral patterns including attention deficit disorder, obsessive compulsive disorder, anxiety, aggression, self-injurious behavior and some patients show autistic features. Children are often non verbal even in the presence of normal hearing.

Neurological

Sensorineural hearing loss is seen in 80 % of children with CdLS [191]. Seizures. Some children have a low pitched cry which tends to disappear in late infancy.

Musculoskeletal

Limb reduction defects are a cardinal feature often with oligodactyly, in particular a single digit. In mildly affected children, there is only small hands and feet. Patients with CdLS are also prone to Raynaud phenomena. Clinodactyly, abnormal palmar crease, radial head dislocation, difficulty in elbow extension, short first metacarpal, proximally placed thumb, bunion, partial syndactyly, scoliosis, pectus excavatum and hip dysplasia or dislocation and all been reported.

Gastointestinal

The most common cause of death and also behavioural abnormalties are related to the gastrointestinal tract, in particular gastroesophageal reflux. Other findings include gastrointestinal malformation, and uncommonly, diaphragmatic hernia. Pyloric stenosis is the most frequent cause of persistent vomiting in the newborn period.

Cardiovascular

Approximately 25 % of patients with CdLS have congenital heart disease [192]. Ventricular septal defects, atrial septal defects, pulmonic stenosis, tetralogy of Fallot, hypoplastic left heart syndrome, and bicuspid aortic valve occur in decreasing order of frequency.

Genitourinary

Micropenis, hypospadias, cryptorchidism, genitourinary malformations have been reported [192].

Ophthalmological Manifestations

Synophrys and long eye lashes although not specific, are seen in over 95 % of children with CdLS. A down sloping V-shaped configuration of the eyebrows as they met and extended onto the upper part of the nasal bridge is common. Brow hypertrichosis may be observed. Down-slanting palpebral fissures are less common. Congenital ptosis with poor levator function may be unilateral or bilateral. Severe ptosis was reported to be found among individuals with truncating (nonsense and frame shift) mutations as compared with individuals with missense mutations [193]. Blepahritis with recurrent blepharoconjunctivitis is extremely common and often misdiagnosed as nasolacrimal duct obstruction which is also if high incidence. Other findings include strabismus, nystagmus, and mild microcornea [194]. In almost all children, fundus examination shows a peripapillary pigment ring. High myopia is frequent but retinal detachment may either be due to the myopia or self induced trauma. Less common ophthalmologic abnormalities include glaucoma, cataract astigmatism, optic atrophy, and coloboma of the optic nerve [195–197]. Other findings include ptosis, blepharitis, tear duct malformation, myopia more than 6 D, and peripapillary pigmentation.

Diagnosis

A diagnosis is done based on clinical features and the diagnostic criteria showed in Table 21.6. DNA testing is available as a panel. Fetal alcohol syndrome shares several features with CdLS. Those include intrauterine growth retardation, failure to thrive, developmental abnormalities, microcephaly, facial hirsutism short palpebral apertures, short upturned nose, smooth underdeveloped philtrum, thin upper lip, and cardiac abnormalities. A history of alcohol use during pregnancy provides further clues to the correct diagnosis. Robert syndrome is also a differential diagnosis.

Management

Ophthalmological

Approximately half of these children have a behavioral profile that is characterized by an extreme aversion to touching of their face. This makes glasses, often need for myopia, quite difficult. Contact lens has been successfully used by a few families. The developmental delay may preclude the need for a distant focal point and myopia may even be advantageous. Consideration should be given to examination under anesthesia for identification of treatable peripheral retinal breaks in highly myopic children to prevent retinal detachment. Care during anesthesia is required as some of these patients are predisposed to malignant hyperthermia [198].

Lid hygiene with baby shampoos scrubs has proven to be extremely effective in this patient population in reduction of recurrent blepharoconjunctivitis and also avoiding nasolacrimal duct surgery. It is recommended that trial of this therapy be used in all patients with CdLS prior to nasolacrimal surgery unless there is clearly an anatomic malformation.

Some children have such severe congenital ptosis that there chin lift precludes ambulation. Early surgery, particularly when ambulation may be developmentally expected, can be very beneficial. Levator slings are usually the first procedure.

De Morsier Syndrome (MIM 182230)

Definition

The cardinal feature of De Morsier syndrome is septo-optic dysplasia (SOD), an early forebrain developmental anomaly with ocular and neurological abnormalities. Some reserve the eponym for those children with a characteristic cranoiofacial dysmorphism including broad forehead, typical facies and enlarged anterior fontanelle. SOD is usually characterized by optic nerve hypoplasia, pituitary hormone abnormalities secondary to pituitary hypoplasia and midline brain anomalies including agenesis of the corpus callosum and septum pellucidum. All the three features are present only in 30 % of the patients. The diagnosis of SOD is a clinical diagnosis and can be made if the patient has at least two of the three clinical features. The presence of only one clinical feature is being currently debated to represent a possible milder form of the spectrum of this condition [199]. Other brain findings may include siezures, cortical heteropias and other neuronal migration abnormalities such as schizencephaly.

Current research suggests a combination of genetic and environmental factors in the pathogenesis of SOD. The environmental risk factors that have been proposed include viral infections and specific medications. The disorder is usually autosomal dominant however and may be associated with mutations in *HESX1*. This gene plays a critical role in embryonic development of the eyes, the pituitary gland, and the forebrain. *HESX1* is a paired-like homeobox gene, which acts as a transcriptional repressor and it is one of the earliest markers of murine pituitary development. The frequency of pathological genetic mutations reported so far is very low and mutations have not been identified in many familial cases possibly suggesting the role of new genes. Disruption in blood flow to certain areas of the brain during critical periods of development due to genetic and environmental factors has also been implicated [200, 201].

History

Reeves in 1941 first described this condition as absence of the septum pellucidum in association with optic nerve abnormalities. Association of pituitary abnormality was described subsequently [202]. It is equally common in both sexes and is more common in infants born to younger mothers [203].

Epidemiology

Septo-optic dysplasia has a reported incidence of 1 in 10,000 newborns [204]. It is more common in children born to young mothers. The incidence of true de Morsier syndrome is much lower as SOD can be part of many other syndromes.

Systemic Manifestations

Endocrine

The most common endocrine abnormality is growth hormone deficiency. Thyroid hormone deficiency may occur. Sudden death has been reported due to disruption of the corticosteroid axis [205]. Panhypopituitarism with hypoglycemia, diabetes insipidus, reduced response to thyroid stimulating hormone, and hypogonadotropic hypogonadism can occur. SOD can be associated with precocious puberty secondary to hypothalamic dysfunction, or secondary to LH and FSH deficiency.

Neurologic

Seizures, developmental delay, and cerebral palsy are the most frequent neurologic associations seen with SOD [206]. The classic MRI finding is absence of the pituitary infundibulum and an ectopic posterior pituitary bright spot, often within the stalk. Other associated brain abnormalities include s cavum septum pellucidum, cerebellar hypoplasia, and aplasia of the fornix and Dandy-Walker malformation. Midline brain defects, including agenesis of the septum pellucidum and/or corpus callosum, are present [207].

Other Findings

Other associated findings include obesity, autistic behavior, developmental delays, hearing impairment and temperature instability. Limb malformations have been associated with some patients with SOD and support possible vascular disruption etiology [201]. Adrenal crisis can be precipitated by fever and dehydration due to corticotrophin deficiency resulting in sudden death [205]. Hypothermia and temperature instability also can result in sudden death.

Ophthalmic Manifestations

The characteristic finding is the presence of optic nerve hypoplasia. The hypoplasia is usually bilateral, but can be unilateral or asymmetric. In severe cases, ON aplasia may occur with a globe, but no identifiable optic nerve(s) or chiasm. Unilateral hypoplasia often causes strabismus and bilateral optic nerve hypoplasia may cause nystagmus. The classic hallmark of optic nerve hypoplasia is the presence of the double ring sign. The outer ring corresponds to the junction of the sclera with the lamina cribrosa and the inner ring corresponds to the actual optic nerve [208]. Other ophthalmological findings may include primitive, disorganized or tortuous retinal vascular patterns, foveal hypoplasiaor optioc atrophy. Astigmatism and amblyopia may further compound the visual loss [209]. Occlusion therapy and refractive correction can optimize visual outcomes Visual acuity is difficult to predict based solely on the appearance of the optic nerve. Microphthalmia and other developmental ocular abnormalities may also be seen in combination with features of SOD.

Diagnosis

There are currently no diagnostic criteria. Newborns with hypoplastic optic nerves, hypoglycemia, jaundice, undescended testes, large anterior fontanelles in the absence of increased intracranial pressure, with or without other associated midline abnormalities should raise strong suspicion of the diagnosis of SOD. Clinical ophthalmic examination and neuroimaging greatly assists in arriving at the correct diagnosis. B scan ultrasonography and MRI can be used to demonstrate the small optic nerves although with the latter one must be cautious that the interpretation is not a result of the MRI cut. Careful clinical examination is needed, particularly in mild cases. Identification of anomalous retinal vessel patterns emanating from the optic nerve and an increased distance between the nerve and the fovea may be subtle clues to the presence of optic nerve hypoplasia. When ordering neuroimaging to confirm the diagnosis of SOD, it is important to specifically request adequate cuts of the pituitary gland and its infundibular stalk. Hormonal testing should include thyroid function even if the neonatal screen was reported as normal. Additional hormonal testing can be conducted as indicated. Patterns of restricted growth are worrisome for growth hormone reduction.

Although *HESX1* is available for clinical testing, there are likely other genes involved in the causation of SOD. Multiple syndromes may have optic nerve hypoplasia or SOD as a manifestation. These can be recognized on the basis of other ocular and/or systemic findings. Clinical genetic testing is available for the *HESX1* gene. *OTX2* and *SOX2* mutations

can cause a picture that resembles SOD with an ophthalmia or microphthalmia.

Management

Systemic

Hormonal replacement therapy may be indicated. Ongoing monitoring of growth is essential. The prognosis is better with early diagnosis as hormonal abnormalities can be corrected earlier and risk for hypoglycemia, adrenal crisis can be reduced or avoided.

Ophthlamic

Comprehensive ophthalmic assessment including careful cycloplegic refraction is required. Patching treatment for amblyopia is indicated in unilateral optic nerve hypoplasia.

Joubert Syndrome (Classic) and Its Related Disorders (JSRD)

Definition

Classic Joubert syndrome (JS) is characterized by congenital malformation of the brainstem, in particular cerebellar vermis hypoplasia or aplasia causing a characteristic finding in MRI called the "molar tooth sign" [210]. Patients usually have hypotonia and developmental delay. Dysregulation of breathing results in episodic tachypnea or apnea. Ataxia and ocular abnormalities in the form of atypical movement disorders and retinal dystrophy can occur.

Joubert syndrome and related disorders (JSRD) includes conditions that share the molar tooth sign and the clinical features of classic Joubert syndrome but have other organ system involvement.

The syndrome is genetically very heterogeneous. Currently, 23 genes and several loci have been associated with Joubert syndrome and JSRD. These account only for approximately 50 % of affected patients. Autosomal recessive inheritance is the most common pattern of inheritance. An X linked recessive form due to mutations in *OFD1* also occurs [211]. A digenic pattern of inheritance also has been reported as well [212].

History

The syndrome was first described by Marie Joubert in 1969, in siblings from a large French-Canadian family with intellectual disability, ataxia, abnormal eye movement and agenesis of the cerebellar vermis presenting with episodic tachypnea [213]. The designation for the syndrome was suggested by Boltshauser and Islerin 1977 [214]. The disease defining molar tooth sign was described later [215].

Epidemiology

The prevalence of Joubert syndrome is approximately 1 in 100,000. Many studies suggest that this could be an underestimate [216].

Systemic Manifestations

A spectrum of systemic findings occurs depending upon the involved gene and hence a very thorough systemic examination will greatly assist the clinician in planning appropriate genetic testing (Table 21.6). Some of the systemic manifestations do not have any genotype-phenotype correlations.

Dysmorphism

Dysmorphic facial features include a long face with bitemporal narrowing, high-arched eyebrows, ptosis, prominent nasal bridge with anteverted nostrils, triangular/trapezoid shaped mouth, an open mouth appearance, tongue hypertrophy, prognathism, and low-set ears [217, 218].

Neurologic

The molar tooth sign is the most consistent finding and its presence is critical for making the diagnosis. It is characterized by the appearance of the brain stem in the shape of a molar tooth at the level of junction of midbrain and pons (see Fig. 21.6). The sign comprises an elongated, thick, and mal-oriented superior cerebellar peduncles, deep interpeduncular fossa and cerebellar vermis hypoplasia [219]. This sign has also been demonstrated sometimes by fetal MRI making prenatal diagnosis in some of the patients [220]. Hypotonia, ataxia, developmental delays and intellectual disability occur:intellectual disability can vary from mild to severe but is usually moderate [221]. The presence of ventriculomegaly and/or seizures in a patient with JSRD should prompt testing for CC2D2A-related JS [222].

Respiratory

Episodic apnea and tachypnea can occur in infancy and usually improves with age [219]. Hence birth history regarding apneic and tachypneic spells provides important diagnostic clues in an infant with retinal dystrophy and abnormal ocular movements. The combination of hypotonia, tongue hypertrophy and or obesity often predisposes to obstructive sleep apnea [223].

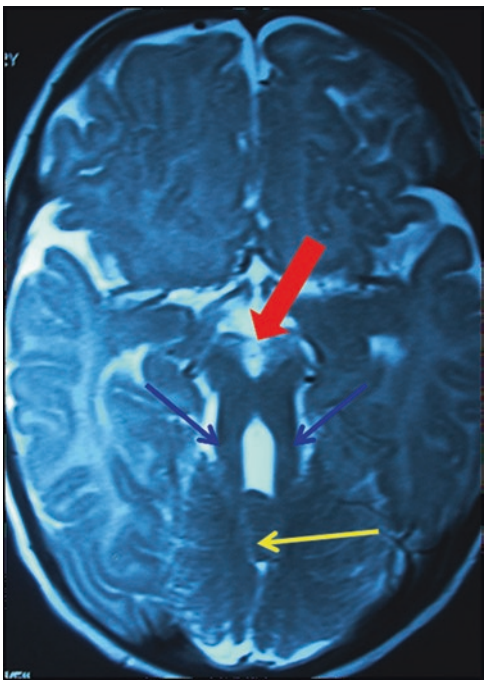

Fig. 21.6 Molar tooth sign in JSRD. Molar tooth sign in Joubert syndrome caused by elongated, thick, and mal-oriented superiorcerebellar peduncles (*blue arrows*), deep interpeduncular fossa (*red arrow*) and cerebellar vermis hypoplasia (*yellow arrow*) (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Renal

Juvenile nephronophthisis is characterized a chronic tubule-interstitial nephropathy that may progress to end stage renal disease. Cysts can occur at later stages. An adult polycystic kidney disease like phenotype has been linked to mutations in the gene *TMEM67* [224].

Retinal involvement usually has coexistent renal cystic involvement and was referred earlier as Dekaban-Arima syndrome [225].

Hepatic

Some of the patients with JSRD have congenital hepatic fibrosis. These patients also have chorioretinal coloboma and sometimes coexistent renal disease. COACH syndrome is an acronym for coloboma, cognitive impairment ("oligophrenia"), ataxia, cerebellar vermis hypoplasia, and hepatic fibrosis [226].

Ophthalmic Manifestations

Nystagmus

The nystagmus is usually bilateral, conjugate and horizontal. Vertical and torsional nystagmus may occur. A see saw form of nystagmus has also been reported [227]. Pendular nystagmus and gaze-holding nystagmus have been reported [228]. Vestibulo-ocular reflex is present but patients may have poor ability to cancel the vestibulo-ocular reflex horizontally and vertically [215]. Tonic deviation of their eyes laterally and alternating hyperdeviation have also been reported [229].

Oculomotor Apraxia

It is horizontal in nature and might be associated with compensatory head thrusting [227].

Abnormalities occur not only in saccades but also in pursuits [227].

Ptosis

Bilateral and asymmetric ptosis may occur [230].

Ocular Coloboma

The coexistence of fundus coloboma and retinal dystrophy in an infant with oculomotor abnormality should raise the suspicion of JSRD. Iris coloboma may or may not be present.

Retinal Dystrophy

A dystrophic retinal appearance or a frank retinal dystrophy might be seen [227]. Electro retinogram is usually attenuated or might be absent. Visual evoked potential may show asymmetric responses suggesting abnormalities in optic nerve decussation. Optic nerve dysplasia has been reported [215]. Disc coloboma and [230] Optic disc drusen have also been reported [231]. Iris neovascularization has been reported [232].

Diagnosis

The most consistent and obligatory sign that is required for diagnosis is the presence of the molar tooth sign.

A diagnosis of Classic or pure Joubert syndrome is based on the presence of three primary diagnostic criteria.

- Molar tooth sign
- Hypotonia during infancy with later development of ataxia
- Developmental delays or intellectual disability

The molar tooth sign is also noted in disorders that were initially identified as distinct syndromes. These include Senior-Loken syndrome, COACH syndrome, Varadi-Papp syndrome and Dekaban-Arima syndrome [233]. These syndromes now form a spectrum under JSRD [212].

Molar tooth sign may also be found in genetically related disorders like nephronophthisis, Cogan syndrome, Meckel syndrome, MORM, Oral-facial-digital syndrome, Hydrolethalus syndrome, Acrocallosal syndrome (ACLS).

Management Recommendations

Systemic

Periodic monitoring of liver, hepatic function is indicated in the absence of genetic testing. Polysomnography may be required to detect sleep apnea.

Ocular

Ptosis and strabismus are managed as indicated. Refractive errors need attention. There is no specific treatment for oculomotor apraxia.

Lowe Syndrome (OCRL MIM 309000)

Definition

Lowe syndrome (Oculo-cerebro-renal syndrome of Lowe, OCRL) is an X-linked recessive disorder which is characterized by involvement of the eyes, central nervous system and kidneys.

Lowe syndrome is caused by mutations in the *OCRL1* gene at Xq25-q26 which codes for the enzyme inositol polyphosphate 5-phosphatase. There is currently no known genotype-phenotype correlation. Sequence analysis detects mutations in 95 % of males and 95 % of female carriers. Several mutations, including truncation mutations, missense mutations, and large deletions have been reported. *OCRL* plays a role in membrane trafficking.

History

The syndrome was first described in 1952 by Charles Lowe and his colleagues [234].

Epidemiology

The incidence of Lowe syndrome is approximately 1 in 1,000,000 worldwide [235].

Systemic Manifestations

Dysmorphic Facial Features

Facial dysmorphisms are often present and consist in frontal bossing, deep-set eyes, chubby cheeks and a fair complexion [236].

Neurologic

Gross hypotonia is evident at birth. This also contributes to a significant delay in motor development and feeding difficulties. Deep tendon reflexes are often absent. Seizures are common. Intellectual disability and learning disability is seen to some degree in all affected males. Maladaptive behavior is also common including temper tantrums, irritability, stereotypy/mannerisms, obsessions/unusual preoccupations, and negativism [237].

Renal

Proximal tubular dysfunction is the main abnormality (Fanconi syndrome). Fanconi Syndrome is a proximal renal tubular defect which results in loss of potassium, phosphorus, bicarbonate, uric acid, glucose, and amino acid. Loss of bicarbonate results in acidosis. Renal phosphate wasting results in the development of renal rickets, osteomalacia and pathological fractures. Loss of bicarbonate, salt and water results in failure to thrive. Hypercalciuria, leads to nephrocalcinosis and nephrolithiasis can occur. All affected boys have some degree of proteinuria. Chronic renal failure accounts for significant morbidity and results in end stage renal failure. Vitamin D-resistant rickets, amino aciduria (relative sparing of branched amino acids), and reduced ammonia production by the kidney occur. Hypokalemia can occur. Nephrocalcinosis and nephrolithiasis may be a result of the Fanconi syndrome or due to vitamin D therapy for rickets.

Other Manifestations

Gastroesophageal reflux, crytporchidism, inguinal hernia and atelectasis, pneumonia, or chronic lung disease, joint dislocation due to hypermobility, delayed onset of puberty and dental malformations can occur. The most frequent causes of death include respiratory illness, and seizures. Patients often experience failure to thrive and short stature; undescended testis may be seen in up to first/third of patients [238].

Female Carriers of Lowe Syndrome

The clinical findings are highly variable due to the pattern of X inactivation (Lyonization) [239, 240].

Ophthalmic Manifestations

Congenital cataract occurs in all affected male children. They are often dense but begin as posterior polar opacities. Lowe syndrome is one of the few conditions which have coexistent congenital cataract and glaucoma [235]. Other ocular manifestations include microphthalmia, band keratopathy, and corneal keloids or scars. The eyes often appear enophthalmic even in the absence of microphthalmia.

Nystagmus and strabismus are secondary findings. Retinal dysfuction may also be observed [241]. Most carrier females especially post pubertal females tend to have fine irregular, punctate, smooth, radially oriented white to gray opacities in the lens cortex sparing the nucleus. Some of the carriers have snow flake like opacities [242].

Diagnosis

The triad of congenital cataract, hypotonia and renal tubular dysfunction in a male child may be considered as a diagnostic triad. Molecular genetic testing is available on a clinical basis. Enzyme assay in cultured fibroblasts is perhaps the best way to make the diagnosis. In affected males, enzyme levels are usually below 10%. Carrier females often have cataract. Dilated slit-lamp biomicroscopy examination to detect cataract is a highly sensitive test for detection of carriers [243].

Differential diagnosis includes Cystinosis, Nance Horan syndrome, congenital myotonic dystrophy, Smith-Lemli-Opitz syndrome and peroxisomal disorders such as Zellweger syndrome. Nance-Horan syndrome is also an X linked recessive disorder with cataract and dental anoamlies. However they lack the facial appearance of sunken orbits and bitemporal hollowing and the renal abnormalities seen in Lowe syndrome. Peroxisomal disorders are characterized by hypotonia, poor feeding and have distinctive facies different form Lowe syndrome (See under perxosomal disorders). Neonatal seizures are common. Bony stippling (chondrodysplasia punctata) of the patella (e) and other long bones may occur. Other findings that may be seen in older children include retinal dystrophy, sensorineural hearing loss, developmental delay, hypotonia, and liver dysfunction. Renal involvement also assists in differentiating Lowe syndrome from other conditions that cause congenital cataract and hypotonia like peroxisomal disorders, mitochondriopathies or congenital myopathies. Low molecular proteinuria is a consistent and a very sensitive marker for renal involvement. OCRL should be considered in boys with congenital cataracts and glomerular disease, even in the absence of any significant renal tubular abnormality [244]. Dent disease shares several clinical features with Lowe syndrome. Dent disease, also an X linked recessive disorder is characterized by proximal tubule (PT) dysfunction with low-molecular-weight (LMW) proteinuria and hypercalciuria, nephrolithiasis, nephrocalcinosis, and progressive renal failure and is seen only in males. Females are carriers. Mutations in *CLCN5* cause (Dent disease type 1) and mutations in OCRL1 cause (Dent disease type 2). However *CLCN5* gene mutations accounts for most Dent disease. Cataracts and neurologic deficits which are always seen in Lowe syndrome do not occur in Dent disease.

Management

Systemic

Hypotonia causes issues with feeding and nutrition. Associated gastroesophageal reflux further complicates nutrition and development. Renal function monitoring and prevention of development of rickets is essential. As these patients are very susceptible to electrolyte and metabolic imbalance especially during illness, dehydration or stress as in surgery, replacement of fluids, electrolytes and bicarbonate is necessary prior surgery.

Ocular

Cataract surgery is often complicated by the presence of coexisting glaucoma. Children may also need surgical procedures for glaucoma. The glaucoma is often difficult to manage. Visual rehabilitation is usually required and the prognosis is guarded.

Mitochondrial Syndromes

Mitochondria are considered the powerhouse of the cell and are critical for generating ATP by oxidative phosphorylation. Mitochondria have their own genome separate from the nuclear DNA but their function also requires proteins that are encoded by nuclear DNA. Disorders of mitochondrial function can be due to mutations in mitochondrial or nuclear DNA [245]. Only mutations in the mitochondrial genome have the mitochondrial pattern of matrilineal inheritance. Since the sperm does not contribute its mitochondria to the zygote, males do not transmit mitochondrial disease. Affected females can transmit the disease to all of their children, affecting both male and female children (with the exception of Leber hereditary optic neuropathy which is more common in male offspring).

Tissues with higher metabolic rate dependent on oxidative phosphorylation are most often affected including brain, muscles and muscles and hearing [246]. The severity of the phenotype depends upon heteroplasmy [247, 248]. Homoplasmy is the state of having only healthy or only mutated mitochondria while heteroplasmy is the mixed population of normal and mutated mitochondria. The proportion of normal and abnormal mutant mitochondrial DNA in each tissue determines the severity and the threshold (proportion of abnormal mitochondria in each tissue required to manifest disease) for the disease manifestation [249]. Patients should avoid medications that are toxic to mitochondria including aminoglycosides, valproate, fluoxetine, amitriptyline, chlorpromazine, haloperidol, diazepam, and alprazolam.

Other features often seen in most mitochondrial disorders like short stature, hearing loss, dementia, limb weakness, and diabetes mellitus may be seen.

Mitochondrial Encephalopathy, Lactic Acidosis and Stroke Like Episodes (MELAS MIM 540000)

Definition

This genetically heterogeneous disorder has multisystem involvement primarily involving the central nervous system and muscles.

MELAS is caused by mutations in mtDNA and is transmitted by maternal inheritance.

MELAS can result from mutations in any one of several genes, including *MT-ND1*, *MT-ND5*, *MT-TH*, *MT-TL1*, and *MT-TV. MT-TL1* is responsible for most cases [250]. Most of theses genes provide instructions for making transfer RNAs (tRNAs) Genetic counselling is complicated due to heteroplasmy for which the recurrence risk in not consistent even if the mutation is known. Males can be assured that their children will be unaffected. Genetic testing is available on a clinical basis. New *in vitro* fertilization techniques have been developed using a donor egg that has its nucleus removed and replaced by an unaffected donor mother's nucleus. Though it is clear that mitochondrial mutations are responsible for MELAS, the exact mechanism as how these abnormal proteins result in a spectrum of clinical findings is still unclear.

History

It was first described in 1984 [251].

Epidemiology

Mitochondrial diseases occur in about 1 in 4000 people. The exact incidence of MELAS is not known.

Systemic Manifestations

It typically begins during childhood. The symptoms usually begin with generalized tonic-clonic seizures, recurrent headaches, nausea, anorexia, and recurrent vomiting. Stroke like episodes occur following seizures. The episodes may be precipitated by physical exercise and heat. Febrile illness may trigger exacerbations. The severity of clinical manifestations depends upon heteroplasmy, a unique feature of all mitochondrial disorders.

Neurologic

The neurologic findings are usually the first symptoms to appear. These invariably occur in early childhood and almost all patients develop symptoms and signs before the beginning of the fourth decade. Stroke-like episodes are often precipitated by exercise. These "Stroke like episodes" are result of focal cerebral metabolic crisis and bear little resemblance to strokes of an atherosclerotic or thrombo-embolic etiology. This distinction is important to avoid misdiagnosis. Even in the absence of a focal deficit there may be focal EEG and MRI abnormalities. A stroke results in a permanent neurological deficit that persists more than 24 h. In a stroke like episode, the neurological function might fully recover after the episode but the resultant neuronal loss causes a gradual step-wise reduction in cerebral function [252]. Transient hemiparesis and cortical blindness can occur after these episodes. Patients may also develop altered consciousness following these attacks. Many patients develop acute migraine during the stroke. Behavioral abnormalities and autistic behavior may occur [253]. Hearing impairment may occur as a primary manifestation [254]. Myoclonus, learning disability, cerebellar signs, increased CSF protein and basal ganglia calcification are some of the other neurological findings seen [255–257].

Some of the neuroimaging findings are transient, occurring only during the time of stroke-like episodes. MRI often shows increased T2 signal, typically involving the posterior cerebrum and do not conform to the distribution of major arteries. Diffusion-weighted MRI might show increased apparent diffusion coefficient (ADC) in stroke-like lesions. Vasogenic edema and in some patients cytotoxic edema is responsible for the imaging findings. A decrease in N-acetylaspartate and an increase in lactate have been reported in H-magnetic resonance spectroscopy [257].

Ophthalmic Manifestations

Optic atrophy, pigmentary retinopathy and ophthalmoplegia are the common ophthalmic manifestations reported. Abnormal photopic and scotopic ERG can occur. Macular retinal pigment epithelial atrophy may be seen. A reversible, homonymous hemianopia, atypical retinitis pigmentosa with marked attenuation of the scotopic ERG, myopia and nuclear cataract has been reported in MELAS [258]. A clinical presentation of Chronic Progressive external ophthalmoplegia (PEO) with diabetes mellitus (DM), cardiomyopathy and deafness has been reported [259].

Diagnosis

The clinical triad of stroke like episodes, encephalopathy with seizures and dementia, and myopathy with lactic

acidosis and red ragged fibers when present along with any two of the three following clinical features, recurrent headache, recurrent vomiting and normal early psychomotor development confirms the diagnosis of MELAS syndrome. Ragged red fibers on muscle biopsy are often diagnostic. In patients with CPEO, the mutation might be seen only in the muscle tissue and may be missed in other tissues.

Kearns-Sayre Syndrome (MIM 530000)

Definition

Kearns-Sayre is a multisystem disorder predominantly affecting the eyes, central nervous system, skeletal muscle, and heart. It is a form of chronic progressive external ophthalmoplegia. KSS is caused by large deletions of mitochondrial DNA (mtDNA), resulting in the loss of genes involved in the oxidative phosphorylation pathway.

History

This triad of CPEO, bilateral pigmentary retinopathy, and cardiac conduction abnormalities was first described in 1958 by Thomas P. Kearns (1922), MD and George Pomeroy Sayre (1911).

The syndrome was described by Kearns in 9 unrelated patients who had known positive family history [260]. Mitochondrial deletions as a cause of KSS were established in 1988 [261].

Epidemiology

It occurs approximately in 1–3 per 100,000 individuals [262].

Systemic Manifestations

Cardiac

Several cardiac anomalies have been reported. The most serious concern for a patient with KSS is sudden cardiac death due to arrhythmias. Cardiac conduction disturbances are the most common. Atrioventricular block is the most common. Cardiac arrest has also been reported [263]. Also co-inheritance of Long QT syndrome and KSS has been documented [264]. Apart from the conduction disturbances, cardiomyopathy can occur [265].

Endocrine

Many endocrine abnormalities occur including hypoparathyroidism, menstrual abnormalities, growth hormone deficiency and diabetes mellitus occur [266]. Short stature, gonadal failure, hyperaldosteronism, hypomagnesaemia, abnormalities in calcification of bone and tooth has also been reported [267] Mitochondria are a prerequisite for steroidogenesis as well as the secretion and action of insulin [268].

Neurologic

Seizures and strokes are rare in Kearne-Sayre syndrome. Cerebellar ataxia, intellectual deficit, dysarthria, bilateral facial weakness are some of the common neurological findings. Calcification of the basal ganglia has been reported. Cerebellar ataxia, increased CSF protein content cerebrospinal fluid (CSF) protein content above 100 mg/dL are important and one of them is required for making the diagnosis apart from the presence of the characteristic triad. Syncope is a manifestation of cardiac arrhythmia.

Hearing

Sensory neural hearing loss can occur

Ophthalmic Manifestations

Ptosis

This is usually bilateral. Rarely patients might develop external ophthalmoplegia ahead of ptosis and may cause diagnostic confusion. Since these patients have poor bells phenomenon, Crutch glasses are recommended.

External Ophthalmoplegia

It is the most common ocular manifestation of all mitochondrial myopathies. Though there is external ophthalmoplegia, patients usually do not complain of double vision, (even when ptosis does not obscure the visual axis). There is progressive limitation of all movements.

Pigmentary Retinopathy

The most common form of retinal pigmentary retinopathy is salt and pepper retinopathy, which typically becomes more prominent with age [269]. it is one of the diagnostic triads of KSS.

Cataract

Cataract is Less Common

Cornea

Corneal abnormalities are less common but have been reported and can precede systemic findings by several years [270].

Optic Atrophy

This could follow optic neuritis [271].

Diagnosis

It is characterized by the triad of pigmentary retinopathy (salt and pepper retinopathy), progressive external ophthalmoplegia and onset before 20 years old of age. The presence of these three features and at least one of the following is required to make the diagnosis: The other three features include cardiac conduction defects, increased CSF protein and cerebellar ataxia. Other features often seen in most mitochondrial disorders like short stature, hearing loss, dementia, limb weakness, and diabetes mellitus may be seen.

Management

Systemic

Treatment of KSS is supportive. Regular periodic follow-up with a cardiologist is recommended. A permanent pacemaker/implantable cardioverter-defibrillator device has been recommended in those with high-grade heart block. Hearing aids may benefit those with sensorineural deafness. Coenzyme Q10 supplementation has been beneficial in some patients.

Ophthalmologic

Ptosis is best managed with crutch glasses. There is no specific cure currently for the pigmentary retinopathy.

Prognosis

Prognosis for vision and life is poor due to arrhythmias causing sudden cardiac death. Most patients die before the third decade due to heart block. The prognosis for life is better in CPEO than in Kearns-Sayre syndrome.

Myoclonic Epilepsy Associated with Ragged-Red Fibers (MERRF MIM 545000)

Definition

MERRF was first described by Fukuhara et al. [272] is characterized by the presence of myoclonus, generalized epilepsy, ataxia and ragged-red fibers (RRF) in skeletal muscle biopsy. Mitochondrial pattern of inheritance was demonstrated initially in a large family by Rosing et al. [273] Many clinical features overlap with MELAS and some patients initially be diagnosed to have one entity develop clinical features of the other during course of time [274–276]. Mutations in the genes *MT-TK*, *MT-TL1*, *MT-TH*, *MT-TS1*, *MT-TS2*, and *MT-TF* have been recognized to cause MERRF. Mutations result in deficiency of enzyme complexes that actively participate in the respiratory chain especially those involving NADH-CoQ reductase.

History

Shoffner at al first demonstrated mutations in mitochondria as a cause for MERRF [277].

Epidemiology

The exact prevalence of MERFF is not known.

Systemic Manifestations

Neruologic

The neurological features include myoclonus, weakness (myopathy), and spasticity.

Myoclonic epilepsy:

The characteristic feature of MERFF is myoclonic seizures.

Myoclonic seizures are sudden brief jerks or twitching of a muscle or group of muscles and the patient does not lose consciousness.

Myoclonic jerks, epilepsy, ataxia, peripheral neuropathy, and gradual deterioration of intellectual function can occur. Other features that have been reported include generalized tonic-clonic seizures, paroxysmal hearing impairment [276]. Migraine, homonymous hemianopia and hemiparesis have been reported [275] Basal ganglia calcification as seen in many mitochondrial disorders occurs [278].

Red Ragged Fibers

Muscle biopsies show many ragged-red fibers which is consistent with mitochondrial accumulation and shows abnormal mitochondria with concentric cristae. The biopsy also reveals COX deficiency. When muscle is stained with Gomori Trichrome, characteristic ragged-red fibers are visible under the microscope. This appearance is due to the accumulation of abnormal mitochondria below the plasma membrane of the muscle fiber. These may increase and extend throughout the muscle fiber as the severity of the disease increases. The mitochondrial aggregates causing an irregular contour of the muscle fiber and hence the name "ragged" fibers.

Others

Short stature and exercise intolerance is noted. There is an increased trendency for subcutaneous lipoma formation [279].

Ophthalmic Manifestations

Retinal pigmentary changes have been reported [280]. A mild form of ophthalmoparesis was reported [281]. Optic atrophy may also be seen.

Diagnosis

Increased blood and CSF lactate is common. The CSF protein is also increased.

Muscle biopsy typically shows ragged red fibers (RRF) with the modified Gomori trichrome stain and hyperactive fibers with the succinate dehydrogenase (SDH) stain. These RRF do not stain with the histochemical reaction for cytochrome c oxidase (COX). Occasionally, Rarely RRF may not be seen [281].

Molecular genetic testing for involved mitochondrial genes is possible.

Management

Systemic
Aerobic exercises may help in reducing the exercise tolerance.

Ophthalmologic
No specific treatment is available for the ophthalmoparesis or pigmentary retinopathy.

Prognosis

Neuropathy, Ataxia and Retinitis Pigmentosa (NARP) (MIM 551500)

NARP is a mitochondrial disorder characterized by the triad of proximal muscle weakness with sensory neuropathy, ataxia and retinitis pigmentosa. NARP is a progressive neurodegenerative disorder caused due to abnormalities in mitochondrial energy generation.

MT-ATP6 is the only mitochondrial gene in which mutations are known to cause NARP. NARP is almost exclusively associated with the m.8993 T>C/G mutation. Mutation m.8989G>C has been reported recently [282]. Other mutations in MT-ATP 6 are associated with Leigh syndrome or Leber's hereditary optic neuropathy (LHON).

History

NARP was first described by Holt et al. [248].

Epidemiology

The prevalence is approximately 1.9/100,000 [283].

Clinical Manifestations

Systemic

Neurologic
Neurogenic muscle weakness with sensory neuropathy is the main neurological finding. Seizures, learning difficulties, and dementia are other neurological findings [284]. Learning disability, developmental delay and ataxia usually appear early in children prior development of ophthalmological findings and neurological findings. Cerebral and cerebellar atrophy may be observed on MRI.

Ophthalmological
The earliest appearance is a salt and pepper retinopathy. The retinopathy is progressive [285]. Classic fundus findings of retinitis pigmentosa (Pale disc, bone spicules and vascular attenuation) occur with progression of disease. The ophthalmological findings usually appear in the second decade. The fundus findings are highly variable [286]. Electroretinogram (ERG) may reveal reduced amplitudes or may be normal. ERG may show predominantly cone dysfunction in some families and rod dysfunction in others [287]. Visual field loss worsens following retina disease progression.

Other Features
Short Stature, seizures, dementia, sleep apnea, hearing loss and cardiac arrhythmias are other findings that may be seen in NARP. Obstructive sleep apnea has been reported [288].

Diagnosis

The diagnosis is based on clinical findings, the presence of high lactate (more consistent in CSF), ERG abnormalities and Neuroimaging. The diagnosis can be confirmed by molecular genetic testing for mutations in the *MT-ATP6* gene. The main differential diagnosis includes maternally inherited Leigh syndrome (MIL) which may sometimes be caused with increased mutational load in the same 8993 T>C/G NARP mutation.

Management

Systemic
There is no specific treatment for NARP.

Ophthalmologic
There is no specific treatment for ocular findings of NARP.

Prognosis

The quality of life is severely affected as most patients become dependent on others and eventually wheel chair bound.

They share several clinical features common to other mitochondria disorders. However the main features of sensory neuropathy and ataxia are the dominating features. Mutations in the *MT-ATP6* gene cause NARP.

The general evaluation of mitochondrial disorders involves several clinical and biochemical tests. Most mitochondrial disorders require a panel of investigations. They include the following. Blood and CSF lactate and pyruvate levels, cardiac evaluation including echocardiogram and electrocardiogram, fasting glucose and HBA1C concentration to screen for and monitor diabetes mellitus, brain MRI and muscle biopsy are required. The characteristic finding in muscle biopsy is the presence of ragged-red fibers (RRF) with the modified Gomori trichrome stain. They are COX negative. Electromyogram and nerve conduction studies may be required. Biochemical studies of respiratory chain enzymes in muscle extracts may show decreased activities of respiratory chain complexes.

Möebius Syndrome (MIM 157900)

Definition

Möebius syndrome is a congenital complex developmental disorder of the brainstem with non-progressive facial weakness and limited abduction of one (rarely) or both eyes. It is currently recognized as one of the congenital cranial dysinnervation disorders (CCDD).

Möebius syndrome probably results from a combination of environmental and genetic factors.

Most cases of Möebius syndrome are sporadic. Autosomal dominant cases have been reported [289–292]. No specific gene has been identified though several loci have been suggested [289]. Cytogenetic studies in some reports have shown a possible location for the gene responsible for Möebius syndrome to be located at region 13q12.2-q13 [293, 294]. Other reports have suggested a possible location at 1p22 [295, 296]. A patient with an inherited inversion of the sixth chromosome has been reported [297]. Other suggested loci include 3q61 and 10q62 [298]. Recently mutations in *PLXND1* and *REV3L* have been reported in Möebius syndrome [299, 300].

Current research suggests that Möebius syndrome may result from a vascular insult to the brainstem during very early stages of embryonic development. Möebius syndrome is a complex regional developmental disorder of the brainstem. Defects at different levels at supranuclear, nuclear, or peripheral levels in different patients were suggested based on electrophysiological studies [301].

Environmental factors especially certain medications taken during pregnancy (Thalidomide and Misoprostol) and drug abuse like cocaine may also be risk factors for Möebius syndrome. Classic features of Möebius syndrome including involvement of the sixth and seventh cranial nerves, aberrant tearing, and recent observations of autism spectrum disorder (ASD have all been reported due to the teratogen thalidomide). Thought the most frequent eye complication due to thalidomide is Duane syndrome, secondary to damage to the cranial nuclei in the brain stem. Hence this condition probably results from a combination of environmental and genetic factors [302].

The recurrence risk appears to be as low as 2%. The absence of skeletal defects appears to increase the risk of recurrence in the family [300].

Based on neuropathology findings, Towfighi et al. proposed four categories of Möebius syndrome (MIM 157900) [303]

Group I: Hypoplasia of cranial nerve nuclei resulting from congenital rhombomeric maldevelopment
Group II: Neuronal loss and neuronal degeneration secondary to a defect in the facial peripheral nerve
Group III: Decreased neurons as well as degeneration, focal necrosis, gliosis, and calcifications in the brainstem nuclei due to vascular insufficiency or infection
Group IV: Primary myopathic changes without lesions in the cranial nerve nuclei or nerves.

History

Von Graffe first described this condition in 1880 [304]. Möebius subsequently described the features more elaborately in 1888 [305].

Epidemiology

The prevalence rate reported is 1/150,000 of babies born alive [306].

Systemic Manifestations

Neurological Features

A characteristic mask like facies is seen due to bilateral facial nerve palsy. Patients have an inability to smile normally. Micrognathia is common with or without Pierre Robin sequence.

Motor abnormalities and poor co-ordination occur. Cerebellar hypoplasia has been reported [307]. Although most patients have normal intelligence, intellectual and learning disability have been described [308]. Behavioral issues and autistic spectrum disorders may occur [309]. Many cranial nerves including the 3rd, 5th, 8th, 9th, 11th and

12th may be affected. The latter may be manifested by crenulations on the side of an extended tongue or deviation when the tongue is extended. Inability to suck may be one of the earliest symptoms. Other symptoms may include difficulty in swallowing, excessive drooling, and speech difficulty. Verzijl et al. suggested that the unusual distribution of the facial weakness in Möebius syndrome possibly suggests that other cranial nerves, including the trigeminal, hypoglossal, or glossopharyngeal nerve, aberrantly innervate some lower facial muscles [310]. MRI demonstrated absence of facial nerves in those patients [310]. Möebius syndrome is part of a more complex congenital anomaly of the posterior fossa as suggested by radiological evidence [311]. Clinical extension beyond the lower brainstem and cerebellum are common. Neuroimaging may reveal hypoplasia of the brain stem, straightening of the floor of the fourth ventricle and absence of the medial colliculus at the level of the pons. There is hypoplasia of cranial nerve nuclei VI and VII. Some patients might also show absence of the hypoglossal eminence at the medulla [311, 312].

Limb Anomalies

Upper limb anomalies include brachydactyly, clinodactyly, and syndactyly. Lower limb anomalies include pes planus, and talipes equinovarus. Poland syndrome (Unilateral absence or hypoplasia of the pectoralis muscle and variable degree of ipsilateral hand and digit anomalies) [313, 314], may be associated with Möebius syndrome.

Other Findings

Hypogonadotropic gonadism has been reported [315]. It includes several other clinical features: hearing loss, other cranial nerve dysfunction, motor, orofacial hypotonia, musculoskeletal, neurodevelopmental, and social problems.

Ophthalmic Manifestations

Bilateral limitation of abduction is the key ocular motility finding. Most patients are orthotropic but esotropia may occur. Limitation of abduction, esotropia, V-pattern strabismus, and compound hyperopic astigmatism were the prominent findings in one of the studies [308]. Isolated abducens nerve palsy, conjugated horizontal gaze paresis, features of DRS, and congenital fibrosis of the extraocular muscles were reported in a major study [289]. convergence may be poor or absent [316]. Co-existent involvement of supranuclear vergence centres in mid brain has been suggested as a cause for defective convergence [317]. Duane retraction syndrome can occur. Vestibulo-ocular reflexes; however, have previously been reported to be absent horizontally in Möebius syndrome Ocular motility deficits similar to congenital fibrosis of the extraocularmuscles (CFEOM) types 1 and 2 have been reported in Möebius syndrome [318–320]. Lagophthalmos due to bilateral facial palsy occurs although ptosis is absent. Exposure keratitis can occur. Epicanthal folds and hypertelorism are common. Abnormal tearing and aberrant innervation of the lacrimal gland can occur.

Diagnosis

It is a clinical diagnosis.

Clinical conditions that share some clinical features with Möebius syndrome include bilateral palsy of cranial nerve VI, Asymmetrical Crying Facies, brainstem syndromes, Duane syndrome, Kallmann syndrome, myotonic diseases, Poland anomaly, Horizontal gaze palsy with progressive scoliosis (HGPPS) and Klippel-Feil anomaly. In congenital facial palsy, there is isolated loss of the facial nerve nuclei unilateral or bilateral without any other coexistent abnormalities of the brainstem or posterior fossa. Duane syndrome has retraction or retraction equivalents (up shoot and down shoot in adduction), which are not seen in Möebius syndrome. In HGPPS, horizontal gaze palsy occurs associated with scoliosis. The scoliosis is progressive. Patients might have horizontal pendular nystagmus but do not have facial palsy seen in Möebius syndrome. The Imaging findings are very different with a split pons being characteristic of HGPPS. Kallmann syndrome is characterized by anosmia. The presence of vertical eye movement disorders or exotropia should raise consideration of a mutation in *TUBB3* [320]. HOXB1 encodes a transcription factor that is important in rhombencephalon development. Mutations in HOXB1 cause hereditary congenital facial paresis, type 3 (OMIM #614744). These patients do not have bilateral horizontal gaze palsy but have accomodative esotropia [300].

The diagnosis is a clinical diagnosis. There are no specific diagnostic criteria. The presence of congenital bilateral limitation of abduction and facial palsy with the inability to smile is strongly suggestive of Möebius syndrome. Other findings that when present support a diagnostic work-up include

Management

Systemic

"Smile surgery" is being performed which involves muscle transfers, and grafting muscles into the corner of the mouth, in order to facilitate smiles. Though this procedure offers the ability to smile, it does not improve other facial expressions [321].

Ophthalmologic

Some authors report that bilateral medial rectus muscle recession alone may not be adequate and hence advocate a

combination of a medial rectus muscle recession and a lateral rectus muscle resection [322]. In more severe cases muscle transposition has also been reported [322]. The prognosis for vision is good and increasingly better results have been reported with strabismus surgery [322]. Conventional surgical approach for an A-pattern esotropia with bi-medial rectus recession with and appropriate muscle displacement was reported with success [323]. Satisfactory long term surgical results improving parent satisfaction and patient self-esteem have been reported [324]. Lagophthalmos should be managed appropriately with lubricants, antibiotic eye ointment if indicated and exposure keratitis prevented. Tarsorraphy may be required in advanced cases.

Usher Syndrome

Definition

Usher syndrome is a group of autosomal recessive disorders characterized by variable congenital hearing impairment and retinitis pigmentosa with or without vestigular disturbance. A contiguous gene deletion involving the USH1C locus resulting in infantile hyperinsulinism, profound congenital sensorineural deafness, enteropathy, has been reported [325].

There are three major types based on onset and severity of hearing impairment and the presence or absence of vestibular symptoms [326–329] (refer Table 21.6).

Usher syndrome Type I is characterized by congenital profound hearing impairment early retinitis pigmentosa and vestibular dysfunction. *USH1B* accounts for most of the type I Usher syndrome [330].

Usher syndrome Type 2 differs from type I in that the deafness is less severe and slightly later in onset. They have normal vestibular function [331]. *USH2A* gene accounts for 74–90 % of cases of Type 2 Usher syndrome [332].

Usher syndrome Type 3 is characterized by late onset but progressive hearing loss. Patients have mild vestibular dysfunction. Mutations in *CLRN1* (USH3A) are responsible. Onset of retinitis pigmentosa is in late childhood.

Usher syndrome is, in general, a ciliopathy. Photoreceptors, auditory hair cells, and vestibular hair cells develop from ciliated progenitors [333]. A generalized abnormality of axoneme structure is present in patients with Usher syndrome. Most of the mutated genes responsible for Usher syndrome result in loss of hair cells in the inner ear and a gradual and progressive loss of photoreceptors resulting in the phenotype [334]. Mutations in the *MYO7A* gene are the most common cause of Usher syndrome [335].

History

Charles Usher first emphasized the hereditary nature of this condition in 1914 [336].

Epidemiology

Usher syndrome has a worldwide prevalence of 3.5/100,000–6.2/100,000. Usher syndrome was estimated to be responsible for 3–6 % of all childhood deafness and approximately 50 % of all deaf-blindness. The prevalence may be as high as one in 6000 [337]. It is the most common cause of combined

Table 21.6 Usher syndrome: types, genes, proteins and major clincial feature

	Type	Gene	Locus	Proteins	Hearing loss	Vestibular function	Other main findings
Usher 1	A		Does not exist		Congenital profound bilateral	No vestibular response	Early onset of RP
	B	*MYO7A*	11q13.5	Myosin VIIa			
	C	*USH1*	11p15.1	Harmonin			
	D	*CDH23*	10.q22.1	Cadherin 23			Delayed onset of walking
	E						
	F	*PCDH15*	10q21.1	Protocadherin 15			
	G	*USH1G*	17q25.1	Sans			
	H		15q22-q23				
	K		10p11.21-q21.1	–			
	J	*CBI2*	21q21	–			
Usher 2	A	*USH2A*	1q41	Usherin	Mild to severe congenital	Normal vestibular function	No delay in onset of walking
	C	*GPR98*	5q14.3	VLGR1	Higher frequencies		
	D	*DFNB31*	9q32	Whirlin			
Usher 3	A	*CLRN1*	3q25.1	Clarin	Post lingual progressive	Variable vestibular function	Late onset RP
	B	*HARS*	20q	–			

RP Retinitis pigmentosa

deafness and blindness in children and adults in the developed world and second only to congenital rubella in underdeveloped countries. Type I is estimated to occur in at least 4 per 100,000 people. Type 1 Usher syndrome may be more common in certain ethnic populations, Ashkenazi Jews and the Acadian population in Louisiana. Type I appears to be the most common type [338]. Type 3 Usher syndrome is common in the Finnish population. It is the least common form of Usher syndrome.

Systemic Manifestations

Hearing Impairment

The hearing impairment is sensorineural, profound and congenital in Usher Type 1. In Type 2 it is moderate and usually affects the higher frequencies tone. Type 3 has mild but progressive hearing impairment. (Pre-lingual deafness) results in unintelligible speech in Type 1.

Vestibular Disturbance

Vestibular dysfunction differentiates type 1 from type 2 Usher syndrome. All patients with retinitis pigmentosa and hearing loss should be evaluated for vestibular function apart from hearing assessment. People with Usher syndrome type 3 may also experience variable difficulties with balance. As a result of vestibular function, there is a delay in the onset of walking. In Type 2 Usher syndrome, walking starts at normal age. Life span is not affected.

Ophthalmic Manifestations

Retinitis pigmentosa is the main clinical finding. Though there is early onset and progressive visual field loss most patients retain some central vision. Posterior subcapsular cataract can develop early. The overall visual prognosis is poor. Multifocal electroretinography (mfERG) may demonstrate a sharp distinction between the area of reduced function and the central area with remaining normal function [339]. Optical coherence tomography (OCT) may show loss of foveal depression with distortion of the foveal architecture in the macula. Electroretinogram often shows abnormality even in young children with Usher syndrome type 1, even in the absence of fundoscopic signs of retinal degeneration and hence any child with delayed walking and congenital severe deafness should have an ERG [340]. Progressive loss of visual acuity and visual field reaches substansial levels between the second and third decades in both Type 1 and Type 2 Usher syndrome [341]. Usher syndrome shows some important genotype-phenotype correlations. Null MYO7A alleles could be associated with milder dysfunction and fewer photoreceptor structural losses as compared to other genotypes [342].

Diagnosis

The clinical diagnosis can be confirmed by molecular genetic testing. Microarray panel technology is available for clinical use. Smith and coworkers suggested that conditions that can cause retinal dysfunction and congenital deafness like intrauterine infections and perinatal causes should be excluded prior making a diagnosis of Usher syndrome [343]. The differential diagnosis includes congenital rubella syndrome and other congenital infections, deafness dystonia optic neuropathy syndrome (DDON), and other syndromes which have retinal dystrophy with hearing loss such as Alstrom syndrome and Bardet-Beidl. DDON an X linked disorder with optic atrophy occuring in the second decade not consecutive to retinal pathology. Psychiatric symptoms can occur in childhood and dementia invariably occurs by the fourth decade. In some Usher syndrome patients, cataract, mental retardation and psychosis can occur. This is known as Hallgren syndrome [344]. It is important to identify the timing of night blindness as some medications used for psychiatric disturbance can result in a static pigmentary retinopathy (pseudoretinitis pigmentosa). One must also rule out Charles Bonnet syndrome in which hallucinations occur secondary to vision loss. In Hallgren syndrome, the clinical phenotype especially night blindness usually manifests early, before psychiatric symptoms become profound. Vestibular dysfunction results in ataxia.

Management

Systemic

Early cochlear implantation can benefit Usher Type 1 syndrome. Speech discrimination skills, speech production quality, and academic performance have been found to correlate with the age at implant [345].

In the shaker 1 mouse model for Usher type 1B that lacks a functional MYO7A gene, it has been shown that subretinally delivered UshStat, a recombinant EIAV-based lentiviral vector expressing human MYO7A, Expression of GFP and myosin VIIa was documented.

Studies have also shown that subretinally delivered UshStat is safe and well-tolerated in macaque [346, 347]. Adeno associated viral vectors have been used in mice models. Both Lenti viruses and adeno associated virus have been used in animal models with success [348].

Ophthalmic

Consideration of ophthalmic screening for retinitis pigmentosa may be considered for hearing impaired patients. Though early diagnosis of usher syndrome may not assist in improving visual symptoms, early cohlear implantation and intensive speech therapy may immensely benefit the patient in not only improving hearing but also in navigation due to improvement in directional sense.

Waardenburg Syndrome

Definition

Waardenburg syndrome is an autosomal dominant pigmentary disorder with characteristic facial dysmorphism, pigmentary abnormalities of skin, hair and eyes and congenital sensorineural hearing loss. There are four subtypes and multiple subtypes (see Table 21.7). All types except type 2 are characterized by the classical feature of dystopia canthorum (lateral displacement of the medial canthi). Type 3 (Klein-Waardenburg) has limb anomalies and Type 4 (Waardenburg-Shah syndrome) has Hirschsprung disease in addition to other features of Type 1.

Table 21.7 Waardenburg syndrome: diagnostic criteria

Major criteria
Congenital sensorineural hearing loss
White forelock, hair hypopigmentation
Pigmentation abnormality of the iris:
• Complete heterochromia iridium (irides of different color)
• Partial/segmental heterochromia
• Hypoplastic blue irides or brilliant blue irides
Dystopia canthorum, W index >1.95*
Affected first-degree relative
Minor criteria
Skin hypopigmentation (congenital leukoderma)
Synophrys/medial eyebrow flare
Broad/high nasal root, prominent columella
Hypoplastic alae nasi
Premature gray hair (age <30 years)

An individual must have two major criteria or one major and two minor criteria to be considered affected [349]. See Table 21.7 for diagnostic criteria and clinical features.

W index: The measurements required to calculate the W index (in mm) are as follows:

Inner canthal distance (a), interpupillary distance (b), and outer canthal distance (c).

Calculate $W = X + Y + a/b$

$X = (2a - (0.2119c + 3.909))/c$

$Y = (2a - (0.2479b + 3.909))/b$

A W index result >1.95 is considered abnormal.

WS shows extensive phenotypic variability [350]. Mutations in several genes cause Waardenburg syndrome (see Table 21.8). Mutations in *EDN3*, *EDNRB*, *MITF*, *PAX3*, *SNAI2*, and *SOX10* genes causes Waardenburg syndrome Types I and III Waardenburg syndrome are caused by heterozygous mutations in the *PAX3* gene. Type II is caused by mutations in the *MITF* and *SNAI2* genes. Type III is caused by mutations in *SMOC1*. *SOX10*, *EDN3* and *EDNRB* genes also play an important role in the development of nerve cells in the large intestine. Hence mutations in any of these genes results in Type 4 WS. Most of these genes are involved in the formation and development of melanocytes. Apart from contributing to skin, hair, and eye color, melaninplays a critical role in development and functioning of the inner ear where it is found in the stria vascularis. Mutations in any of these genes disrupt the normal development of melanocytes, leading to the clinical phenotype.

History

The classic syndrome was first delineated by Waardenburg in 1951 [351].

Table 21.8 Waardenburg syndrome: types, genes, and clincial features

Type of Waardenburg syndrome	Main feature	OMIM phenotype number	Gene	LOCI
Waardenburg syndrome, Type 1; WS1	Waardenburg syndrome with dystopia canthorum	#193500	*PAX3*	2q35
Waardenburg syndrome, Type 2; WS2A	Waardenburg syndrome without dystopia canthorum	#193510	*MITF*	3p14-p13
Waardenburg syndrome, Type 2; WS2B		600193		1p
WS Type 2C		606662	*WS2C*	8p23
WS2D		608890	*SNAI2*	8q11
WS Type 2E		611584	*SOX10*	22q13
WS2OA	Waardenburg syndrome, Type 2, with ocular albinism	#103470	*MITF* and *TYR*	3p14-p13 and 11q14.3
Waardenburg syndrome, Type 3; WS3 (digenic inheritance)	Waardenburg syndrome withupper LIMB abnormalities	#148820	*PAX3* (AR, AD)	2q36.1
	Klein-Waardenburg			
Waardenburg syndrome, Type 4; WS4A	Waardenburg-shah syndrome with hirschsprung disease	#277580	*EDNRB*	13q22
Waardenburg syndrome, Type 4; WS4B	Waardenburg-shah syndrome	#148820	*EDN3*	20q13
Waardenburg syndrome, Type 4; WS4C			*SOX10*	22q13

Epidemiology

Waardenburg syndrome affects an estimated 1 in 40,000 people. Types I and II are the most common forms and types III and IV are rare. WS Type 4 is less common.

Systemic Manifestations

Dysmorphic Facial Features

Patients have prominent nasal root, round or square tip of nose, hypoplastic alae, smooth philtrum, and a thin upper lip shaped like a cupids bow. Patients may have a wide mandible. The most important feature, dystopia canthorum, or lateral displacement of the medial canthi, which is defined by the W index as detailed below. WS type 2 can be differentiated from Type 1 in that there is normal canthal index in type 2.

Hearing Loss

Hearing impairment is one of the most consistent non-ocular findings in Waardenburg Syndrome. The deficit is sensorineural, congenital and typically non-progressive. It can be unilateral, bilateral or asymmetric. There is significant intrafamilial variation in the severity and laterality of the hearing loss. The temporal bone shows several abnormalities including enlargement of the vestibular aqueduct and upper vestibule and narrowing of the internal auditory canal opening, absence of cochlear nerve, bilateral agenesis or hypoplasia of the semicircular canals or both, associated with a cochlear deformity [352].

Hair Color

Hair can show several pigmentary abnormalities, the most common being the presence of a frontal white forelock of hair. The white forelock may be present at birth and may disappear or become more evident in the second decade. A history of using hair dye needs to be elicited in a patient who is suspected to have Waardenburg syndrome but does not have the white forelock. It is usually in or near the midline but occasionally may be seen in other areas. There may be a family history of premature graying of scalp hair without the white forelock [353]. Rarely, a black forelock can occur [354].

Limb Anomalies

The association of limb anomalies with Waardenburg syndrome was first reported by Kline [355]. Upper limb anomalies include hypoplasia of the musculoskeletal system, flexion contractures, fusion of the carpal bones, syndactyly, and flexion contractures of the fingers [356]. A child with dystopia canthorum, partial albinism, and very severe upper-limb defects was reported and the child was born to parents who both had mild Type I, was found to be homozygous for *PAX3* (Type 3) [357].

Hirsprung Disease

Hirschsprung disease (aganglionic megacolon; 142623) was first observed in patients with Waardenburg syndrome by McKusick [358]. Subsequently this association was observed by many [358, 359]. A defect in the neural crest was suggested as a possible cause in a child with bicoloured iris and Hirschsprung disease [360]. It is seen in Waardenburg syndrome type 4 and is caused by heterozygous mutations in *EDNRB* gene. Dystopia canthorum may or may not be present.

The mutation was found to be dose sensitive with both heterozygotes and homozygoted having risk for developing Hirschsprung disease [361].

Other Findings

Other less common findings that have been reported include cleft lip, [362] cleftpalate or spina bifida [363] and leukoderma. An unusual demyelinating peripheral neuropathy has been reported in a patient [364].

WS type 2 can be differentiated from Type 1 in that there is normal canthal index in type 2. Hearing impairment, heterochromia iridum are more common in Type 2 while white forelock and leukoderma are more common in Type 1.

Ophthalmic Manifestations

It is characterized by bushy eyebrows with medial eyebrow flare or, occasionally synophrys. The most consistent feature is dystopia canthorum [365]. Hypertelorism is seen in all subtypes except type 2. Pigmentary abnormalities of the eye include heterochromia irides, and pigmentary abnormalities of the fundus in the form of retinal pigment epithelial mottling. The heterochromia can be complete or segmental. Hypoplasia of the iris and brilliant blue irides can occur. Iris and choroidal hypopigmentation have been reported. Eyebrows and eyelashes may be also show hypopigmentation in some patients. Medial eye brow flare is more common and consistent than synophrys.

Diagnosis

Diagnosis of Waardenberg syndrome is based on diagnostic criteria (Table 21.1).

The differential diagnosis includes piebaldism (172800), an autosomal dominant disorder which can sometimes coexist with Waardenburg syndrome (see Fig. 21.7a, b). The ocular findings of dystopia canthorum and pigmentary abnormalities of the eye are very rare in isolated piebaldism. Piebaldism is characterized by ventral amelanotic patches on

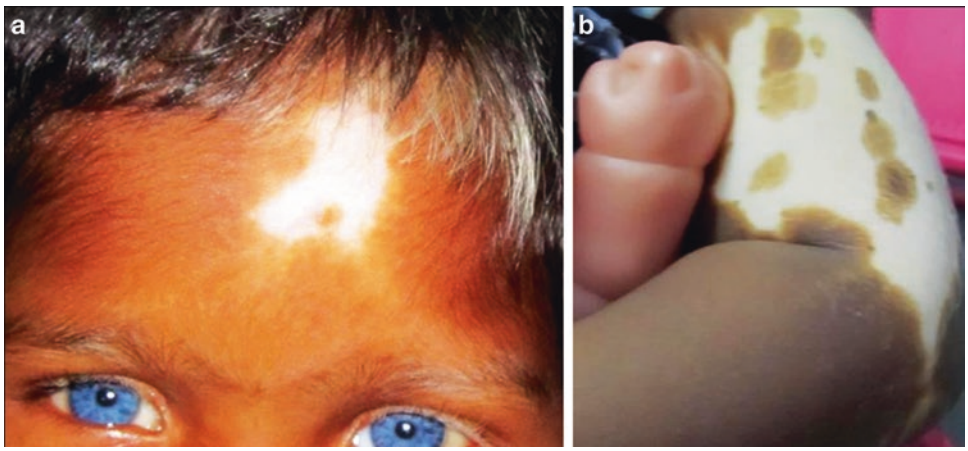

Fig. 21.7 Waardenburg syndrome with Piebaldism. (**a**) Photograph of a female child with piebaldism and Waardenburg syndrome. (**b**) Skin findings in the same patient due to piebaldism (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

the skin, sometimes with hyperpigmented borders [366]. Mutations of the genes *KIT* and *SNAI2* are responsible for piebaldism. Tietz syndrome (OMIM 277740) is characterised by white forelock of hair and multiple malformations [356]. Other findings in this syndrome include atrial septal defect, prominent thoracic and abdominal veins, hypoplastic or absent terminal phalanges of toes. Segmental atelectasis of the lungs due to segmental bronchomalacia was also observed. X linked carriers of Ocular albinism may manifest abnormal iris. A overlap of ocular albinism and Waardenburg syndrome has also been reported [367]. A digenic pattern of inheritance with mutations involving the *MITF* and *TYR* genes was suggested [368].

Management Recommendations

Ocular

Prognosis is excellent and no ophthalmic problems require specific management.

Systemic

Cochlear implant has been shown to be successful [369].

Weill-Marchesani Syndrome

Definition

Weill-Marchesani Syndrome (WMS) is a rare disorder primarily affecting connective tissue and the eyes. Alternative names that were used earlier include spherophakia-brachymorphia syndrome and congenital mesodermal dysmorphodystrophy. It is characterized by lens abnormalities, proportionate short stature, brachydactyly and joint stiffness [370]. Autosomal recessive inheritance is more common than autosomal dominant. A WMS-like syndrome sharing some features of WMS like ectopia lentis, microspherophakia and cardiac defects has been reported. However brachydactyly and joint stiffness are absent [371].

The autosomal recessive form is due to homozygous mutations in *ADAMTS10* gene [372]. Mutations in *LTBP2* have also been shown to cause autosomal recessive WMS [373]. The autosomal dominant form occurs due to mutations in the gene *FBN1*, the gene that makes fibrillin [374]. They usually have an affected parent and mutations in which are also responsible for Marfan syndrome. ADAMTS10 is a member of the extracellular matrix protease family and is expressed in skin, fetal chondrocytes, and fetal and adult hearts. This protein plays a role in development of the eyes, heart, and skeleton. Interaction between *ADAMTS10* protein and FBN1 protein has been demonstrated [375].

History

Weill first described the features in 1932 followed by Marchesani in 1939 [376, 377].

Epidemiology

The estimated prevalence of WMS is 1 in 100,000 people.

Systemic Manifestations

Skeletal

Proportionate short stature is the most consistent clinical finding. Patients also exhibit brachydactyly due to shortening to the metacarpals. They may experience poor mobility

of the joints that can give the hands a somewhat clenched appearance and leaves the elbows incompletely extended. Primary osteoporosis has also been reported [378]. Joint limitations appears to more common in autosomal dominant WMS [379].

Cardiac

Reported cardiac abnormalities include aortic stenosis, prolonged QT interval, and mitral valve pathology [380]. If there are no cardiac abnormalities the prognosis for life is good. Cardiac anomalies appears to more common in autosomal recessive WMS [379].

Dental Anomalies

Other

Intelligence is usually normal but mild intellectual disability can occur [379].

Ophthalmic Manifestations

The primary lenticular abnormality is microspherophakia, which usually remains central although subluxation can occur. Patients have lenticular myopia. The lens position becomes progressively anterior resulting in angle closure as the iris is pushed forward. Lens contact with the iris also may cause posterior synechia and iris atrophy which is often paradoxically worse on the anterior surface of the iris. Secondary glaucoma results from angle closure. Rarely, corneal decompensation can occur due to intermittent lenticular-endothelial touch. Blunt ocular injury can predispose to dislocation of the lens due to trauma induced weakening of the zonules Patients with autosomal dominant WMS have a lower incidence of lens related problems. Liquefied vitreous has been reported in the autosomal dominant form of WMS [381]. The central corneal thickness has been found to be higher [382] and can cause falsely high IOP measurements and might make management of glaucoma difficult.

Diagnosis

There are no specific diagnostic criteria. There are several conditions that cause ectopia lentis but most of them (Marfan, homocystinuria, sulfite oxidase deficiency) cause tall stature with or without arachnodactyly in contrast to short stature and the brachydactyly seen in WMS. Ectopia lentis et pupillae is an autosomal recessive disorder characterized by correctopia (displacement of the pupil) and the lens in the opposite direction. These patients are systemically normal and have anormal sized lens without progressive anterior migration. Although they do have persistent pupillary membrane strands to the lens surface, best seen after pupil dilation, these arise form the iris collarette rather than the pupil margin as in posterior synechia. Glaucoma-lens ectopia-microspherophakia-stiffness-shortness (GEMSS) syndrome closely resembles WMS [383]. A WMS like syndrome sharing all other clinical features except brachydactyly and joint stiffness has also been described [371]. Mutations in ADAMTS17 has been reported to cause WMS like syndrome [371].

Management: Recommendations

Systemic Management

Maxillary hypoplasia, misalignment of teeth and neck stiffness can cause difficulty in intubation for anesthesia [384]. Preoperative cardiac assessment and echocardiography are recommended. Intra venous induction and a reinforced laryngeal mask airway (RLMA) has been recommended to avoid the difficulties with endotracheal intubation and a cardio-stable anesthesia is recommended [385].

Ophthalmic

The lenticular myopia is often high and cannot be satisfactorily corrected by glasses. Further the refraction is often fluctuating and contributes to amblyopia. Miotics are contraindicated as they can precipitate further anterior lens movement with acute angle closure. In young children, strong cycloplegic agents, such as topical atropine, may initially have some success in deepening the anterior chamber by posterior rotation of the iris-ciliary body diaphragm. Peripheral iridectomy is rarely helpful. Rather, early lensectomy, before the angle begins to close, may prevent the development of glaucoma. Lensectomy is also technically much more challenging later as the anterior chamber can be narrowed to a slit over time. Patients are best left aphakic as an intraocular lense implant in the bag will also be susceptible to anterior movement. In addition, the capsular bag in these children is often found to be quite abnormal, lacking the normal tensile strength of an unaffected lens, sometimes crinkling up into a lens membrane made after the lens is removed.

If glaucoma develops and is not manageable by medications, surgical planning must keep in mind the peripheral irido-corneal adhesions that invariably develop, especially if the lens is not removed early. This may make tube placement challenging. Intraocular pressure measurement must be considered in view of increased CCT if present.

Table 21.9 provides a comprehensive, but incomplete, list of syndromes of ophthalmic importance.

Table 21.9 Genes, loci, ophthalmic and systemic features of some syndromes of ophthalmic importance

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Acro-Dermato-Ungual-Lacrimal-Tooth (ADULT) It is an allelic disorder of Hay-Wells syndrome/ulnar mammillary syndrome	103285	*TP63*	3q28	AD	Lacrimal duct atresia nasolacrimal duct obstruction	Ectrodactyly,
						syndactyly,
						Finger and toenail dysplasia,
						Hypoplastic breasts and nipples,
						Intensive freckling,
						Primary hypodontia
						Photosensitive skin sparse hair
						Frontal alopecia
Ankyloblepharon-Ectodermal defects-Cleft lip/palate (AEC) syndrome (Hay-Wells)	106260	*TP63*	3q28	AD	Ankyloblepharon filiforme adnatum	Cleft Lip
					Lacrimal punctal atresia	Cleft Palate
						Syndactyly
						Camptodactyly
						Ectrodactyly
						Hearing loss
						Hypospadias
Arts	301835	*PRPS1*	Xq22.3	XLR	Optic atrophy and Nystagmus	Intellectual disability
Charcot-Marie-Tooth type 5 (cmtx5)						Profound congenital sensorineural hearing impairment
Fatal X-linked mental retardation-- ataxia-deafness						Early-onset hypotonia and delayed motor development, Ataxia, seizures, Areflexia
						Recurrent upper respiratory tract infections
Athabascan syndrome (ABDS) and Bosley-Salih-Alorainy syndrome (BSAS)	601536 601853	*HOXA1*	7p15.2	AR	Congenital horizontal gaze palsy	Developmental delay
						Seizures
						Deafness
						Central hypoventilation
						Vestibular abnormalities
						Congenital cardiac defects
						Vocal cord weakness/paralysis
						Internal carotid abnormalities
Branchio-oculo facial	113620	*TFAP2A*	6p24.3	AD	Strabismus	Bronchial cleft sinuses
					Nasolacrimal duct obstruction	Broad nasal bridge protruding upper lip
						Carp-shaped mouth
CAPOS syndrome	601338	*ATP1A3*	19q13.3	AD	Optic atrophy	**C**erebellar ataxia,
						Areflexia
						Pes cavus
						Sensorineural hearing loss

CCFDN—Congenital cataracts, Facial dysmorphism, and Neuropathy	604168	*CTDP1*	18q23	AR	Bilateral congenital cataracts, microcornea, microphthalmia,	Demyelinating, symmetric, distal peripheral neuropathy
					Miosis	Developmental delays and intellectual deficit
					Mildly dysmorphic facial features	Short stature
					Nystagmus	Hypo gonadotropic hypogonadism
						Para infectious rhabdomyolysis is a potentially life-threatening complication can occur following infections.
Chanarin-Dorfman	275630	*CGI58 gene*	3p21.33	AR	Cataract	Congenital ichthyosis
Neutral lipid storage disease with ichthyosis					Nystagmus	Hepatosplenomegaly,
						Vacuolated granulocytes (Jordans anomaly), myopathy
Chitayat-Hall	208080	*Not yet identified*	*Not yet identified*	AR	Facial anomalies ('boxy' head, square face, small tipped nose, Chubby cheeks, and micrognathia microcephaly. oval face with frontal bossing, full cheeks, small nose with depressed nasal bridge, microphthalmia, retinal coloboma.	Distal Arthrogryposis (Camptodactyly of fingers and hammertoes), hypopituitarism, severe mental retardation,).
						Aminoaciduria, hypokalemia,
						Abnormal/incomplete thoracic vertebrae.
						Delayed myelination in neuroimaging
						Reduction in cortical folding
Cleidocranial dysostosis (CLCD)	119600	*RUNX2*	6p21.1	AD	Hypertelorism	Persistently open skull sutures
						Bulging calvaria, hypoplasia or aplasia of the clavicles, wide pubic symphysis, short middle phalanx of the fifth fingers, dental anomalies
						Vertebral malformations
						Wermian bones
						Syringomyelia
						Scoliosis
Coffin-Siris	135900	*ARID1A, ARID1B, SMARCA4, SMARCB1, or SMARCE1 gene*	7q32.34	AR	Ptosis	Thick eyebrows, flat nasal bridge, anteverted and wide nasal tip
						Intellectual disability coarse facial features
						Hypertrichosis
						Hypoplastic or absent fifth fingernails or toenails
						Generalized hypertrichosis, scalp hypotrichosis, absence of the distal phalanges of the fifth fingers and of the second to fifth toes, small patellas, inguinal hernia
						Sucking and feeding difficulties.
						Dandy-Walker malformation
						Endocrinologic deficiency

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
COFS	MIM 214150	*ERCC6 gene*	10q11	AR	Congenital cataracts	Facial dysmorphism
There are four subtypes COFS-1 is referred as Pena-Shoker					Microphthalmia	Prominent nose, micrognathia
					Nystagmus	Large ear pinna overhanging upper lip.
						Congenital microcephaly,
						Severe mental retardation
						Severe developmental delay
						Post natal growth failure
						Arthrogryposis
						Hypotonia
						Failure to thrive
						Widely set nipples
						Kyphoscoliosis
						Osteoporosis
						Hearing loss
						Seizures
						Hypoplasia of the corpus callosum, ventriculomegaly
						Delayed myelination
						Intra cranial calcification
						Cryptorchidism
Cohen syndrome	MIM 216550	*VPS13B*	8q22.2	AR	High myopia	Facial Dysmorphism:
					Retinal dystrophy	Microcephaly (usually mild)
						Thick hair,
						Thick eye brows and lashes and low hairline
						Wide and wave-shaped palpebral fissures.
						Short philtrum, apparently prominent central incisors and a
						Grimacing on attempted smiling.
						High nasal bridge, maxillary malar hypoplasia, and upslanting
						Long and tapering fingers
						Hyper extensibility of the joints
						Truncal obesity
						Intellectual disability
						Cerebellar hypoplasia/degeneration
						Prominent Corpus callosum
						Intermittent isolated neutropenia,
						Cheerful disposition and psychomotor retardation
						Childhood hypotonia
						Isolated growth hormone deficiency
						Increased space between the first and second toes (sandal gap)
						Repeated gingival or skin infections
						A relatively enlarged corpus callosum in a microcephalic head associated with normal gray and white matter signal intensity should alert the clinician to suspect Cohen syndrome.
						Laryngomalacia, laryngeal stenosis, and vocal cord paralysis

Cerebro-Oculo-Nasal Syndrome	605627	*Not yet known*	Not yet known	AD	Ocular hypertelorism, Telecanthus, Epicanthic folds, downslanting palpebral fissures, medial abnormally placed eyebrows, and sparse eyelashes	Malar hypoplasia, a large philtrum, a High-arched and narrow palate, posteriorly rotated ears
						Hypoplastic tragus
						A proboscis-like appearance of the nose presence of small and atypical appendage-like structures.
					Anophthalmia	Developmental delay.
Ectrodactyly, ectodermal dysplasia, and cleft lip/palate (EEC1)	129900	*Not yet known*	7q11.2-q21.3	AD	Keratitis	Ectrodactyly
					Photophobia, blepharitis,	Cleft lip
					Entropion,	Cleft palate
						Growth hormone deficiency
						Anomalies of the urinary tract
						Genital anomalies
						Choanal atresia
						Hearing loss (sensory and conductive)
Facio-Oculo-Acoustic-Renal (FOAR) syndrome)/Donnai Barrow syndrome (DBS)	222448	*LRP2*	2q31.1	AR	Hypertelorism, down-slanting	Moderate sensorineural hearing loss
					Palpebral fissures, macrocephaly, broad forehead, and an enlarged anterior fontanelle, facial anomalies	Low molecular weight
					Iris coloboma, iris hypoplasia	Proteinuria
					Cataract, High myopia, retinal detachment, posterior subcapsular lens opacity, choroidal atrophy	Hypertelorism and either CDH or omphalocele by prenatal imaging should raise suspicion of DBS.
Fasio scapulohumeral dystrophy (FHSD)	158900		4q35	FHSD1 is AD	Lagophthalmos	Muscular weakness especially involving the face, shoulder and upper limb
			SMCHD1 and D4Z4	FSHD2 is digenic	Exposure keratitis	Winging of the scapula
					Peripheral retinal nonperfusion with secondary terminal neovascularization, exudate and hemorrhage	Foot drop
						Hearing loss
						Rarely cardiac abnormalities
Frank-Terhaar syndrome; FTHS/	249420	*TKS4*	5q35.1	AR	Prominent forehead, hypertelorism, downslanting palpebral fissures, broad and flat nasal bridge, broad nasal tip, anteverted nostrils, high-arched palate, gingival hypertrophy	Short stature
Melnick-Needles		*SH3PXD2B*			Megalocornea	Mental retardation
					Congenital glaucoma	Multiple skeletal abnormalities
					Hypertelorism	Developmental delay
						Large anterior fontanel, pectus excavatum, prominent coccyx

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Fraser	MIM 219000	*FRAS1, FREM2*	4q21.21	AR	Cryptophthalmia	Facial Dysmorphism:
		GRIP1	12q14.3		Microphthalmia	Cryptophthalmos (most common abnormality)
			13q13.3		Nasolacrimal duct malformation/obstruction	Microphthalmia, anophthalmia
						Hypertelorism
						High palate
						Cleft lip/cleft palate
						Laryngeal stenosis
						Fusion of labia and enlargement of clitoris,
						Bicornuate uterus and malformed fallopian tubes
						Cryptorchidism in males
						Ambiguous genitalia
						Renal agenesis (unilateral or bilateral)
						Syndactyly
						Middle and outer ear malformations.
Growth retardation-Alopecia-Pseudoanodontia-Optic atrophy (GAPO)	230740	*ANTXR1*	2p13.3	AR	Frontal bossing, high forehead, mid-facial hypoplasia and wide-open anterior fontanel, depressed nasal bridge, Large ears, prominent cheeks, thin lips, large tongue, unerupted teeth, micrognathia	Short stature
					Optic atrophy	Progeria like appearance
						Alopecia
						Dilated cardiomyopathy
						Large genitalia.
Gillespie	206700	*PAX6*	11p13	AR	Aniridia	Cerebellar ataxia
						Intellectual disability
						Developmental delay
						Speech delay
Gomez-Lopez- Hernandez (GLH)	601853	*Not yet known*	Not yet known	Not yet known	Hypertelorism	Triad of rhombencephalosynapsis, trigeminal anesthesia, often giving rise to corneal opacities, and bilateral parietal or parietooccipital alopecia
Cerebello-Trigeminal-Dermal dysplasia					Corneal opacities secondary to corneal hypoesthesia	Craniosynostosis
					Ptosis	Mid-face hypoplasia, scalp alopecia, low-set and posteriorly rotated ears,
					Strabismus	Common:
						Rhombencephalosynapsis (fusion of cerebellar hemispheres, agenesis or hypogenesis of the vermis, fusion of the dentate nuclei and the superior cerebellar peduncles)
						Ataxia, trigeminal anesthesia, cerebellar anomalies
						Mental retardation, short stature and partial growth hormone deficiency
						Psychiatric disorders
						Absence of the septum pellucidum, ventricular enlargement with a thin cortex are other findings

Hallerman- Streiff-Francois	234100			New dominant mutation/AR	Microphthalmia	Facial Dysmorphism
	257850	*GJA1*	6q22.31	AR	Cataract (can be self-absorbing)	hypotrichosis, microphthalmia, cataracts, 'Bird-like' face
					Strabismus	Beaked nose, micrognathia, skin atrophy, dental anomalies, and proportionate short stature.
					Nystagmus	Lack of mandibular angle and hypoplasia of the clavicles and ribs.
						Snoring and/or daytime hypersomnolence
						Tracheomalacia
Heimler	234580	*PEX1*	7q21.2	AR	Retinal dystrophy	Sensorineural hearing loss
		PEX6	6p21.1			Beau lines on nails
						Leukonychia
						Tooth enamel hypoplasia
						Amelogenesis imperfecta
HGPPS—Horizontal gaze palsy with progressive scoliosis	607313	*ROBO3*	11q24.2	AR	Congenital horizontal gaze palsy	Progressive scoliosis
						Butterfly shaped medulla with anterior flattening and an unusual midline cleft.
						Flattening of the basis pontis and hypoplasia of the pontine tegmentum
						Absent or hypoplastic abducent nerve nuclei, the medial longitudinal fasciculus, and the pontine paramedian reticular formation are also involved
						There is no other significant neurological abnormality.
Jalilli Cone-rod dystrophy and Amelogenesis Imperfecta	217080	*CNNM4*	2q11.2	AR	Cone rod dystrophy	Amelogenesis imperfecta
					Photophobia	Dental caries
					Nystagmus	
Jeune syndrome Short-rib thoracic dysplasia SRTD1	208500	*ATD*	15q13	AR	Retinal degeneration resembling Leber congenital amaurosis	Long, narrow thorax, short stature, short limbs, polydactyly, Renal cystic disease, skeletal findings like cone-shaped epiphyses in hands and feet, irregular metaphyses, shortened ilium, and trident-shaped acetabulum
						Hepatic fibrosis
SRTD-2	611623	*IFT80*	3q25.3			Congenital hydrocephalus
SRTD-3	613091	*DYNC2H1*	11q22.3			'Trident' appearance of the acetabular roof
SRTD-4	613819	*TTC21B*	2q24.3			
SRTD-5	614376	*WDR19*	4p14	AR		
SRTD-6	263520	*NEK1*	4q33			
SRTD-7	614091	*WDR35*	2p24.1			
SRTD-8	615503	*WDR60*	7q36.3			
SRTD-9	266920	*IFT140*	16p13.3			
SRTD-10	615630	*IFT172*	2p33.3			
SRTD-11	615633	*WDR34*	9q34.11			
SRTD-13	616300	*CEP120*	5q23.2			
SRTD-14	616546	*KIAA0586*	14q23.1			

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Johanson-Blizzard syndrome	OMIM 243800	*UBR1 gene.*		AR	Upslanting palpebral fissures	Facial Dysmorphism:
					Nasolacrimal duct malformations	Aplasia or hypoplasia of the nasal alae, small beaked nose, abnormal hair patterns or scalp defects, and oligodontia
						Mental retardation usually mild
						Hypothyroidism, pancreatic exocrine insufficiency
						Sensorineural hearing loss,
						Imperforate anus
						Urogenital abnormalities, polycystic dysplasia of the kidneys and hydro ureter, double vagina and double uterus.
						ASD, dilated cardiomyopathy
						Total situs inversus
Kabuki syndrome	OMIM 147920	*KMT2D*	12q13.12	AD	Arched eyebrows, long eyelashes, Long palpebral fissures with partial eversion of lateral lid margin of lower eye lid (euryblepharon)	Developmental delay and intellectual disability
		KDM6A		X LD	Ptosis, epicanthic folds, strabismus, blue sclera, nystagmus	Short stature
						Microcephaly
						Seizures, hypotonia
						Cleft palate
						Persistent fetal finger pads, clinodactyly, brachydactyly
						Otitis media and hearing loss
						Large protuberant ears
Klippel-Feil anomaly	118100	*GDF6*	8q22.1	AD	Möebius syndrome, Duane syndrome (Wildervanck syndrome)	Hearing loss (sensorineural, conductive, or mixed type), Scoliosis, Sprengel anomaly and facial asymmetry
Klippel-Feil syndrome (KFS1)						Malformation of laryngeal cartilages
						Fusion of the carpal and tarsal bones, and restricted flexibility of the hands, wrists, elbows, feet, and legs
						External ear malformation, ossicular chain abnormalities, and structural abnormalities of the inner ear
						Cleft palate
KFS2	214300	*MEOX1*	17q21.31	AR		
KFS3	613702	*GDF3*	12p13.31	AD		
KFS4	616549	*MYO18B*	22q12.1	AR		Myopathy facial dysmorphism

Kniest Dysplasia	156550	*COL2A1*	12q13.11	AD	Myopia	Short stature (disproportionate with short chest)
					Retinal detachment	Widening of the joints
					Glaucoma	Pain and stiffness with restriction of joint movements
					Cataract	Dumb bell shaped long bones, Club foot
					Ectopia lentis	Kyphoscoliosis
						Hearing impairment
						Inguinal and umbilical hernia
						Tracheomalacia
						Cleft palate
Knobloch	267750	*COL18A1*	21q22.3	AR	Pathological myopia	Occipital alopecia, cutis aplasia, bony abnormality or encephalocele
					Geographic macular atrophy	
					Retinal detachment	
					Vitreoretinal degeneration	
					ectopia lentis	
					Cataracts	
					Featureless iris	
Lacrimo-Auriculo-Dento-Digital (LADD)	149730	*FGFR2*	10q26.13	AD	Nasolacrimal duct obstruction	Hearing abnormalities usually mixed hearing loss
Levy-Hollister		*FGFR3*	4916.3		Aplasia of the punctum	Cupped ears
		FGF10	5p12		Alacrima	Dental anomalies including Hypodontia
						Limb anomalies
						Pre-axial polydactyly
						Digitalization of the thumb
						Renal agenesis
Lathosterolosis	607330	*SC5DL*	11q23.3	AR	Cataract	Microcephaly, receding forehead, anteverted nares, micrognathia, prominent upper lip, highly arched palate,
Sterol C5-Desaturase Deficiency						Multiple congenital anomalies, intellectual disability, postaxial hexadactyly, syndactyly
						Arnold-Chiari malformation
						Increased levels of lathosterol in cells and plasma
Lenz microphthalmia	300166	*BCOR*	Xq11.4	X LR	Colobomatous or non-colobomatous microphthalmia	Microcephaly
Oculo-Facial-Cardio-Dental					Ptosis	Cleft lip, cleft palate and abnormal spacing of teeth.
					Cataract	Thumb duplication or hypoplasia
						Syndactyly, camptodactyly, clinodactyly,
						Hypospadias, cryptorchidism and urogenital anomalies
						Narrow thorax and sloping shoulders
						Renal agenesis, hydronephrosis
						Cardiac abnormality
						Cognitive impairment

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Limb-Mammary Syndrome (LMS)	603543	*TP63*	3q28	AD	Nasolacrimal duct obstruction	Hypohidrosis,
						Hypodontia
						Cleft palate
						Hypergonadotropic hypogonadism
LOGIC	245660	LAMA3	18q11.2	AR	Conjunctival scarring	Altered cry
laryngeal and ocular granulation tissue in children from the Indian subcontinent						Defective enamel of teeth
						Granulation formation and subsequent ulceration
						Usually fatal
Macroblepharon, Ectropion, Hypertelorism, and Macrostomia (MEHM)	602562	*Not yet found*	Not yet found	Not yet determined	**Ocular**:	**Dysmorphic facial features:**
Verloes-Lesenfants					Lagophthalmos	Severe hypertelorism, large palpebral fissures, lower lid ectropion, broad raised nasal base, a wide nasal tip, long smooth philtrum, macrostomia, irregularly placed teeth and Micrognathia.
					Corneal xerosis, secondary Chronic conjunctivitis and exposure keratitis.	Mandibulo-facial dysostosis
						Large fontanels, broad metopic suture, and osseous hypertelorism
Marden-Walker	248700	*PIEZO2*	18p11.22-p11.21	AD	Blepharophimosis	Micrognathia, kyphoscoliosis,
MWKS						Limb contractures, pigeon breast, arachnodactyly
						Renal microcystic disease
						Joint contracture
Marinesco-Sjogren Syndrome (MSS)	248800	*SIL1*	5q31.2	AR	Congenital cataracts	Cerebellar ataxia,
						Progressive myopathy
						Delayed psychomotor development
						Short stature
						Hyper-gonadotropic hypogonadism,
						Skeletal deformities
						Increased serum creatine kinase
						Muscle biopsy shows chronic dystrophic changes
Martsolf	212720	*RAB3 GAP2*	1q41	AR	Congenital cataract	Intellectual disability
Cataract-Mental Retardation-Hypogonadism					Microphthalmia	Hypogonadism
					Microcornea	Short stature
						Digital anomalies
						Micropenis
						Cryptorchidism
Matthew-Wood	601186	*STRA6*	15q24.1	AR	Microphthalmia/hypoplastic or absent optic nerves	Diaphragmatic defect
						Neonatal respiratory distress
					Cystic eye	Hypoplastic and often malformed lungs
						Congenital Cardiac malformations
						Diaphragmatic hernia
						Hiatal hernia
						Renal abnormality

Micro syndrome	600118	*RAB3GAP1*	2q21.3	AR	Microcephaly	Cortical dysplasia,
Warburg micro syndrome-1 (WARBM1)					Microspherophakia	Pachygyria
					Prominent root of the nose, large anteverted ears, facial hypertrichosis	Hypoplasia of the corpus callosum, severe mental retardation, spastic diplegia, hypogonadism
					Microphthalmia, microcornea, membranous cataracts, optic atrophy,	Hypotonia, mild to moderate spastic palsy with hip dislocations
					Miosis	Developmental delay
					Posterior synechiae	Urinary incontinence
						Ectopic kidney
						Bulbous nose
Mohr-Tranebjaerg	304700	*TIMM8A*	Xq22.1	X LR	Progressive visual loss due to optic atrophy	Progressive sensory neural hearing loss (pre lingual or post lingual
Deafness-Dystonia-Optic Neuropathy (DDON)					Photophobia	Normal vestibular function
					Reduced visual acuity,	Dystonia (Not seen in MELAS)/Ataxia
					Acquired color vision defect, and central scotoma.	Brisk tendon reflexes (unlike as in Friedreich ataxia), ankle clonus, and extensor plantar responses
					Retinal evaluation and ERG is normal	Behavioral problems
						Dementia
						Dysphagia and aspiration pneumonia
						Normal fertility
						No Cardiomyopathy (Common in Friedreich ataxia, which is an autosomal recessive disorder)
						Muscle biopsy shows normal mitochondria, normal enzyme activity.
						No Anorexia and recurrent vomiting as in MELAS
						Agammaglobulinemia as part of the contiguous gene deletion syndrome when the *BTK* gene is also involved.
MORM	610156	*INPP5E*	9q34.3	AR	Non-progressive visual impairment	Small penis in the absence of testicular abnormalities (Different from BBS)
Mental retardation					Mottled retina	Polydactyly
Obesity						
Retinal dystrophy						
Micropenis						
Mowat-Wilson syndrome	235730	*ZEB2*	2q22.3	AD	Microphthalmia	
					Cataract	
					Coloboma	
					Posterior embryotoxon	

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Nail Patella syndrome (NPS)	161200	*LMX1B*	9q33.3	AD	Juvenile open angle glaucoma (JOAG), ptosis, microcornea, microspherophakia, cataract, keratoconus	Nail hypoplasia, splitting of the nails, longitudinal ridging of nails
					Listers sign (dark central pigmentation usually petaloid shaped iris	Hypoplastic patella, absent patella, hypoplastic lateral femoral condyle
						Proteinuria, hematuria, renal failure, palpable iliac spur in mid-part of the ilium
						Psychosis, limitation of joint motility (supination and pronation of forearm, knees, renal failure), hypoplastic scapulae
Nance-Horan syndrome (NHS)	302350	*NHS*	X p22.13	X LR	Congenital cataract	Dysmorphism
					Microcornea	Large pointed anteverted ears
						High nasal bridge
						Dental anomalies
						Supernumerary centrally situated upper incisor
						Hutchinsonian incisors
						Developmental delay
						Intellectual disability
Neuhauser	249310				Megalocornea	Frontal bossing, hypertelorism, depressed and broad nasal root, long philtrum, micrognathia, and high-arched palate.
Megalocornea-mental retardation						Bifid uvula
						Cerebral cortical atrophy
Nicolaides-Baraitser syndrome (NBS)	601358	*SMARCA2*	9p24.3	AD	Vitreoretinopathy	Dysmorphic features:
					Glaucoma	Brachycephaly, thick
						Medially sparse eyebrows
						Long lashes
						Deep-set eyes
						Severe Mental retardation
						Sparse scalp hair with normal eyebrows and
						Eyelashes
						Flaredalaenasi, low columella, broad and long philtrum, ears with thick overfolded helices, wide mouth, and large protruding tongue, thick and everted lower vermilion, and frequent drooling
						Prominent lower lip, brachydactyly, and prominent interphalangeal joints.
						Refractory seizures, Short stature, obesity, complete alopecia, eczema,
						Narrow nasal bridge, broad nasal base and tip,

Nikawa-Kuroki Kabuk2	300867	*KDM6A*	Xp11.3	XLD	Long eyelashes, long palpebral fissures with eversion of the lateral third of the lower eyelids (similar to the make-up of actors of Kabuki, a Japanese traditional theatrical form)	Peculiar facies, a broad and depressed nasal tip, prominent and large earlobes, a cleft palate
					Strabismus	Postnatal dwarfism,
						Scoliosis, short fifth finger,
						Persistence of foetal finger pads,
						Recurrent otitis media in infancy
						Radiographic abnormalities of the vertebrae, hands, and hip joints
						Hirsuitism
Noonan	163950	*PTPN11, SOS1,, RAF1, KRAS, RAS, BRAF, MAP2K1*		AR	Blue or blue-green iris, hypertelorism,	Short stature and developmental delay
					Epicanthal folds thick lids or ptosis	Congenital heart defect
					Strabismus, refractive errors, amblyopia, and nystagmus	Webbed neck
						Apparently low-set nipples
						Cryptorchidism
						Pulmonary valve stenosis
						Hypertrophic cardiomyopathy
						Structural defects frequently observed include atrial and ventricular septal defects, branch pulmonary artery stenosis
						Bleeding diathesis/coagulopathy/bruising
						Lymphedema
						Genitourinary abnormalities
						Increased risk for
						Arnold-Chiari I malformation
						Hepatosplenomegaly
						Juvenile myelomonocytic leukemia (JMML)
						Low-set, posteriorly rotated ears with fleshy helices
						Can be associated with NF1
Oculoauricular	612109	*HMX1*	4p16.1	AR	Microphthalmia, microcornea, anterior segment dysgenesis, cataract, ocular coloboma, retinal pigment epithelium abnormalities, rod-cone dystrophy,	External ear malformations

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Oculo-Dento Digital Dysplasia (ODDD)	257850	*GJA1*	6q22.31	AD	Prominent epicanthic folds	Narrow, pinched nose with hypoplastic alaenasi, prominent columella and thin anteverted nares together with a narrow nasal bridge
				AR	Microphthalmia, microcornea	Microdontia
					Glaucoma, optic nerve dysplasia	Dental caries
					Retinal dysplasia	Syndactyly
						Camptodactyly
						Spastic paresis
						Abnormal white matter changes in brain
						Sparse scalp hair
						Nail abnormalities
						Lymphedema
Oculoectodermal	600268	*Not Yet Known*	Not Yet Known	Possible new mutation	Epibulbar Dermoids	Aplasia cutis congenita
				Possible AR cannot be excluded	Strabismus	Cutaneous hyperpigmentation
					Eyelid coloboma	Macrocephaly
						Intellectual disability
Oculo-Facio-Cardio-Dental	300166	*BCOR*	Xp11.4	X LD	Ocular defects (unilateral/ bilateral microphthalmia	Facial anomalies (narrow face with a broad nasal tip, separated nasal cartilage, cleft palate),
					Congenital cataracts	Congenital heart defects (septal defects),
						Skeletal anomalies.
						A diagnostic feature is dental root radiculomegaly
						Mild mental retardation
						Conductive or sensorineural hearing loss
Ohdo	249620			AR likely	Blepharophimosis	Mental retardation, congenital heart disease, teeth
				Other patterns of inheritance also possible		Cryptorchidism
						Cleft palate
						Bladder diverticulum
Oliver-McFarlane	275400	*PNPLA6*	19p13.2	AR	Long eye lashes	Intellectual disability
OMCS					Long eye brows	Sparse scalp hair
					Retinal pigmentary degeneration resembling choroideremia	Hypogonadism
						Micropenis
						Cryptorchidism
						Growth limitation
						Ataxia
						Titubation of the head
						Peripheral neuropathy

Ondine Curse	209880	*PHOX2B (Most common)*	4p13	AD	Anisocoria	Hirschsprung disease
		GDNF				Tumours of the neural
		RET				A characteristic box-shaped face is seen in patients with polyalanine repeat expansion mutations (PARMs).
		BDNF				Crest
		ASCL1				Hypoventilation during sleep
		EDN3				Near normal respiration during awake state
						Gastroesophageal reflux
						Constipation
						Hypotonia
						Hypothermia and thermal instability
						Alterations in blood pressure
						Autonomic dysfunction
Ophthalmo-Acromelic syndrome—OAS	206920	*SMOC1*	14q24.2	AR	Microphthalmia	Syndactyly of the fingers, metacarpal synostosis, polydactyly, fusion of carpal bones.
						Ectrodactyly
						Cryptorchidism
PHARC—Polyneuropathy Hearing loss Ataxia retinitis pigmentosa Cataract	612674	*ABHD12*	20p11.21	AR	Retinitis Pigmentosa	Pes cavus and Achilles tendon contractures
					Cataract	Hyporeflexia, hyperreflexia, extensor plantar responses, and neurogenic changes on EMG. Extensor plantar responses and cerebellar atrophy
						Ataxic and/or spastic gait disturbances progressive sensorimotor peripheral neuropathy.
						Hearing Loss
						Normal cognition
Pallister-Hall syndrome—PHS	146510	*GLI3*	7p14.1	AD	Coloboma	Common:
						Bifid epiglottis
						Hypothalamic hamartoma and hypopituitarism
						Polydactyly: Mesoaxial and postaxial polydactyly
						Y-shaped metacarpal or metatarsal bone
						Growth hormone deficiency and genital hypoplasia
Pearson	557000	N/A	N/A	Mitochondrial deletion/ duplications	Ptosis	Sideroblastic anemia
					Ophthalmoplegia	Pancreatic insufficiency
					Cataracts	Low birth weight, failure to thrive, hypoplastic anemia
					Pigmentary retinopathy	Renal impairment
Pierson	609049	*LAMB2*	3p21.31	AR	Microcoria and unreactive pupils	Congenital nephritic syndrome
					Hypoplasia of ciliary and papillary muscles	Hypotonia
					Lenticular anomalies	Neurodeveopmental defects

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Proteus	176920	*AKT1*	14q32.33	A mosaic somatic mutation of is seen in most patients.	Calcific band keratopathy	Dysmorphic facial features
					Abnormal vitreous structure chorioretinal hamartoma associated with serous retinal detachment vitreous hemorrhage	Dolichocephaly
					Myopia	Long face
					Cataract	Down slanting palpebral fissures and/or minor ptosis
						Depressed nasal bridge
						Wide or anteverted nares
						0pen mouth at rest
						Asymmetric overgrowth
						Gigantism, nevi, hemihypertrophy, and macrocephaly
						Partial gigantism
						Cerebriform Nevus,
						Lipoma
						Lung Cysts
						Intellectual disability
						Deep vein thrombosis
						Macrodactyly
						Cerebriform connective tissue nevi (CCTN)
						Linear verrucous epidermal nevus (LVEN)
						Hyperostosis of the skull
						Hyperostosis of the external auditory canal
						Megaspondylodysplasia
						Splenomegaly/thymus enlargement
Ramos-Arroyo	122430	*Not yet found*	Not yet found	AD	Hypoesthetic corneas	Dysmorphic facial features consisting of hypertelorism, flat Facial profile, Frontal bossing, depressed nasal bridge, and mid-facial hypoplasia
					Absence of peripapillary choriocapillaris and retinal pigment epithelium	Bilateral sensorineural hearing loss
						Persistent ductus arteriosus
						Moderate mental retardation
						Hirschsprung disease
Robert	268300	*ESCO2*		AR	Hypertelorism	Microcephaly
					Mid-facial capillary hemangioma	Intellectual disability
					Blue sclera	Cleft lip/cleft palate
					Corneal clouding	Limb anomalies usually all four limbs (upper limb>lower limb) Reduction in length of limbs
						Reduction in length or and number of digits
						Syndactyly, brachydactyly and Clinodactyly
						Flexion contractures
						Polycystic kidney disease
						Sparse silvery blonde scalp hair
						ASD/VSD/PDA
						Moyamoya

Robinow	268310 180700	*ROR2* *WNT5A*	9q22.31 3p14.3	AR AD	Hypertelorism	**Dysmorphic facial features:**
					Prominent eyes Down-slanting palpebral fissures	Broad forehead, prominent and widely spaced eyes, a short nose with an upturned tip, and a wide nasal bridge
					Rare: infantile glaucoma	Macrocephaly and Frontal bossing
						Skeletal abnormalities
						Shortening of the long bones in the arms and legs, particularly the forearms
						Brachydactyly, clinodactyly, dysplasia of nails
						Hemi-vertebrae leading to kyphoscoliosis
						Fused or missing ribs
						Short stature
						Small penis, clitoris, cryptorchidism,
						Triangular mouth and
						Down turned angles of the mouth
						Micrognathia
						Posteriorly rotated ears
Rubenstein-Taybi	180849 613684	*CREBBP* *EP300*	16p13.3 22q13.2	AD AD	High arched eyebrows	Dysmorphic facial features
					Long lashes	Characteristic grimacing/abnormal smile
					Refractive errors	Broad nasal bridge, beaked nose high arched palate, mild micrognathia, and
					Nasolacrimal duct obstruction/ malformation	Short stature
					Ptosis	Intellectual disability
					Epicanthus	Developmental delay
					Strabismus and nystagmus	Broad thumb and broad toe often angulated
					Glaucoma	Broad distal Phalanges
					Enophthalmos	Cryptorchidism
					Cataract	Congenital heart defects
					Coloboma	Constipation
						Talon cusps
						Sleep apnea syndrome
						Puberty and sexual development are normal
Russell-Silver	180860 312780	Uniparental disomy	7p11.2	AR X linked	Blue sclera	**Facial dysmorphism:**
					Refractive errors	Craniofacial features such as a triangular shaped face, Broad forehead and pointed, small chin with a wide, thin mouth.
					Subnormal stereoacuity	Intrauterine growth retardation, poor postnatal growth, body asymmetry.
					Remote near point of convergence.	Clinodactyly, camptodactyly
					Hypermetropia and anisometropia	Gastroesophageal reflux disease, esophagitis
					Smaller optic discs and tortuosity of retinal vessels.	Failure to thrive and aversion to food.

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Say-Barber	209885	*TWIST2*	2q37.3	AD	Telecanthus, ectropion	Facial dysmorphism:
					Partial or complete agenesis of the lids	Macrostomia, eyelid deformities, abnormal and low-set ears, bulbous nasal tip with hypoplastic nasal alae, and low frontal hairline
						Severe hypertrichosis,
						Hyper laxity and redundancy
						Macrostomia, atrophic skin, marked hypertrichosis, and growth retardation.
Schinzel-Giedion Midface Retraction	269150	*SETBP1*	18q12.3	AD	Alacrima	Severe mid-face retraction,
					Corneal hypoesthesia	Multiple skull anomalies (short and sclerotic base, multiple wormian bones, wide cranial sutures and fontanels)
						Short and sclerotic skull base, wide occipital synchondrosis, increased cortical density or thickness, or broad ribs
						Congenital heart defect
						Hydronephrosis
						Hypertrichosis
						Embryonal malignancy
						Choanal stenosis,
						Tricuspid regurgitation, hypospadias, Seizures, hearing loss, camptodactyly
						Mega ureter
Senior-Loken	266900	*NPHP1*	2q13	AR	Leber congenital amaurosis	Juvenile nephronophthisis
		NPNH2/INVS				Diabetes insipidus
	606955	*NPHP3*	3q22			
	606996	*NPHP4*	1p36			
	609254	*NPHP5*	3q21			
	610189	*NPHP6*	12q21			
	613615	*SDCCAG8*	1q44			
SHORT	269880	*PIK3R1*	5q13.1	AD	Telecanthus, deeply set eyes,	Intra Uterine Growth Retardation, developmental delay, delayed dental eruption,
Short Stature					Axenfeld-Rieger spectrum with or without	Sensory neural hearing loss, triangular facies, prominent ears, micrognathia
Hernia +/− Hyper-extensibility of Joints					Glaucoma	
Ocular depression						
Rieger anomaly						
Teething delay						

Sotos	117550	*NSD1*	5q35.2-35.3	AD	Astigmatism	Facial Dysmorphism:
					Cataract	Acromegaly like facial features High-arched palate and prominent jaw
					Strabismus	Large hands and feet
					Optic atrophy	Advanced bone age, Joint hypermobility
						Non-progressive cerebral disorder with mental retardation.
						Abnormal dermatoglyphics
						Hamartomatous polyps of the intestine
						Congenital heart defects
						Cryptorchidism, melanin spots of the penis
						Vertebral anomalies
						Absence of premolar tooth.
Townes-Brocks	107480	*SALL1*	16q21.1	AD	Less common:	Imperforate anus,
Renal-Ear-Anal-Radial syndrome (REAR)					Iris coloboma, microphthalmia, lamellar cataract, chorioretinal coloboma	Triphalangeal thumbs, fusion of metatarsals, absent bones, and supernumerary thumbs. sensorineural deafness
						Renal dysfunction
						Congenital heart disease
						Hypospadias, vaginal aplasia with bifid uterus, bifid scrotum, cryptorchidism
Traboulsi	601552	*ASPH*	8q12.3	AR	Ectopia lentis, micro spherophakia	Flat cheeks
					Iridocorneal adhesions	Beaked nose
					Iris atrophy	Retrognathia,
					Spontaneous subcutaneous filtering blebs	
Vanden Ende-Gupta syndrome (VDEGS)	600920	*SCARF2*	22q11.21	AR	Blepharophimosis	Triangular face, malar hypoplasia due to hypoplastic maxilla, narrow and beaked nose, everted lips,
						With or without cleft palate
						Thin ribs, hooked clavicles,
						Arachnodactyly
						Contractures that are usually self-limiting
						Ambiguous genitalia
						Retardation, microcephaly, failure to thrive, and severe joint limitation.
Warburg Micro syndrome-2	614225	*RAB3GAP2*	1q41	AR	Congenital cataract	Microcephaly, polymicrogyria, hypoplasia of the corpus callosum, and severe developmental delay
					Microphthalmia	

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Warsaw Breakage	613398	*DDX11*	12p11	AR	Optic disc coloboma	Facial dysmorphism
					Strabismus	Microcephaly (small and receding forehead, short nose, small nares, short neck, bilateral epicanthal folds, relatively large mouth, and cup-shaped ears) and high-arched palate
						Growth retardation,
						Hearing impairment,
						Ventricular septal defect, tetralogy of Fallot
						Hypotonia, Intellectual disability
						Single palmar crease, clinodactyly, syndactyly of toes,
						Abnormal skin pigmentation,
						Increased chromosomal breakage induced by mitomycin C, and premature chromatid separation.
Wolfram	222300	*WFS1*	4p16.1	AR	Optic atrophy (Onset before 16 years)	Diabetes Insipidus
(DIDMOAD)		*CISD2*	4q24		Usually after onset of diabetes mellitus	Diabetes Mellitus (usually the first to manifest)
						Sensory neural hearing loss
						Hypogonadism
						Cerebellar ataxia, peripheral neuropathy, dementia, psychiatric illness, and urinary tract atony)
						Delayed/absent puberty
						Non-autoimmune hypothyroidism
						Growth retardation

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WMS

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Ocular Manifestations of Vitamin Disorders

22

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Introduction

Vitamins are organic compounds that are essential to life and are obtained through the diet. Adequate intake of vitamins is necessary for maintenance of health, as well as normal growth and development of a child. When there is a significant lack of consumption, absorption, and/or utilization of these essential nutrients, deficiency states can develop and lead to both systemic and ocular symptoms. In particular, deficiency of vitamins A, B complex, C, D, E, and K can have a profound effect on the eye and cause damage to the cornea, retina, or optic nerve. Among these, vitamin A deficiency is the most important cause of ocular disease. Vitamin disorders are seen most frequently in developing countries secondary to dietary insufficiencies and are a major contributor to blindness worldwide. However, patients with absorptive defects (e.g. celiac disease, cholestasis, pancreatic insufficiency) are also at risk for developing vitamin deficiencies and must be monitored carefully for ocular signs. In this chapter, the systemic and ophthalmic manifestations of various hypovitaminosis states will be described (Table 22.1), followed by a brief discussion of hypervitaminosis. Recognition of high-risk situations and an understanding of the changes that occur in the eye secondary to vitamin related disorders will enable early identification of the disease and initiation of appropriate therapy to prevent irreversible blindness.

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Disease

Vitamin A Deficiency

Definition

Vitamin A is a fat-soluble vitamin found in liver, egg yolks, and dairy products. It may also be obtained in the form of carotenoid precursors, which are present in carrots, green leafy vegetables, yellow fruits, and red palm oil [1]. Vitamin A deficiency occurs when there is poor dietary intake, insufficient absorption or storage, or rapid loss of the vitamin from the body [2]. In its early stages, vitamin A deficiency is most commonly expressed as night blindness. Prolonged deficiency, however, can induce significant pathological changes to the eye in the form of xerosis and keratomalacia, which may lead to total and irreversible blindness [3].

History

The ocular manifestations of vitamin A deficiency have long been recognized and described. Ancient Egyptians observed that night blindness could be treated with liver extracts [4]. Throughout the eighteenth and nineteenth centuries, night blindness was commonly reported and various cures were utilized including the administration of cod liver oil [5]. Hubbenet [6] and Bitot [7] independently reported the association between night blindness and white foamy lesions on the outer conjunctiva, now known as "Bitot's spots." Cases of advanced xerophthalmia were seen with more severe deficiency, often in children who were near death from malnutrition [8].

Systemic animal experiments in the early twentieth century identified the specific fat-soluble vitamin essential for normal growth and integrity of the eye [9, 10]. By the 1930s, the cause and clinical features of vitamin A deficiency had

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Table 22.1 Ocular and systemic manifestations of vitamin deficiencies

Vitamin	Ocular manifestations	Systemic manifestations
A	Night blindness, xerosis, keratomalacia	Keratinization of mucous membranes and skin, growth retardation, anemia
B_1 (thiamine)	Nystagmus, diplopia, ophthalmoplegia, angular blepharoconjunctivitis; blepharoptosis in infantile beriberi; optic neuropathy	Beriberi, Wernicke-Korsakoff syndrome
B_2 (riboflavin)	Peripheral corneal vascularization, superficial keratitis, angular blepharoconjunctivitis	Cheilosis, angular stomatitis, glossitis, seborrheic dermatitis, anemia
B_3 (niacin)	Optic neuropathy	Pellagra (diarrhea, dermatitis, dementia)
B_6 (pyridoxine)	Angular blepharoconjunctivitis, optic neuropathy	Seizures, anemia, dermatitis, hyperirritability
B_9 (folic acid)	Optic neuropathy	Megaloblastic anemia, neuropathy
B_{12} (cobalamin)	Optic neuropathy, retinal hemorrhages, nystagmus, ophthalmoplegia	Pernicious anemia, posterior column deficits, ataxia, areflexia
C (ascorbic acid)	Hemorrhage in lids, orbit, conjunctiva, anterior chamber, and retina; proptosis in infantile scurvy; delayed healing of corneal wounds and ulcers	Scurvy (hemorrhagic signs, joint pain)
D	Proptosis	Rickets, osteomalacia
E	Ophthalmoplegia, gaze paresis, decreased adduction, adductor nystagmus; retinopathy of prematurity	Progressive neurologic disorder, hemolytic anemia
K	Retina hemorrhages	Systemic hemorrhagic manifestations

been elucidated [11]. While the incidence of vitamin A deficiency fell dramatically in wealthy countries with a concurrent rise in nutritional status, it continued to be a leading cause of blindness and death in the developing world. A number of randomized field-based trials conducted in rural Asia and Africa, showing a reduction in mortality with vitamin A supplementation, were instrumental in the development of global vitamin A fortification programs [12–14]. Since then, many countries have adopted WHO's guidelines to implement universal distribution of vitamin A for their preschool-age populations.

Epidemiology

Vitamin A deficiency is associated with increased morbidity and mortality in preschool-age children in developing countries [12, 15]. WHO reports that between 1995 and 2005, vitamin A deficiency was a moderate to severe public health problem in 122 countries—mostly in Africa and Southeast Asia—where economical and social deprivation was prevalent [16]. Annually, five to ten million children develop xerophthalmia, the most direct manifestation of vitamin A deficiency [17]. Furthermore, vitamin A-deficient children are more susceptible to respiratory and intestinal infections such as measles or diarrhea, which may exacerbate the poor intake of vitamin A and contribute to the increased risk of mortality [18, 19]. WHO estimates that between 250,000 and 500,000 children with vitamin A deficiency lose their sight every year, half of whom die within a year of going blind. Vitamin A supplementation in high-risk areas has shown to be effective in preventing childhood morbidity and mortality, reducing the overall risk of death by 24 % [20].

Vitamin A deficiency also occurs in developed nations, most often due to malabsorption or underutilization of vitamin A. Gastrointestinal or liver diseases, such as cystic fibrosis, cirrhosis, ulcerative colitis, celiac syndrome, short bowel syndrome and hepatitis, can interfere with proper absorption and storage of vitamin A [21–24]. Additionally, patients who undergo bariatric surgery, including gastric bypass and biliopancreatic diversion, may develop ocular symptoms caused by vitamin A deficiency [25–27].

Systemic Manifestations

In addition to its role in ocular health, vitamin A has important systemic functions. First, it is required for proper differentiation of mucosal epithelium in various organs. In vitamin A deficiency, mucous membranes lining the respiratory, gastrointestinal, and genitourinary tracts undergo keratinization, thereby compromising local resistance to bacterial infection [28–30]. This damage to the epithelial integrity is thought to be partially responsible for the increased risk of respiratory infections, chronic dry cough, and pyuria observed in severely deficient children [28, 29]. Keratinizing metaplasia also occurs in the skin, resulting in dry, scaly skin and follicular hyperkeratosis [2].

Another systemic manifestation of vitamin A deficiency is growth retardation. The fat-soluble compound was first identified by animal studies in which vitamin-deprived rats failed to grow as rapidly as their normal counterparts [9, 10]. The effect of vitamin A on human growth was later confirmed; moderate-to-severe deficiency marked by xerophthalmia was shown to impair normal physical growth in Nepalese children [31]. Vitamin A deficiency is also thought to play a role in the pathogenesis of anemia, although the exact biological mechanism remains unclear [16, 32].

Ophthalmic Manifestations

Vitamin A plays three essential roles in ocular metabolism. First, it serves as a precursor for the visual photosensitive pigment rhodopsin, which initiates neural impulses from photoreceptors to enable vision. Second, vitamin A is

involved in rod outer segment turnover as well as phagocytosis of the outer segment material. Third, vitamin A is necessary for maintaining the structural and functional integrity of corneal epithelial cells [3].

In the body, vitamin A exists in four forms: retinol, retinal, retinoic acid, and retinyl ester. Approximately 50–90 % of ingested vitamin A is absorbed in the small intestine and transported to the liver, where it is stored as retinyl ester [17]. From the liver, it is transported to the eye as retinol in combination with retinol-binding protein. In the eye, vitamin A compounds reside in the outer segment of photoreceptors and retinal pigment epithelium (RPE). Vitamin A is required for the synthesis of rod rhodopsin and cone iodopsin, which consist of 11-*cis*-retinal covalently bound to opsin and photopsin, respectively. When rhodopsin is exposed to light, isomerization of 11-*cis*-retinal to all-*trans*-retinal occurs, inducing a conformational change in the protein and release of the retinal. This process, known as bleaching, initiates a neural impulse and is responsible for phototransduction [33].

Xerophthalmia is the most specific ocular manifestation of vitamin A deficiency and is also the leading cause of childhood blindness in developing countries. The term 'xerophthalmia' encompasses a spectrum of ocular manifestations ranging from night blindness to keratomalacia, as classified by WHO (Table 22.2). Because of vitamin A's essential role in photoreceptor function, night blindness is the primary and most common expression of vitamin A deficiency. Children with night blindness have impaired adaptation to darkness, often unable to move about in dim light or after sunset. Cone dysfunction occurs more slowly and less completely than rod dysfunction, explaining the relative preservation of visual acuity in the presence of night blindness [34]. At early stages, night blindness is reversible and responds rapidly to vitamin A replacement [17].

With prolonged deficiency, the conjunctival epithelium undergoes pathological changes, from the normal stratified columnar type to the stratified squamous type. These changes cause a loss of mucous-secreting goblet cells, formation of a granular cell layer, and keratinization of the conjunctival epithelium, resulting in conjunctival xerosis. Clinical features of conjunctival xerosis include dryness, wrinkling, loss of luster, thickening, and roughening of the bulbar conjunctiva, characterized by fine droplets or bubbles on the surface [17]. In some cases, white triangular foamy plaques known as Bitot's spots can occur temporally on the bulbar conjunctiva. These lesions result from the accumulation of keratinized debris and saprophytic bacilli on the xerotic surface [17]. Although Bitot's spots are easily recognized, they may not serve as an adequate indicator of disease states. Bitot's spots sometimes persist in the absence of active vitamin A deficiency, representing generalized malnutrition or a previous episode of deficiency [35]. Conjunctival xerosis and Bitot's spots typically begin to resolve within 2–5 days of vitamin A therapy, with most dissipating by 2 weeks [17].

More severe deficiency can lead to corneal xerosis, ulceration, and keratomalacia. Initially, the cornea loses its normal luster and develops a hazy, opaque, and dry appearance (xerosis) near the inferior limbus, as seen in Fig. 22.1. Keratinized patches resembling Bitot's spots may also form on the corneal surface, most commonly in the interpalpebral zone. As the disease progresses, corneal ulceration, perforation, and keratomalacia may develop. Ulceration and necrosis are often caused not by vitamin A deficiency alone, but by infections or trauma occurring in a vitamin-deficient state [36]. Ulceration or keratomalacia covering less than a third of the corneal surface generally leaves the central pupillary zone intact, and some useful vision may be preserved with immediate treatment. More widespread keratomalacia tends to result in perforation, extrusion of intraocular contents, and loss of the globe [17]. Children with untreated keratomalacia have a mortality rate of 90 % [37].

Table 22.2 Classification of xerophthalmia (World Health Organization)

Classification	Ocular signs
XN	Night blindness
X1A	Conjunctival xerosis
X1B	Bitot's spot
X2	Corneal xerosis
X3A	Corneal ulceration/keratomalacia (<1/3 corneal surface)
X3B	Corneal ulceration/keratomalacia (≥1/3 corneal surface)
XS	Corneal scar
XF	Xerophthalmic fundus

Source: [16]

Diagnosis

Vitamin A levels are used as the biochemical indicator of vitamin A deficiency. Serum retinol concentrations lower than 0.7 μmol/l and 0.35 μmol/l represent deficiency and

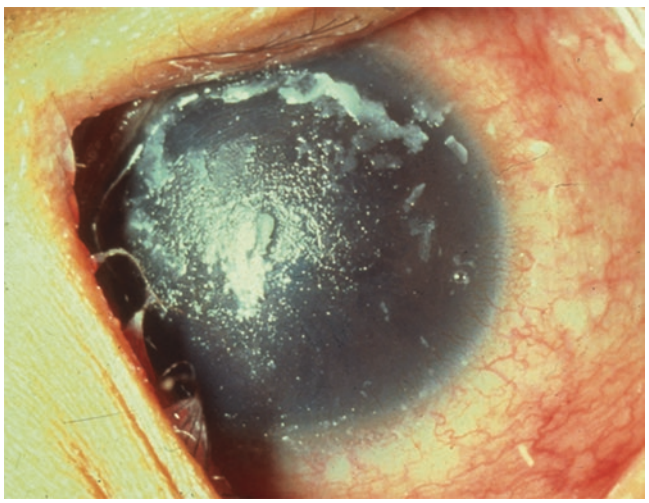

Fig. 22.1 Corneal xerosis in a patient with vitamin A deficiency. Note the dryness, lack of luster, and granular appearance of the corneal epithelium

severe deficiency, respectively [16]. Clinical diagnosis can also be made by examining the eyes for signs of xerophthalmia. Conjunctival impression cytology, in which a conjunctival specimen is collected, fixated, and stained, is a method for detecting preclinical and clinical xerophthalmia [36], although the validity of this technique has been debated [38–41]. Dark adaptation tests, which assess a patient's response to dim light, may serve as a helpful complement to the diagnosis. Whenever possible, diagnosis should be made based on multiple indicators to accurately assess the vitamin A deficiency state.

Management

Xerophthalmia should be recognized as a medical emergency and be treated immediately with vitamin A supplementation. Prompt therapy is usually successful in reversing early stages of vitamin A deficiency, including night blindness, conjunctival xerosis and Bitot's spots, but more advanced corneal damage may persist after therapy. For treatment of xerophthalmia, WHO recommends immediate oral supplementation of vitamin A for two consecutive days (100,000 IU for children <1 year of age and 200,000 IU for children >1 year of age), with the same dosage repeated 2 weeks later (Table 22.3) [42]. In settings where vitamin A deficiency is of public health concern, a high-dose supplementation regimen (Table 22.3) is proven to be safe and effective in preventing childhood xerophthalmia and death [43]. Acute side effects such as headache, nausea, vomiting, and diarrhea may occur in a small percentage of children receiving 100,000–200,000 IU of vitamin A. However, these symptoms are transitory and generally disappear within a day of dosing [44].

In addition to systemic therapy, topical lubrication with retinoic acid may accelerate corneal healing in children with corneal xerophthalmia [45]. An antibiotic eye ointment such as tetracycline or chloramphenicol is recommended for treatment and prevention of secondary infections; however, steroid-containing ophthalmic ointments should never be used in these instances [42]. Corneal surgery may be indicated for complications of keratomalacia [2].

Table 22.3 Vitamin A supplementation schedule for treatment and prevention of Xerophthalmia (World Health Organization)

Population	Dose	Frequency
For treatment:		
<6 months of age	50,000 IU	Immediately on diagnosis, next day, and 2 weeks later
6–12 months of age	100,000 IU	
>12 months of age	200,000 IU	
Prophylaxis:		
6–11 months of age	100,000 IU	Once
12–59 months of age	200,000 IU	Every 4–6 months

Source: [42, 43]

Of additional interest, vitamin A supplementation has been shown to slow the progression of retinal degeneration in patients with retinitis pigmentosa (RP) [46]. The essential role that vitamin A plays in photoreceptor cell function may explain its efficacy in treating RP, which is characterized by a gradual loss of rods and cones. A daily dose of 15,000 IU of vitamin A palmitate is recommended for treatment of adults with typical forms of RP [47].

Vitamin B Complex Deficiency

Definition

Vitamin B complex consists of several water-soluble compounds—thiamine (B_1), riboflavin (B_2), niacin or nicotinic acid (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folic acid (B_9), and cyanocobalamin (B_{12}). The B vitamins generally act as coenzymes in metabolic processes, often working synergistically with one another. Food sources of vitamin B complex include whole grains, dried beans, green leafy vegetables, legumes, dairy products, liver, and meat. Water-soluble vitamins, including the B vitamins, must be consumed daily, because any excess amounts are readily excreted in the urine. Vitamin B_{12} is the only B vitamin that can be stored in large concentrations in the liver. Deficiency of vitamin B complex can result in ocular symptoms in addition to a multitude of systemic disorders, including beriberi and Wernicke-Korsakoff syndrome (thiamine deficiency), pellagra (niacin deficiency), and pernicious anemia (vitamin B_{12} deficiency).

History

While disorders of vitamin B deficiency had been recognized and described for centuries, the individual vitamins responsible for these disorders were not identified until the twentieth century [48]. As the functions of B vitamins became clearer, many countries have mandated adding these vitamins to polished rice, flour, cereal, etc. to replace the micronutrients that are removed during the refining process. In the United States, white flour and other refined grains have been enriched with thiamine, riboflavin, and niacin since the 1940s; folic acid fortification of grain products was mandated in 1998 [48, 49].

Epidemiology

Although the occurrence of vitamin B-related disease has declined, sub-clinical manifestations of vitamin B complex deficiency are still widespread in populations under various stress situations [50]. In developing countries where diets are not fortified with micronutrients, vitamin B deficiency results mainly from inadequate intake. In wealthy countries, vitamin B deficiency is primarily seen in people with self-imposed dietary restrictions, malabsorption syndromes, or chronic

alcoholism. Thiamine deficiency, for example, occurs most often in chronic alcoholics, who have impaired gastrointestinal absorption and utilization of thiamine. Thiamine deficiency has also been observed relatively frequently in patients who have undergone bariatric surgery [51, 52]. Vegetarians and vegans are at particular risk for developing a deficiency of vitamin B_{12}, which is only available from meat and dairy products. Breast-fed infants of mothers who adhere to a strict vegan diet may develop symptoms related to vitamin B_{12} deficiency. Autoimmune disease is also associated with vitamin B_{12} deficiency, due to impaired absorption.

Systemic Manifestations

Thiamine functions as an essential coenzyme in carbohydrate metabolism and energy utilization. Thus, its deficiency is particularly deleterious to the nervous system, which harnesses energy largely from glucose oxidation [3]. The classic systemic manifestation of thiamine deficiency is beriberi. In dry beriberi, the peripheral nervous system undergoes damage, leading to neuropathy, ataxia, loss of muscle strength, and eventually paralysis. In wet beriberi, the cardiovascular system is affected and congestive heart failure can occur. Cerebral beriberi, also known as Wernicke's encephalopathy, affects the central nervous system; symptoms include mental disturbance and ataxia, and if left untreated, Korsakoff syndrome may develop. Infantile beriberi can occur in babies breast-fed by mothers who are alcoholic or malnourished [53]. Infants with acute beriberi develop a loss of appetite, irritability, vomiting of milk, edema and hoarseness, and often die within a few days of onset if not treated promptly [54, 55].

Riboflavin is the precursor for two essential redox cofactors involved in energy production, FMN and FAD. Deficiency of riboflavin results in "ariboflavinosis," which refers to the clinical symptoms of glossitis, anemia, sore throat, seborrheic dermatitis, angular stomatitis, and cheilosis.

Niacin is the precursor for two other cofactors critical in energy metabolism—NAD and NADP. Niacin deficiency causes pellagra, a disease that is characterized by diarrhea, dermatitis, and dementia. Symptoms of pellagra in infants and children include irritability, anxiety, apathy, and anorexia. Young patients with pellagra may also present with dry, scaly skin and sore tongues and lips.

Pyridoxine serves as a cofactor in amino acid, carbohydrate, and lipid metabolism as well as in hemoglobin synthesis. Vitamin B_6 deficiency most often occurs in combination with other vitamin B deficiencies; deficiency of pyridoxine alone is rare [56]. In infants and children, symptoms of vitamin B_6 deficiency include seizures, anemia, dermatitis, and hyperirritability. Because the need for vitamin B_6 is closely linked to protein intake, the symptoms may worsen as more protein is consumed.

Folate is involved in one-carbon transfers of methylation reactions and nucleic acid synthesis, and is therefore essential for cell division and growth. Folic acid deficiency in pregnant women has been linked to neural tube defects in early embryo development. Severe and prolonged deficiency may result in megaloblastic anemia and neuropathy [57].

Vitamin B_{12} is the largest of the B vitamins, consisting of a porphyrin-like ring with a cobalt atom at the center. Vitamin B_{12} is critical for the normal functioning of the nervous system, and its deficiency can lead to neurologic symptoms including peripheral neuropathy, sensory or motor defects, and wide-based gait. In infants, low levels of vitamin B_{12} can disrupt myelination of the brain, thereby interfering with early brain development [58]. The most common cause of vitamin B_{12} deficiency is pernicious anemia, an autoimmune disease that destroys parietal cells of the stomach. Parietal cells are responsible for secreting intrinsic factor, which is needed for normal absorption of vitamin B_{12}; a lack of intrinsic factor causes malabsorption and deficiency of vitamin B_{12}. Furthermore, because vitamin B_{12} is necessary for erythrocyte production in the bone marrow, its deficiency can in turn result in pernicious anemia. Vitamin B_{12} deficiency is also associated with long-standing vegan diets, i.e. when the diet contains no animal source foods. Although there typically are extensive hepatic stores of the vitamin, these can be depleted over time, particularly over the course of a reproductive cycle including both pregnancy and lactation.

Ophthalmic Manifestations

Optic nerve degeneration is the primary ocular manifestation of vitamin B deficiency. In particular, deficiency of vitamin B_{12} can cause an optic neuropathy in which the vision loss is bilateral, symmetric, gradual, and painless. The optic nerve appears normal during the early stages of disease, while visual field testing generally reveals central and cecocentral scotomas [36]. The optic neuropathy resulting from vitamin B_{12} deficiency clinically resembles Leber's hereditary optic neuropathy (LHON). One study suggests that in patients carrying a primary LHON mtDNA mutation, optic neuropathy may be precipitated by vitamin B_{12} deficiency [59].

Deficiencies of thiamine, riboflavin, niacin, pyridoxine, and folic acid have also been associated with optic neuropathy; however, the causal role of these vitamins remains controversial [60–63]. In one study, vitamin B complex deficiency in school children was negatively associated with visual acuity, which improved following vitamin B supplementation [64].

Eye movement disorders such as nystagmus, diplopia, and ophthalmoplegia has been shown to occur with thiamine deficiency, particularly in patients with Wernicke's encephalopathy [33, 54]. Blepharoptosis is commonly seen associated with infantile beriberi [55]. Rarely, eye movement disorders can be caused by vitamin B_{12} deficiency; cases of ophthalmoplegia, downbeat nystagmus, and upward gaze palsy have been described [65].

Vitamin B_{12} deficiency has also been directly linked to vascular changes in the retina. Retinal hemorrhages, edema, and dilatation have been observed with megaloblastic anemia [3]. The hemorrhages usually occur at the posterior pole of the eye and rarely interfere with central vision.

In addition to the optic nerve and retina, the anterior segment of the eye can be affected by vitamin B deficiency. Peripheral corneal vascularization and superficial keratitis with thin opacities in the center of the cornea have been reported to occur with riboflavin deficiency [66]. Although the biochemical role of riboflavin in the cornea is unclear, a decrease in oxygen uptake by the corneal epithelium has been noted [67, 68]. Thiamine, riboflavin, and pyridoxine deficiencies can also result in angular conjunctivitis and blepharoconjunctivitis [66, 69].

Diagnosis

Because the clinical symptoms of vitamin B deficiency can be nonspecific, diagnosis is typically made on the basis of serum vitamin levels or urinary excretion [50]. The specific diagnostic tools used for each vitamin are listed in Table 22.4. The Schilling test may be used as a confirmatory test to identify vitamin B_{12} deficiency and pernicious anemia, and is helpful for determining the root cause of deficiency.

Management

Treatment of vitamin B complex deficiency is achieved by individual vitamin supplementation, as listed in Table 22.4. Because the metabolic pathways of the B vitamins are closely interrelated, diverse clinical manifestations resulting from multiple deficiencies may be seen in one individual. Therefore, a patient presenting with a specific vitamin B deficiency is generally treated with the entire group of B-complex vitamins. While vitamin B replacement therapy will resolve most symptoms, any damage to the nerve may be permanent.

Vitamin C Deficiency

Definition

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin involved in various enzymatic reactions in the body. It is found in fresh vegetables and fruits, including tomatoes, spinach, cabbage, green pepper, and citrus fruits. Vitamin C is an essential cofactor in the synthesis of collagen, which is necessary for the integrity of vascular basement membranes. Its deficiency results in a systemic disease known as scurvy, which includes several hemorrhagic manifestations.

History and Epidemiology

In the fifteenth century, many seamen suffered and died from scurvy as they were forced to subsist on diets consisting of dried grains and beef for months. A British surgeon in 1753 reported his discovery that consuming citrus fruits would prevent against these illnesses [70]. Subsequently, the use of lime juice by the English Royal Navy gave British sailors the nickname "limey." Although the prevalence of vitamin C deficiency has declined over the centuries, 7.1 % of healthy US middle class was found to be vitamin C-deficient by the 2003–2004 National Health and Nutrition Examination Survey [71]. Similarly, a 2008 study reported that 25 % of men and 16 % of women from low-income populations in the United Kingdom showed signs of vitamin C deficiency [72].

Systemic Manifestations

The clinical features of scurvy include swollen or bleeding gums, intracranial bleeding, petechial hemorrhages, and joint pain associated with swelling of the extremities [56]. In infantile scurvy, the lesions primarily occur where bone growth is most active.

Subperiosteal hemorrhages and extreme pain upon movement can cause a pseudoparalysis of the limbs; swelling and hemorrhages are common in gums surrounding erupting teeth [50].

Table 22.4 Diagnosis and treatment of vitamin B deficiencies

Vitamin	Diagnostic test	Suggested doses for treatment
B_1 (thiamine)	Urinary thiamine excretion; Erythrocyte transketolase activity; Serum thiamine levels	Initial week: 10 mg/day Several subsequent weeks: 3–5 mg/day Thereafter: 1–5 mg/day for maintenance
B_2 (riboflavin)	Urinary flavin excretion; Erythrocyte glutathione reductase activity; Erythrocyte flavin concentration	3–10 mg/day
B_3 (niacin)	Urinary excretion of methylated metabolites (ratio of 2-pyridone to N′-methyl-nicotinamide); Erythrocyte pyridine and NAD levels	100–300 mg/day in divided doses
B_6 (pyridoxine)	Plasma PLP levels; Erythrocyte aminotransferase activity; Urinary xanthurenic acid excretion after tryptophan ingestion	For deficiency states: 5–25 mg/day For pyridoxine-dependent seizures: 100 mg (single dose) by parenteral route
B_9 (folic acid)	Erythrocyte folate concentration; Plasma homocysteine levels	0.5–1 mg/day
B_{12} (cobalamin)	Plasma vitamin B_{12} level; Plasma homocysteine and MMA levels; Schilling test	1 mg/day orally OR 1 mg/week intramuscularly for 8 weeks, followed by 1 mg/month for life

Ophthalmic Manifestations

In the eye, vitamin C deficiency manifests as a hemorrhagic tendency affecting the lids, conjunctiva, orbit, anterior chamber, iris, and retina [2]. The most common ocular lesions are subconjunctival and orbital hemorrhages, typically superior and subperiosteal [73, 74]. In about 10 % of babies with infantile scurvy, proptosis occurs as a result of hemorrhage in the orbital bones [75]. Paralysis of extraocular muscles may result from orbital hematomas [33]. Vitamin C also plays an important role in wound healing, and its deficiency may delay the healing process of corneal ulcers and wounds.

Diagnosis

Serum or leukocyte ascorbic acid levels are used as a diagnostic test for vitamin C deficiency. A serum concentration <11.4 μmol/L of ascorbic acid is considered to be a vitamin C-deficient state, when clinical features of scurvy may appear [76].

Management

Children with vitamin C deficiency respond rapidly to supplementation with 100–300 mg of ascorbic acid per day. Although clinical improvement is usually seen within 1–2 weeks, continuation of therapy for up to 3 months is recommended for complete recovery. Treatment should be complemented with consumption of vitamin C-rich foods, such as citrus fruits and juices.

Vitamin D Deficiency

Definition

Vitamin D is a fat-soluble vitamin essential for maintaining normal levels of calcium and phosphate. These minerals are necessary for bone mineralization, muscle contraction and nerve conduction, among many other cellular functions. Vitamin D deficiency results from inadequate exposure to sunlight, malnutrition, or abnormal metabolism of vitamin D in the kidney or liver. The systemic disease caused by vitamin D deficiency is rickets in children and osteomalacia in adults.

Ophthalmic Manifestations

Ocular involvement in vitamin D deficiency is rare. Zonular cataracts were thought to be caused by tetany and rickets associated with vitamin D deficiency, but later studies have shown that decreased calcium levels are the cause for these cataracts [3, 36]. Proptosis has been reported to occur in children with rickets due to orbital hemorrhage [3].

Diagnosis and Management

Serum 25-hydroxy-vitamin D levels are used as a measure of vitamin D deficiency. For treatment of deficiency in children, a 2- to 3-month regimen of high-dose vitamin D therapy is recommended: 1000 IU daily in neonates, 1000 to 5000 IU daily in infants 1–12 months of age, and 5000 IU daily in children over 1 year of age. This can be followed by a maintenance dose of 400 IU per day after sufficient vitamin D levels are achieved [77]. Children should also receive adequate dietary intake of calcium and phosphorus, by milk, formula, or other dairy products.

Vitamin E Deficiency

Definition

Vitamin E, or α-tocopherol, is a fat-soluble antioxidant that is involved in the glutathione peroxidase pathway. The biological role of vitamin E is to scavenge free radicals and to protect cellular components from oxidative damage, e.g. polyunsaturated fatty acids (PUFAs) which are highly susceptible to free radical oxidation. Dietary sources of vitamin E include nuts, seeds, and vegetable oils. In developed countries, vitamin E deficiency occurs most commonly in premature infants and in children with fat malabsorption syndromes, such as abetalipoproteinemia (Bassen-Kornzweig syndrome), cystic fibrosis, biliary atresia and other cholestatic liver diseases, and lipid transport abnormalities. Clinical vitamin E deficiency is characterized by neurologic defects and hemolytic anemias.

Systemic Manifestations

A progressive neurologic syndrome has been reported in children with vitamin E malabsorption related to chronic liver disease [78–80]. Symptoms included areflexia, ataxia, gait disturbance, and decreased sense of vibration and proprioception. In some children, ocular manifestations were present including ophthalmoplegia, paresis of gaze, decreased adduction of the eyes, adductor nystagmus, and transient loss of vision [78, 79]. It has been suggested that vitamin E deficiency occurring during nervous system development is the cause of this syndrome, as similar lesions have been found in animals with experimentally induced vitamin E deficiency [81, 82].

Vitamin E deficiency in premature infants is also associated with hemolytic anemia [83]. Preterm infants are susceptible to vitamin E deficiency because a significant amount of vitamin E transfer occurs during the last trimester of pregnancy. Deficiency in premature infants is characterized by a low serum tocopherol level from birth and development of hemolytic anemia at 6–10 weeks of age, which is treatable by vitamin E therapy.

Ophthalmic Manifestations

In addition to the eye movement disorders associated with the neurologic syndrome (see *Systemic Manifestations* above), vitamin E deficiency may contribute to retinopathy of prema-

turity in preterm infants, characterized by an abnormal growth of blood vessels in the retina. While most cases of retinopathy are mild and resolve spontaneously, severe disorder can lead to bleeding, retinal detachment, and eventual loss of vision. Numerous studies support vitamin E's role in the normal functioning of the retina. Photoreceptor outer segment membranes are concentrated with PUFAs and are therefore highly prone to oxidative damage. Vitamin E, present in the rod outer segment, is the only well-recognized, fat-soluble antioxidant *in vivo*. It thus appears that a deficiency of vitamin E can have a deleterious effect on retinal membrane function by exposing PUFAs to peroxidative degradation [84]. In animals with experimentally induced vitamin E deficiency, retinal degeneration and loss of visual function have been reported [85, 86]. Similarly, patients with chronic vitamin E deficiency resulting from untreated abetalipoproteinemia almost invariably develop progressive retinal degeneration, similar to that seen in retinitis pigmentosa [87, 88]. However, further research is needed to elucidate the biochemical function of vitamin E in normal and pathological retinal metabolism.

Diagnosis

Because serum vitamin E levels can be elevated by the presence of high serum lipids, vitamin E deficiency is best diagnosed by measuring the ratio of α-tocopherol to serum lipids. A ratio <0.6 mg/g is considered abnormal in infants less than 1 year of age, and a ratio <0.8 mg/g signals deficiency in older children and adults [89].

Management

For treatment of vitamin E deficiency in neonates, 25–50 IU of α-tocopherol is given daily for one week, followed by adequate dietary intake. Larger doses may be required in patients with fat malabsorption disorders or with symptoms of neuropathy.

In preterm and very low birth weight infants, retinopathy of prematurity may be prevented by continuous supplementation of vitamin E from the first hours of birth until retinal vascularization is complete. However, because high doses of vitamin E have been associated with an increased risk of sepsis, routine supplementation in preterm infants by intravenous injection at high doses is currently not recommended [90]. For very severe retinopathy of prematurity, laser treatment can be performed on the outermost part of the retina to halt the abnormal growth of blood vessels and to decrease the risk of retinal detachment and blindness.

Vitamin K Deficiency

Definition

Vitamin K is a naphthoquinone involved in the normal synthesis of prothrombin, clotting factors II, VII, IX, and X, and coagulation inhibitor protein C [91]. Naturally occurring vitamin K_1 is fat soluble and found in high concentration in liver, soybeans, and alfalfa, and in lessor amounts in spinach and tomatoes. Vitamin K_2 is produced by intestinal bacterial flora, and represents an important source of vitamin K in humans. Vitamin K_3 is menadione, a synthetic water-soluble substance with vitamin K activity often used for supplementation in vitamin K deficiency. As adult gastrointestinal flora produce vitamin K, and a varied diet contains enough vitamin K to meet adult nutritional requirements, vitamin K deficiency is quite rare in adults [92].

Several factors predispose infants to vitamin K deficiency. A normal neonate is born with low hepatic stores of vitamin K, as only a small amount of the nutrient crosses the placenta during gestation. Newborns have only 30–60 % of adult clotting factor levels, and do not yet have vitamin K-producing gastrointestinal flora [93, 94]. Breast-fed infants are at an increased risk for vitamin K deficiency compared to formula-fed infants, since cow's milk contains four times as much vitamin K as human breastmilk [95]. Breastfeeding is also associated with decreased production of vitamin K by gastrointestinal flora. Vitamin K is necessary for normal homeostasis in infancy, and an infant with a significant deficiency may develop vitamin K deficiency bleeding (VKDB) [93, 96].

VKDB may manifest up until 6 months old, and is classified according to the infant age at which symptoms present. *Early VKDB* presents within the first 24 h of life [92], and is due to vitamin K-inhibiting drugs—most commonly anticonvulsants, antitubercular drugs, anticoagulants, or cephalosporins—taken by the mother during pregnancy [96, 97]. *Classic VKDB* presents between days 1–7 of life, and can be caused by maternal drugs but is most often idiopathic [93]. *Late VKDB* is variably defined as hemorrhagic symptoms occurring after week 2 of life [92], disease presenting between weeks 2–12 [92, 98, 99], between months 1–3 [100], and between months 1–6 [97]. Late VKDB occurs most often between weeks 3–6 and is seen primarily in breast-fed infants who have not had prophylactic vitamin K at birth [92, 101]. Late VKBD is also seen in infants with and without prophylaxis who have undergone antibiotic treatment or who have α_1 antitrypsin deficiency, biliary atresia, celiac disease, cystic fibrosis, or hepatitis and suffer from intestinal fat malabsorption [92, 93, 102, 103]. Late VKDB may also be idiopathic [92, 93].

History

The term "hemorrhagic disease of the newborn" was first used in 1984 by Townsend to describe a self-limiting bleeding condition he observed in a cohort of infants less than two weeks old. Vitamin K, named after its German designation as *koagulationsvitamin,* was discovered in 1929 after Danish scientist Henrik Dam observed that chicks fed low fat diets developed hemorrhagic disease [93, 104]. In 1961, prophylactic vitamin K became standard of care for neonates in the US, resulting in a dramatic decrease in VKDB observed during the first week

of life [105]. Sutor et al. suggested changing the name of the disease in 1999 from "hemorrhagic disease of the newborn" to "vitamin K deficiency bleeding", as there are other causes of hemorrhage in the newborn period, and as the hemorrhagic disease caused by vitamin K deficiency may present beyond the newborn period [106].

Epidemiology

In healthy infants who have not had vitamin K prophylaxis at birth, the incidence of VKDB in the first week of life ranges from 0.25 to 1.7 cases per 100 [92]. Early-onset VKDB is the rarest type of VKDB and not affected by perinatal vitamin K administration [107]. Early-onset VKDB may instead be preventable by vitamin K supplementation provided to the mother during the last 2–4 weeks of gestation [100]. Following the institution of intramuscular vitamin K prophylaxis for newborns, classic VKDB has become "virtually nonexistent" among US infants who receive prophylaxis [93].

Late VKDB is seen in 4.4–7.2/100,000 live births among infants who do not receive prophylaxis; intramuscular vitamin K prophylaxis virtually eliminates late VKDB. In countries employing oral vitamin K prophylaxis, rates of late VKDB range from 1.2 to 1.8/100,000 live births, suggesting the superiority of the intramuscular route of administration [92]. Late VKDB occurs in 25/100,000 live births in Japan, where the majority of cases are diagnosed as idiopathic [107]. Vitamin K deficiency was first implicated in the etiology of infantile retinal hemorrhage by a 1944 study, which demonstrated that among two cohorts of infants, those whose mothers received vitamin K during pregnancy had a lower rate of retinal hemorrhages at birth than those whose mothers received no supplement [108].

The overall mortality rate for late VKDB is estimated to be between 10 and 20 % [98, 109]. No mortality data has been published for early or classical forms of the disease. Up to 40 % of surviving infants suffer neurologic sequelae following recovery, including microcephaly, developmental delay, and seizures [109–112].

Systemic Manifestations

In early VKDB, newborns may present with a scalp cephalohematoma, widespread bruising, umbilicus or circumcision site bleed, or with devastating intra-thoracic, intra-abdominal, or, less commonly, intracranial hemorrhage [93]. Classic VKDB often presents a milder clinical picture: although affected infants may have umbilical and venipuncture oozing, skin purpura, gastrointestinal or nasal mucosal bleeding, serious intrathoracic and intracranial hemorrhages are rarely seen in this VKDB subtype [99].

Intracranial hemorrhage is seen in 50–60 % of infants with late VKDB, and can be neurologically devastating. Babies may present with obvious neurological symptoms—bulging fontanel, seizure, paralysis, or coma [96]—or may display only nonspecific symptoms, such as irritability, poor suck, sudden pallor, or vomiting [112, 113]. These spontaneous hemorrhages occur when clotting factors fall below 25 % of adult levels [114]. Of those with intracranial hemorrhage, 13–50 % involve subdural bleeding, 50 % intraparenchymal bleeding, 42 % intraventricular, and 10–100 % subarachnoid with 67 % of intracranial bleeds involving more than one of these hemorrhage sites [115, 116]. "Warning bleeds" prior to the major intracranial hemorrhage are seen in 30–40 % of cases; usually a superficial ecchymosis. These warning bleeds appear benign and vitamin K deficiency often goes undiagnosed until more sinister symptoms appear [96]. Extracranial hemorrhages are observed in 20 % of infants with late VKDB, and may manifest as gastrointestinal bleeding, nodular purpura, profuse bleeding from wounds or venipuncture sites, and periosteal elevation on X-ray [93].

Several unusual presentations of VKDB reported in the literature emphasize the broad range of symptoms attributable to this disease. A case report of a 137-day-old infant describes an intracerebral hemorrhage as a rare manifestation of late VKDB [98]. Hepatomegaly, clay-colored stools, hematuria, and hemiparesis were described in four infants with coexisting late VKDB and cholestasis [117]. In another report of hepatobiliary disease and vitamin K deficiency, a 7 week old infant presenting with jaundice, fixed and dilated pupils, unilateral retinal hemorrhages (no further details provided), ipsilateral subarachnoid hemorrhage and cerebral edema was misdiagnosed with shaken baby syndrome [105]. Also misdiagnosed as shaken baby syndrome was a 10 week old infant with deep buttocks swelling, palpable thigh bruises, bilateral retinal hemorrhages (no further details provided), and subdural hemorrhage, all secondary to late-onset VKDB [118]. These case reports highlight the imperative to maintain a broad differential when examining an infant with intracranial or other hemorrhage.

Ophthalmic Manifestations

Vitamin K deficiency is considered as a contributory etiology of birth-related retinal hemorrhages, although the precise incidence and characteristics of retinal hemorrhages in infants with vitamin K deficiency bleeding have not yet been elucidated in the literature [100, 108]. The first paper reporting early-VKDB-associated retinal hemorrhages described them as flame-shaped intraretinal and preretinal hemorrhages located primarily in the papillary region of the posterior pole, many of which may have been due to birth trauma, that resolved within 2 weeks, while preretinal hemorrhages took 2–3 months to resolve [108].

Several more contemporary studies and case reports describe bilateral retinal hemorrhages in infants with late-onset VKDB, although few provide a detailed ophthalmic exam. All reports describe retinal hemorrhages in exclusively breastfed infants only [105, 111, 119, 120].

In one case, an affected 10 week old infant had intraretinal flame and dot/blot hemorrhages too numerous to count, most of which were perivascular and concentrated between the nasal edge of the disc and the fovea [118]. Among reported ophthalmic outcomes in surviving infants are proptosis, cataract, and macular scar [118]. Further research is needed to give clinicians a clearer understanding of the incidence of VKDB-related retinal hemorrhages, their time course and outcomes.

Diagnosis

Vitamin K deficiency should be considered when hemorrhagic signs are present and even more strongly suspected when potential clinical conditions exist that could be associated with impaired intake, intestinal synthesis, or absorption of vitamin K. As the systemic manifestations of VKDB overlap with symptoms of other illnesses, such as coagulation factor deficiencies, disseminated intravascular coagulation (DIC), and abusive head trama (AHT), it is critical during initial management to order a panel of tests that will allow for rapid identification of the correct diagnosis. Initial evaluation should include prothrombin time (PT), activated partial thromboplastin time (aPTT), INR, and a complete blood count with differential [94]. Testing for the serum marker PIVKA-II (proteins induced by vitamin K's absence) is also helpful, as vitamin K deficiency leads to liver undercarboxylation of proteins which may be detected even before coagulation markers become abnormal [99].

Patients with VKDB have a grossly elevated PT, normal to elevated aPTT, and an abnormally high PIVKA-II with a normal platelet count, along with decreased levels of factor II, VII and X. Elevated PIVKA-II has not been reported in the absence of elevated PT [96, 107] By contrast, patients with DIC or sepsis would have an increased PT and aPTT with a dramatically decreased platelet count; patients with factor I, II, V, or X deficiency would have elevated PT with normal aPTT and platelets; patients with factor VIII, XI, or IX deficiency would have an elevated aPTT with normal PT and platelets; patients with SBS would have normal or elevated PT with normal aPTT and platelets [100, 121].

More precise characterization of the types of retinal hemorrhage seen in VKDB will assist clinicians in better differentiating between retinal hemorrhages due to VKDB and those due to non-accidental head trauma, various coagulopathies, birth trauma and other etiologies.

Management

A prophylactic 0.5–1 mg dose of intramuscular vitamin K at birth is now considered standard of care [92]. In infants who develop early, classic or late VKDB, a dose of 1 mg of intramuscular vitamin K has been demonstrated to reverse elongated PT/aPTT and restore normal coagulation [122]. Infants with medical conditions that impair the availability of vitamin K (e.g. cystic fibrosis) should receive the vitamin regularly as a dietary supplement [92].

Hypervitaminosis

Definition

Hypervitaminosis most often occurs with fat-soluble vitamins, which are stored in the body for a longer time than water-soluble vitamins. Generally, hypervitaminosis states result from excessive intake of vitamins from supplements rather than from dietary sources, as foods rarely contain toxic levels of vitamins. Adverse systemic and ocular effects have been reported with excessive amounts of vitamins A and D.

Systemic Manifestations

Hypervitaminosis A can occur in children with chronic daily intakes of vitamin A >20,000 IU. Clinical symptoms include headache, vomiting, anorexia, alopecia, dryness of mucous membranes, bone abnormalities, and bulging fontanelle in infants. Toxic effects have not been observed with excessive intake of carotenoid precursors, except for a yellow coloring of the skin which resolves when the intake is discontinued [56].

Hypervitaminosis D is characterized by symptoms of dehydration, hypotonia, anorexia, vomiting, hypertension, and renal failure, which commonly appear after 1–3 months of ingesting high doses of vitamin D. An excess of vitamin D also causes hypercalcemia, which can lead to metastatic calcification in various soft tissues.

Ophthalmic Manifestations

Hypervitaminosis A can cause pseudotumor cerebri, a condition characterized by diplopia, strabismus, and papilledema leading to eventual loss of vision. Toxic effects of vitamin D in the eye include clouding and calcification of the conjunctiva and cornea (band keratopathy).

Management

Symptoms of hypervitaminosis disappear rapidly when excessive intake is discontinued. Calcium intake must be decreased in patients with hypervitaminosis D, and corticosteroid therapy may be indicated for severely affected patients. Most people recover fully within a month. However, renal and cardiovascular damage resulting from excessive intake of vitamin D may be irreversible.

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Index

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