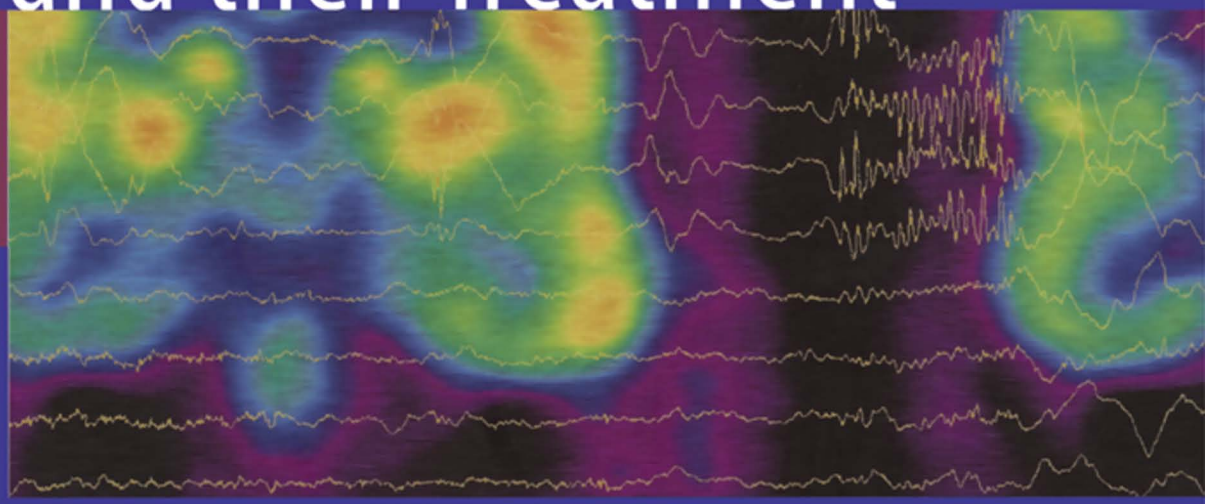
CP Panayiotopoulos

A Clinical Guide to

Epileptic Syndromes and their Treatment



Second Edition

Based on the ILAE classifications and practice parameter guidelines

Springer

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Epileptic Syndromes and their Treatment

Revised Second Edition

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British Library Cataloguing in Publication Data:
A catalogue record for this book is available from the British Library

ISBN: 978-1-84996-160-8

Springer Science+Business Media
springeronline.com

To my wife Thalia

because

she is a beautiful woman

my muse

the flower, the smile and the angel in my life

acknowledgements

I am grateful to the following eminent experts who have frequently provided me with valuable advice over the last 10 years during the preparation of my books on epilepsies:

Adachi, N.
Akanuma, N.
Benbadis, S.
Berg, A.
Berkovic, S.F.
Blumenfeld, H.
Boyd, S.G.
Caraballo, R.H.
Covanis, A.
Crawford, P.
Eeg-Olofsson, O.
Dravet, C.
Duncan, J.S.
Engel, J., Jr.
Fejerman, N.
Ferrie, C.D.
Galanopoulou, A.S.
Genton, P.
Grünewald, R.A.
Hirsch, E.
Jallon, P.
Kanazawa, O.
Kasteleijn-Nolst Trenite, D.G.A.
Koutroumanidis, M.
Kuzniecky, R.
Kwan, P.
Livingston, J.H.
Martinovic, Z.
Mole, S.
Morrow, J.I.
Moshe, S.L.
Nordli, D.R., Jr.
Oguni, H.
Ohtahara, S.
Patsalos, P.
Plouin, P.
Sander, J.W.A.S.
Scott, R.C.
Shorvon, S.D.
Sisodiya, S.M.
Stephenson, J.B.P.
Thomas, P.
Tomson, T.
Vajda, F.J.E.
Vigevano, F.
Walker, M.C.
Watanabe, K.
Whitehouse, W.
Wilkins, A.
Yoshinaga, H.
Zifkin, B.G.
Zuberi, S.M.

The continuing assistance of S. Sanders and S. Rowlinson, both expert EEG technologists, is, as always, greatly appreciated.

I would also like to thank Ian Stoneham, Publisher, and his team, particularly Hannah Cole and Nadine Lemmens, Editors, and Keith Baker, Designer; their professionalism, dedication and enthusiasm have made this a better book and enabled me to continue updating it to just a few weeks before publication in December 2009. They have been a pleasure for an author to work with.

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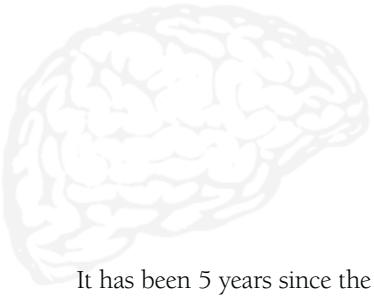

preface to the second edition

It has been 5 years since the first edition of this book was published. I have been encouraged to write a new edition by the success of the first, which sold over 10,000 copies and received excellent reviews. Even more rewarding than this has been the feedback from physicians who have been using the book in the environment for which it was written: the clinic. It is gratifying that patients and their families have also found it useful and recommend it in dedicated websites as a reliable source of information. A particularly reassuring aspect is that proposals made in the previous edition have been adopted by the ILAE Task Force in their latest report, published in 2006.

This second edition has been systematically updated to include the most recent advances in clinical epileptology. It has been written with the same principles and aims in mind as its predecessor and remains a relatively concise book, the main purpose of which is to promote proper diagnosis and appropriate management of epileptic seizures and syndromes. It is evidenced-based, achieved by integrating years of clinical experience with the best available external evidence from clinical research.

The opening chapters concentrate on the definitions and general aspects of epilepsies, describe epileptic seizures and status epilepticus, detail the imitators of epileptic seizures, provide advice on the optimal use of EEG and brain imaging in the diagnosis of epilepsies and offer insights into the principles of management. The subsequent chapters are devoted to the epileptic syndromes, which are organised according to age at onset and their main category in the ILAE classification. The presentation of each syndrome follows a common format: classification, demographic data, clinical manifestations, aetiology, diagnostic procedures, differential diagnosis, prognosis and management.

Following the advice and recommendations of reviewers and colleagues, I have included new chapters dedicated to the non-epileptic paroxysmal disorders that imitate epileptic seizures and the diseases frequently associated with epileptic seizures, in particular progressive myoclonic epilepsies. Some clinically useful sections from my previous, more specialist-orientated book, '*The Epilepsies: Seizures, Syndromes and Management*', have also been added and properly modified to suit the intended audience.

With regards to classification, particular emphasis has been given to the new ILAE report and I have provided further evidence-based proposals for consideration. The refreshing impact of Peter Wolf, President of the ILAE, Anne Berg, Chair of the ILAE Classification Committee, Phil Schwartzkroin and Simon Shorvon, Editors-in-Chief of *Epilepsia* is felt and appreciated.

The most difficult parts to prepare were the sections on anti-epileptic drugs. My recommendations are evidence-based, drawing on laborious and in-depth assessment of clinical trials, meta-analyses, formal guidelines and the best clinical evidence from eminent practising physicians. This approach has been verified because much of the advice offered in the previous edition has since been confirmed in subsequent controlled trials and in clinical practice. I am confident that my updated recommendations in this book will prove just as reliable and useful.

Realistically, I have to accept that there may be some unintentional errors and I regret any such instances. I would welcome these being brought to my attention along with any comments and suggestions for the improvement of future editions or reprints.

Finally, new practices are emerging that allow for the proper diagnosis and treatment of patients with epileptic seizures. As in all other areas of medicine, diagnostic precision is a prerequisite for meaningful management in the epilepsies, and I wish that this text will help advance and disseminate this knowledge.

C P Panayiotopoulos MD PhD FRCP

London, 28th June 2007

preface to the revised second edition

It is rewarding that the second edition of A Clinical Guide to Epileptic Syndromes and their Treatment published in 2007 appears to be fulfilling its purpose as a concise book promoting the accurate diagnosis and appropriate management of epilepsies. Like its predecessor, it has received excellent reviews and has been widely used and cited by readers, including seasoned and novice physicians, and other healthcare professionals, as well as patients and their families.

With the first print run now sold out, I felt that the time was ripe to revise rather than to reprint the second edition. This is mandated by the need to update with information on emerging therapies, important recent publications and new guidelines and ILAE proposals.

This book is mainly based on the ILAE classifications and practice parameter guidelines. A new ILAE report on classification and terminology that is currently under consultation is an important document for consideration and reflection as it contains the thoughts of the leading authorities in the epilepsies. Regarding practice parameters, the American Academy of Neurology and the American Epilepsy Society have published a three part evidence-based review focusing on pregnancy in women with epilepsy. These new proposals and guidelines are discussed extensively in this revision.

The sections concerning therapy have been expanded to include newly licensed AEDs, new indications for previously approved drugs and adverse reactions that have emerged since the first publication. Again, the recommendations made aim to be of practical use and to follow as truly as possible the principles of evidence-based medicine. New sections have been added on the principles of pharmacological management in women and the elderly, and on psychological, behavioural and cardiac adverse effects of AEDs. The recent ILAE position paper on therapeutic drug monitoring is also extensively covered.

This revision has also been updated to include significant advances, reports, reviews and debates; new citations up to a few weeks before publication have been added.

The goal of this book, as with all previous editions, is to encourage the accurate syndromic diagnosis of the epilepsies. To some extent this has now been achieved, as all current formal recommendations and guidelines make clear that a syndromic diagnosis is a prerequisite for appropriate management and good clinical practice. However, there are still uncertainties over the precise features and boundaries for each epileptic syndrome and a lack of terminological precision, which this revised edition addresses. Overall, this book remains a guide for practising physicians on how best to diagnose the epileptic syndromes and achieve optimal management.

C P Panayiotopoulos MD PhD FRCP

London, 2nd December 2009

abbreviations

AAN-AES	American Academy of Neurology–American Epilepsy Society
ACTH	adrenocorticotrophic hormone
ADCME	autosomal dominant cortical tremor, myoclonus and epilepsy
ADNFLE	autosomal dominant nocturnal frontal lobe epilepsy
ADR	adverse drug reaction
AED	anti-epileptic drug
AHS	anticonvulsant hypersensitivity syndrome
APEC	atypical benign partial epilepsy of childhood
BCECTS	benign childhood epilepsy with centrotemporal spike
BCSSS	benign childhood seizure susceptibility syndrome
BOLD	blood oxygen level dependent
CAE	childhood absence epilepsy
cAMP	cyclic adenosine monophosphate
CI	confidence interval
CNS	central nervous system
CONSERT	Consolidated Standards for Reporting of Trials
CRMP	collapsin response mediator protein
CSE	convulsive status epilepticus
CSF	cerebrospinal fluid
CSTB	cystatin B
CSWS	continuous spike-and-wave during sleep
CT	computed tomography
CTS	centrotemporal spike
CVS	cyclic vomiting syndrome
CYP	cytochrome P450
DMS	*Diagnostic and Statistical Manual of Mental Disorders*
DRPLA	dentatorubral-pallidoluysian atrophy
EBM	evidence-based medicine
ECG	electocardiogram
EEG	electroencephalogram
EFS+	epilepsy with febrile seizures plus
EGTCSA	epilepsy with GTCS on awakening
EM-AS	epilepsy with myoclonic–astatic seizure
eMC	electronic Medicines Compendium
EMEA	European Medicines Agency
EMG	electromyography
EPC	epilepsia partialis continua
ERG	electroretinogram
ESES	extreme somatosensory evoked spike
EURAP	European and International Registry of Antiepileptic Drugs in Pregnancy
EUROCAT	European Surveillance of Congenital Anomalies
FDA	US Food & Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FLAIR	fluid-attenuated inversion recovery
FLTLE	familial lateral temporal lobe epilepsy
fMRI	functional magnetic resonance imaging
FMTLE	familial mesial temporal lobe epilepsy
FMZ	[^{11}C]flumazenil
FOS	fixation-off sensitivity
FS+	febrile seizures plus
GABA	Gamma-aminobutyric acid
GABA-T	GABA-transaminase
GEFS+	generalised epilepsy with febrile seizures plus
GEPR	genetically epilepsy-prone rat
GnRH	gonadotrophin-releasing hormone
GPSWD	generalised polyspike–wave discharge
GSWD	generalised spike–wave discharges
GTCS	generalised tonic–clonic seizure
GTC-SE	generalised tonic–clonic status epilepticus
HLA	human leukocyte antigen
HR	hazard ratio
IBE	International Bureau of Epilepsy
ICOE-G	idiopathic childhood occipital epilepsy of Gastaut
IGE	idiopathic generalised epilepsy

IL	interleukin
ILAE	International League Against Epilepsy
IM	intramuscular
IPOE	idiopathic photosensitive occipital lobe epilepsy
IPS	intermittent photic stimulation
IQ	intelligence quotient
IV	intravenous
JAE	juvenile absence epilepsy
JME	juvenile myoclonic epilepsy
LGI	leucine-rich, glioma-inactivated
LKS	Landau–Kleffner syndrome
LTLE	lateral temporal lobe epilepsy MAE epilepsy with myoclonic absences
MCM	major congenital malformation
MDVU	Movement Disorders Virtual University
MEG	magnetoencephalography
MEI	myoclonic epilepsy in infancy
MELAS	mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
MERRF	myoclonus epilepsy with ragged-red fibers
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MSA	multiple source analysis
MSI	magnetic source imaging
MSLT	multiple sleep latency test
mtDNA	mitochondrial DNA
MTLE	mesial temporal lobe epilepsy
MTLE-HS	mesial temporal lobe epilepsy with hippocampal sclerosis
nAChR	neuronal nicotinic acetylcholine receptor
NCL	neuronal ceroid lipofuscinosis
NEPE	non-epileptic paroxysmal event
NMDA	*N*-methyl D-aspartate
NREM	non-rapid eye movement
OPS	occipital seizures precipitated by photic stimuli
PAS	periodic acid–Schiff
PCR	polymerase chain reaction
PEHO	progressive encephalopathy with edema, hypsarrhythmia and optic atrophy
PET	positron emission tomography
PGTCS	primarily generalised tonic–clonic seizure
PI	package insert
PIL	patient information leaflet
PLED	pseudoperiodic lateralised epileptiform discharge
PMA	perioral myoclonia with absences
PME	progressive myoclonic epilepsy
PNEPE	psychogenic non-epileptic paroxysmal event
PPR	photoparoxysmal response
PPT	palmitoyl-protein thioesterase
PS	Panayiotopoulos syndrome
RBD	REM sleep behaviour disorder
RCT	randomised controlled trial
REM	rapid eye movement
SE	status epilepticus
SGTCS	secondarily generalised tonic–clonic seizure
SMA	supplementary motor area
SmPC	Summary of Product Characteristics
SMR	standardised mortality ratio
SPECT	single photon emission computed tomography
SSEP	somatosensory evoked potential
SUDEP	sudden unexpected death in epilepsy
SV2A	synaptic vesicle protein 2A
SWI	spike–wave index
TAS	typical absence seizures
TDM	therapeutic drug monitoring
TLE	temporal lobe epilepsy
TPP	tripeptidyl-peptidase
UGT	uridine diphosphate glucuronosyltransferase
VDU	visual display unit
VEP	visual evoked potential
VER	visual evoked response
VGSC	voltage gated sodium channel
VNS	vagus nerve stimulation
WEMOVE	Worldwide Education and Awareness for Movement Disorders
WHO	World Health Organisation

one

General aspects of epilepsies

Epileptic seizures and epileptic syndromes have high prevalence and incidence rates affecting all ages and all races of both sexes. They constitute an important part of the everyday clinical practice of general and specialist health care professionals.

Patients with epileptic seizures and their families are entitled to diagnosis, prognosis and management that are specific and precise.

Medical diagnosis is the identification of a disease by investigation of its symptoms and history, which provides a solid basis for the treatment and prognosis of the individual patient.

Accurate diagnosis is the golden rule in medicine and epilepsies should not be an exception to this. Current practice that limits the diagnosis to 'epilepsy' or 'seizures' is unsatisfactory to the patient and physician alike, and may result in avoidable morbidity and mortality. Such a non-specific diagnostic label fails to provide guidance on important items such as severity of disease, prognosis, short- and long-term therapeutic decisions, and genetics (research and counselling), which are all factors that crucially affect personal, family and social life, education and career choices of patients.

'Epilepsy' is not a single disease entity. Epilepsies are many syndromes and diseases that have a multitude of different manifestations and causes. Epileptic syndromes and diseases are now largely well defined and easy to diagnose. Defining the type of epilepsy should be considered mandatory because it offers the best guide to both management and prognosis. The short- and long-term management of epilepsies is syndrome related and differs markedly between the various syndromes, thereby emphasising the need for accurate diagnosis. The benefits of syndromic diagnosis over seizure/symptom diagnosis, or an inclusive diagnosis such as 'epilepsy', far outweigh any morbidity from miscategorisation that may arise in difficult cases.

Unspecified diagnosis in epilepsies commonly results in avoidable morbidity and sometimes mortality.

Important reminder

Traditional medical teaching and attitudes to the diagnosis and management of epilepsies often differ from those applied in other medical conditions. This should be corrected.

Physicians who rightly seek bedside confirmation of muscle fatigability in a patient with a clear-cut history of myasthenia gravis, should also request to view the seizures, which if frequent can be easily captured even by mobile phones.

Physicians who rightly emphasise the differential diagnosis between spinal muscular atrophies and limb girdle muscular dystrophy should give the same emphasis to the differentiation between absence seizures of idiopathic generalised epilepsies and complex focal seizures.

Major paediatric journals that often emphasise a rare disease should at least give the same space to highlighting the fact that childhood autonomic status epilepticus is a common and costly cause of misdiagnosis and mismanagement, adversely affecting thousands of children around the world (see page 81).

What is epilepsy? Definitions

The definition of epilepsies should be simple, brief, precise and unambiguous. However, this is not the case and there is no consensus.

The newly proposed ILAE definition is:

> Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition.[1]

This definition of epilepsy 'requires the occurrence of at least one epileptic seizure' with the pre-condition that this is 'in association with an enduring disturbance of the brain capable of giving rise to other seizures'.[1] It would not require 'at least two seizures' or that the seizure be 'unprovoked', which were prerequisites of previous definitions of epilepsy.

> The central concept in [this] definition is an enduring alteration in the brain that increases the likelihood of future seizures… A single epileptic seizure due to an enduring epileptogenic abnormality that increases the likelihood of future seizures would indicate epilepsy, and a single epileptic seizure in a normal brain would not.[1]

This definition also proposes that part of the epileptic condition can involve behavioural disturbances, psychological consequences for the patient and for the family, and social stigma, exclusion, restrictions, overprotection and isolation.

Comment on the new ILAE definition

This proposal has been rightly criticised by eminent epileptologists[2] with whom I share the following concerns.

First: What is 'enduring' and how long does this last? This word 'enduring' has created the same questions and problems when used in the definition of status epilepticus. Enduring (adj.) = lasting, continuing, durable, unceasing, abiding, imperishable; permanent, continuing or enduring without marked change in status or condition or place.

Second: Most patients do not have at least one of the preconditions 'cognitive, psychological and social consequences' attached to epilepsy.

Third: Why is the singular 'epilepsy' preferred to the plural 'epilepsies'? This contradicts the facts and I quote from the same report 'Epilepsy is not one condition, but is a diverse family of disorders, having in common an abnormally increased predisposition to seizures… Some writers prefer the plural term, "the epilepsies," but we will use the singular phrase while recognizing this diversity'.[1]

Certainly, there must be a better definition of what epilepsies are. The following would be my proposal:

> Epilepsies are disorders of the brain with a clinically manifested liability to epileptic seizures.

Other formal definitions of epilepsy

Epileptic disorder: A chronic neurological condition characterised by recurrent epileptic seizures.[3]

Epilepsies: Those conditions involving chronic recurrent epileptic seizures that can be considered to be epileptic disorders.[3]

Epilepsy: A condition characterised by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause (operational definition for epidemiological purposes).[4,5] Multiple seizures occurring in a 24-h period are considered as a single event. An episode of status epilepticus is considered to be a single event. People who have had only febrile seizures or only neonatal seizures, as herein defined, are excluded from this category.[4,5] *Author's note:* in this definition the type of 'epileptic seizures' is not defined, but this probably refers to generalised tonic–clonic seizures (GTCSs).

'Active' epilepsy: A prevalent case of active epilepsy is defined as a person with epilepsy who has had at

least one epileptic seizure in the previous 5 years, regardless of anti-epileptic drug (AED) treatment. A case under treatment is someone with the correct diagnosis of epilepsy receiving (or having received) AEDs on prevalence day.[4,5]

Epilepsy in remission with treatment: A prevalent case of epilepsy with no seizures for ⩾5 years and receiving AED treatment at the time of ascertainment.[4,5]

Epilepsy in remission without treatment: A prevalent case of epilepsy with no seizures for ⩾5 years and not receiving AED treatment at the time of ascertainment.[4,5]

Making the correct diagnosis in epilepsies

The assessment of a patient referred for epileptic seizures should follow the same approach as any other disorder:

- medical history
- physical examination (and developmental assessment in children)
- presumptive diagnosis
- differential diagnosis
- comprehensive investigative procedures
- final diagnosis (which could be definite, probable, possible or undiagnosed)
- management (including that of the family).

Medical history

The diagnosis of epileptic or non-epileptic seizures is almost always based solely on the clinical history, which should be obtained in an expert way, often requiring lengthy interrogation(s) of the patient and witnesses. Children also (if verbal) have a surprising insight into their illnesses. In certain cultures children are often left outside the consultation process by overprotective parents, and this should be approached with sensitivity.

Inadequate history is the most common reason for misdiagnosis.

In taking the medical history, every piece of information should be patiently gathered in order to synthesise the whole pattern of these transient events from the time that they started to their end, and up to normality. The medical history should include:

- details of the paroxysmal events (not only the most dramatic ones) as they have been experienced by the patient and witnesses
- the circumstances under which the paroxysmal events occurred
- timing and circadian distribution
- position (standing, sitting or lying)
- leisure or occupation (at rest or during exercise)
- possible triggering, precipitating or facilitating factors
- personal and family medical history.

Circadian distribution (on awakening, nocturnal and diurnal) and precipitating factors (flickering lights, sleep deprivation, alcohol indulgence, stress and reading) often provide invaluable clues for the correct diagnosis and may also prompt the appropriate EEG procedure.

Useful clinical note

The presence or absence of a single symptom is not sufficiently diagnostic of a particular disease and may be misleading.

The clinical diagnosis is often easy and secured only if individual elements of clinical events are meaningfully synthesised with regard to quantity, quality, location, onset, chronological sequence, development, speed of progress and duration.

Lengthy medical interviews may seem to be 'luxury' medicine, but this is by far outweighed by the benefits to patients, their families and their physicians. Constraints on the physicians' time should not be an excuse for allowing misdiagnosis and mismanagement to occur. With experience the time taken for an appropriate medical history is significantly shortened. Personally, I devote more time to eliciting the events preceding a GTCS than detailing what happened during the convulsive phase (if I am satisfied that this was a genuine GTCS), and directing the witnesses to portray what they saw rather than allocating time to endless descriptions of how they felt and what they did (although I fully respect this).

A second interview frequently provides more observations and recollections after learning what is desired during the initial consultation.

Useful recommended practice

Asking the patient/guardian to complete a purposely designed questionnaire, which should be made available prior to consultation, has many advantages:

- it provides the patient/guardian with an understanding of the type of information needed and allows them time to collect such information
- written information is often more reliable than verbal communication during a time-limited and often emotionally loaded interview
- it provides the physician with a good insight of the case prior to the consultation.

'That's it!' phenomenon[6]

It is often necessary for the physician to imitate and demonstrate physically or, when in doubt, show video-taped examples of different epileptic or non-epileptic seizures to patients and witnesses. 'That's it' is their common reaction for the presentation that closely resembles the events under investigation.

Home-made video recordings

Sometimes the diagnosis is easy, based on clinical history alone. Home-made video recording should be routinely requested if diagnosis is uncertain. Videotaping the clinical events is the only practical means of demonstrating and objectively documenting the symptoms of paroxysmal disorders. Genuine epileptic seizures or non-epileptic paroxysmal events (NEPEs) are often frequent and sometimes predictable. They can be recorded by relatives or friends and sometimes by the patients themselves. Today this is easier with the availability of digital recording and mobile phones.

Laboratory diagnostic procedures

Laboratory procedures (blood and urine tests, ECG, EEG, brain imaging and others such as metabolic or toxicology screening, CSF analysis, molecular genetic testing) should be appropriately prioritised and tailored to the particular clinical problem and individual patient. The aim is to obtain supplementary evidence of the clinical suspicion, which may provide definite diagnosis of a specific disorder. Investigative procedures are more demanding in children than in adults, or in those in whom seizures are the presenting symptom of a disease than in those where the underlying disease has already been established.

The EEG, the most significant investigative procedure in the diagnosis of epilepsies, is often misunderstood, undermined and misused. Brain imaging, another top diagnostic procedure, provides *in vivo* visualisation of structural causes of epilepsy such as hippocampal sclerosis, malformations of brain development and tumours, as well as other brain diseases.

Blood, urine and sometimes CSF studies have an important role in the evaluation of the child with epilepsy.[7]

Genetic testing has become available for a growing number of hereditary disorders associated with epileptic seizures (see Chapters 14 and 17).

The significance and the role of the EEG and brain imaging in the diagnosis and management of epilepsies is outlined in Chapter 6. Other laboratory procedures are discussed when appropriate in the relevant chapters.

Differential diagnosis

Misdiagnosis in epilepsies, when considering their dimensions and consequences, is a colossal and costly medical problem. Common disorders and even normal phenomena may imitate epileptic seizures and, conversely, certain types of epileptic seizures may imitate symptoms of other diseases. Misdiagnosis has serious repercussions. Patients with non-epileptic disorders incorrectly diagnosed as having epileptic seizures are likely to be mistreated with AEDs and also denied specific and possibly life-saving treatment (Figure 1.1). Similarly, patients with epileptic seizures erroneously diagnosed as migraine, encephalitis or other NEPEs are likely to be mismanaged with inappropriate treatments and also deprived of specific therapies (Figure 1.2).

It should also be emphasised that serious and adverse consequences to patient management often arise from misdiagnosing one type of epileptic seizure for another, or one type of epileptic syndrome for another.

There are three important steps to take in order to make a correct specific diagnosis, which will determine prognosis and management:

1. *First step:* are the paroxysmal events epileptic seizures?
2. *Second step:* what type of epileptic seizures?
3. *Third step:* what is their cause and what is the epileptic syndrome or disease?

First step: Are the paroxysmal events epileptic seizures?

The first step towards the correct diagnosis of epilepsies is to establish whether a paroxysmal clinical event was actually an epileptic seizure or a non-epileptic paroxysmal event (NEPE). The differential diagnosis includes all causes of episodic impairment of awareness, aberrations of mental function, falls, sensory/motor phenomena and generalised convulsive movements, which are common presenting symptoms of epileptic seizures. This is often easy for physicians adequately trained in the recognition of the various forms of epileptic seizures, who are able to obtain a clear history of the events from the patient and witnesses. However, even the most experienced epileptologists repeatedly have great difficulties in reaching an unequivocal diagnosis for reasons such as atypical seizure presentations, inadequate historical data or overlapping symptom manifestations.

The differentiation between seizures and other causes of transient neurological disturbance and collapse is epitomised by the familiar theme 'fits, faints and funny turns'.[6,8] Distinguishing epileptic (*fits*) from paroxysmal symptoms of non-epileptic disorders, particularly syncopal (*faints*) or psychogenic attacks (*funny turns*), should be a core skill of all trained physicians as detailed in any medical textbook. However, this is often simplistic and frequently perpetuates certain myths such as that urinary incontinence or postsyncopal confusion are rare in syncopes (Figure 1.1) or tongue biting and injuries are exceptional features in psychogenic non-epileptic seizures, as further detailed in Chapter 4.

NEPEs that have been misdiagnosed as epileptic seizures affect as many as 20–30% of patients diagnosed with epilepsy; these patients have often received treatment for epilepsy for many years or have been admitted to tertiary care epilepsy units.[9–11] The problem is complicated by the fact that approximately 30% of patients with genuine epileptic seizures also suffer from non-epileptic, mainly psychogenic seizures. In one study, the mean time lapse between the first attack and the correct diagnosis of non-epileptic seizures was over 9 years.[12] In financial terms the annual cost of such a misdiagnosis was estimated at US$4 billion.[13]

NEPEs[14–16] are common and are numerous episodic clinical manifestations of diverse aetiologies that mimic or look like, but are not, epileptic seizures. These imitators of epileptic seizures are detailed in Chapter 4.

Epileptic seizures imitating non-epileptic attacks

Epileptic seizures may imitate syncope, psychogenic attacks, migraine, sleep disorders or sinister acute brain insults. Their diagnosis is also demanding, as documented by the fact that, until recently:

Man aged 34 with video-EEG/ECG-documented potentially life-threatening cardiogenic syncopes imitating epileptic convulsive seizures

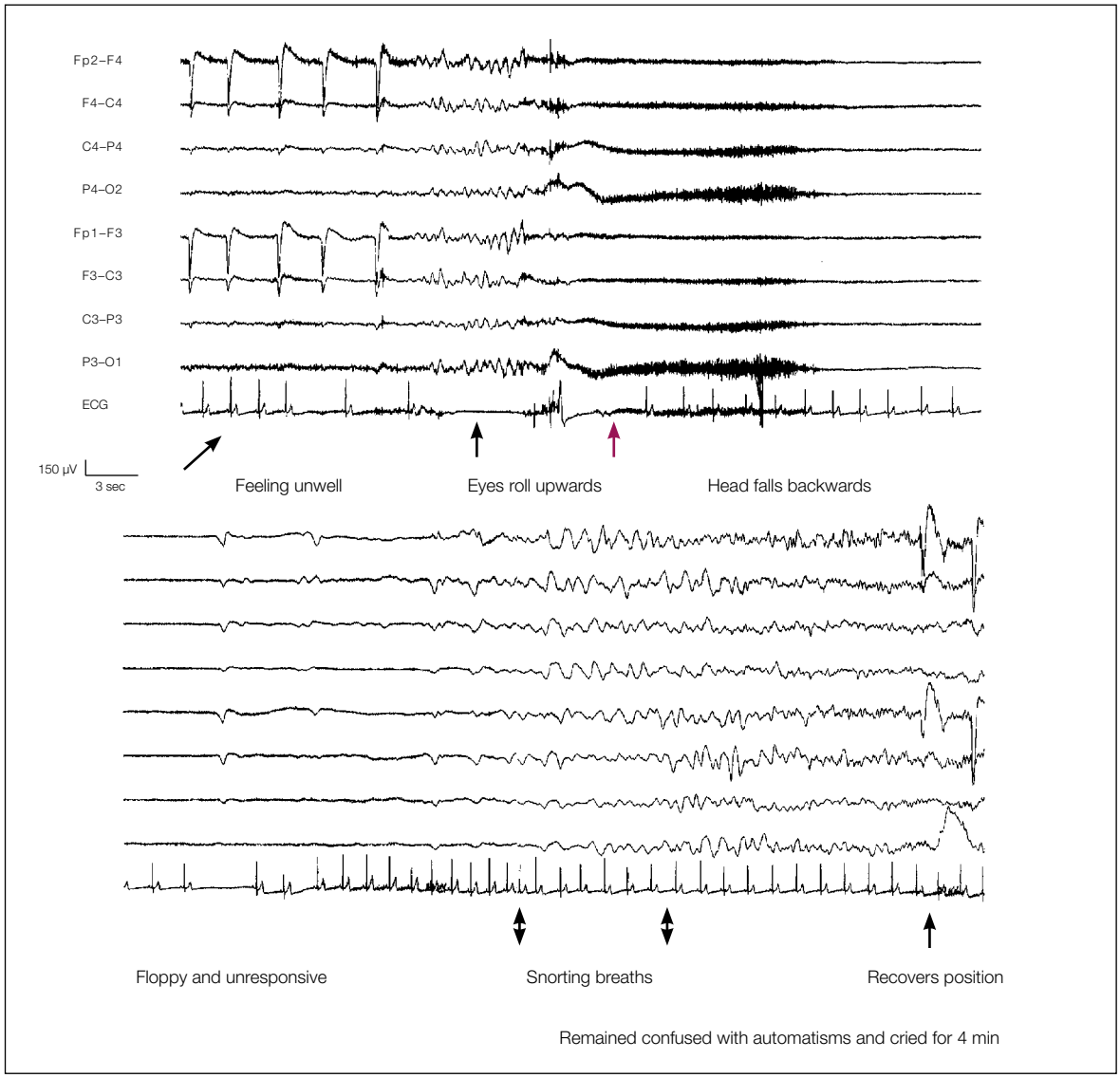

Figure 1.1 A 34-year-old man was referred for routine EEG because of 'two episodes of GTCSs in the last 2 months. The first occurred on his way home after work. He does not recall events until waking in the ambulance with the paramedics telling him that he had a seizure. He had no memory of the preceding 20 minutes. He did bite his tongue but there was no incontinence… This is likely to be generalised epilepsy… Treatment with valproate was initiated'. In accordance with our policy this was a video-EEG (page 155). A few minutes after the start of the recording he developed sinus bradycardia and then ventricular standstill for 9 s with one escape ectopic beat as documented with ECG (bottom trace). Clinically, at the oblique arrow the technician asked him if he felt okay and he said no. At the first vertical black arrow his eyes rolled slowly upwards to the extreme. At the red arrow, his head dropped backwards and he became flaccid and unresponsive. Some recovery started at the double-headed arrows when he took two snorting breaths. At the second black arrow, he resumed his position as before the syncope. Afterwards he was confused, he could not answer questions and, when asked again what happened to him, he was distressed and cried. He did not come back to normal until after more than 4 min from the start of the syncope. A cardiac pacemaker has been implanted and the patient remained well in the next 6 months of follow-up.

Cardiac asystole as an ictal symptom of right-sided temporal lobe seizures

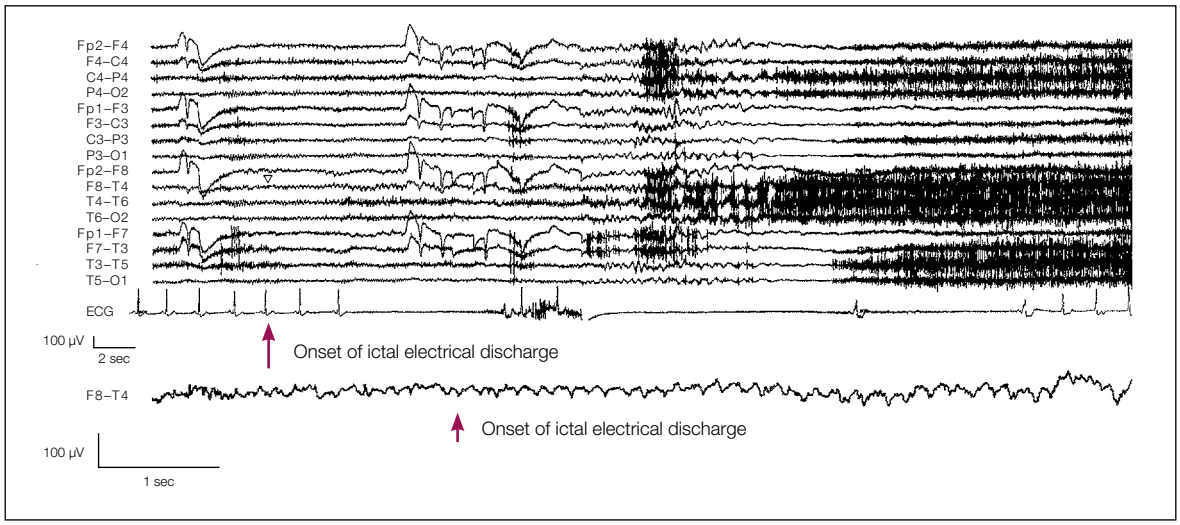

Figure 1.2 One day prior to this video-EEG a 60-year-old man said he felt unwell, went for a walk, but half an hour later became confused with repetitive questioning about his orientation and when the next meeting was to take place. On examination he was globally amnesic with a period of retrograde amnesia for about 1 month, which gradually shortened as he recovered after about 2 to 3 hours. His past medical history at that stage was thought to be unremarkable. He was known to have high cholesterol. There was a strong family history of early ischaemic heart disease. Physical and thorough neurological and cardiological examinations were normal. All relevant blood tests, ECG and brain MRI were normal. It was the video-EEG that established the diagnosis. He had three focal epileptic seizures with onset from the right temporal areas. The most severe one started with a rising epigastric sensation, which he retrospectively recalled as the same feeling that he had experienced the previous day. This led to almost immediate complete cardiac asystole for 26 s. During this seizure he became pale, lost consciousness and had a number of myoclonic jerks. He recovered without immediate need for cardiac resuscitation. The patient was treated with an appropriate AED and permanent cardiac pacemaker. He is well at follow up 6 months later. *Figure courtesy of Dr Michael Koutroumanidis, Department of Clinical Neurophysiology and Epilepsies, St. Thomas' Hospital, UK. Patient history courtesy of Dr Paul Holmes, Department of Neurology, St. Thomas' Hospital, London, UK.*

- frontal seizures from the supplementary sensorimotor area were considered to be sleep disorders (see page 459)
- ictus emeticus and autonomic status epilepticus, common in children, were dismissed as non-epileptic events or misdiagnosed as migraine or encephalitis (see page 355)
- visual seizures were confused with basilar migraine or migraine with visual aura (see page 125).

Simple focal seizures of epigastric aura and 'panic attacks' are unlikely to raise suspicion of epilepsy either by the patient or by the general physician (see Figures 1.2 and page 15.4). These patients are often investigated for gastroenterological and psychological disorders or hypoglycaemia, until more salient seizure features appear with the development of complex focal seizures and secondarily GTCSs (see page 451).

Second step: What type of epileptic seizures?

Having established that a paroxysmal event is genuinely epileptic, the next, but not the final, step is to define the type of seizure(s).

There are numerous types of epileptic seizures, as detailed in Chapter 2. Their features may be minor or dramatic, brief or long, frequent or sparse, or singular. Clinical manifestations of seizures range from the dramatic events of a GTCS to the mild myoclonic flickering of the eyelids or a focal numb-

ness of the thumb and mouth. The same patient may suffer from different types of minor and major seizures, independently or evolving from one to the other. Even if frequent, minor seizures are unlikely to raise concerns and promote a medical consultation. Conversely, a major seizure such as a GTCS invariably draws medical attention.

Minor seizures are more important than major ones for diagnostic procedures, correct diagnosis and appropriate management strategies.[17]

A single GTCS does not require medication, but if the patient also has other, even minor, seizures, treatment is usually mandatory (Figure 1.3). Similarly, it may be unwise to advise the withdrawal of medication for a patient with minor seizures even if free of convulsive seizures for many years.

Minor seizures should be thoroughly sought during the clinical evaluation (Figure 1.3). Patients are unlikely to report minor seizures because they do not appreciate that these are epileptic events or their significance. Minor seizures may go unnoticed for many years or be ignored as normal variations in a person's life. It is the physician's responsibility to detect and evaluate them. Patients may often suffer many minor seizures long before the reported 'first seizure' or long after what is considered to be their 'last seizure'.[17]

Useful reminder

Approximately three-quarters (74%) of patients with 'newly identified unprovoked seizures' (mainly GTCSs) had experienced multiple seizure episodes before their first medical contact.[18] Yet, studies on the prognosis and treatment of the 'first seizure' mainly refer to a GTCS, although this may not be the first seizure in the patient's life.

Third step: What is their cause and what is the epileptic syndrome or disease?

Having established that a paroxysmal event is epileptic, the next step is to establish an aetiological and syndromic diagnosis. The diagnosis by the non-specialist is often limited to excluding structural abnormalities of the brain or predisposing medical disease. However, simply diagnosing 'epilepsy' or 'seizures' is insufficient. Aetiology and syndromic diagnosis of epilepsies provides a firm foundation for short- and long-term therapeutic decisions and enables natural history, inheritance, treatment efficacy and prognosis of epilepsies to be studied scientifically. Chapter 5 discusses the classification of the epileptic syndromes.[19]

Imprecise syndromic diagnosis commonly results in avoidable morbidity and sometimes mortility.[20]

Important features of a syndrome include:

- the type of seizures, their localisation and frequency
- the chronological sequence of the events
- circadian distribution
- precipitating factors
- age at onset
- mode of inheritance
- physical and mental symptoms and signs
- response to treatment
- prognosis.

Although some symptoms predominate and may indicate the underlying disease, no single symptom or sign can be considered entirely pathognomonic. The process of differential diagnosis requires close scrutiny of the clinical data before a list of possible diagnoses can be drawn up and the final diagnosis reached. It should be realised that some epilepsies are easy to diagnose and some more difficult, but this is not unusual in medicine. Molecular genetics is already providing decisive discoveries in the identification of epilepsies (see Chapters 14 and 17).

A syndromic diagnosis of epilepsies is now a basic recommendation of good clinical practice.[10]

The delay in the general acceptance of this concept has led to significant time and resources being lost and patient safety being jeopardised. Just for the few readers who may still doubt the significance of the syndromic diagnosis of epilepsies, I refer again to the arguments utilised and emphasised on many occasions in the near past,[20–22] and to previous editions of this book.

Video-EEG of a 16-year-old girl referred because of a 'first generalised tonic–clonic seizure'

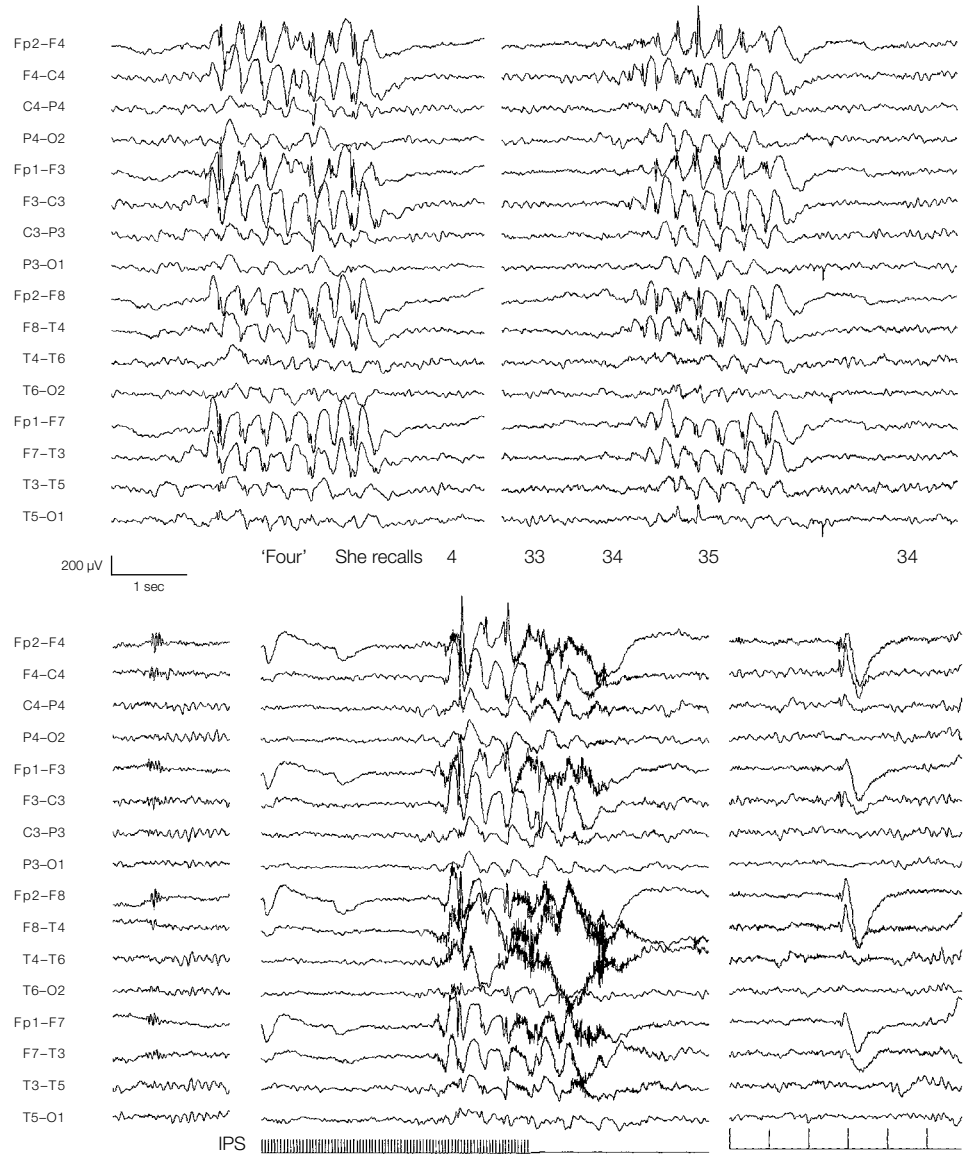

Figure 1.3 This girl had her first GTCS in the morning on her way to school for examinations. She suddenly became vague and nearly simultaneously fell on the ground with generalised convulsions. On questioning by the EEG technologist, it was revealed that 1 year before the GTCS she had mild jerks of the fingers in the morning interpreted as clumsiness. The EEG had generalised discharges of 3–4 Hz spike/multispike and slow wave. The girl recalled the number shouted to her during the discharge. However, breath counting during hyperventilation was disturbed during a similar discharge (annotated numbers). In addition, there were photoparoxysmal discharges. Brief frontal asymmetrical bursts of polyspikes or spike and slow wave could be erroneously interpreted as 'frontal lobe epilepsy with secondary bilateral synchrony'. On clinical and EEG grounds the diagnosis of JME was established and appropriate treatment was initiated because she had many more seizures (myoclonic jerks) prior and in addition to the single GTCS.

The results to be expected from the syndromic diagnosis of epilepsies can be compared to the advances that have accrued from the widespread acceptance of syndromic diagnosis of other medical disorders such as neuromuscular diseases.[20] If diagnosed on a few symptoms alone, distinction would be impossible even among the broad categories of muscular dystrophies, inflammatory myopathies and motor neurone diseases, which all manifest with muscle weakness and muscle atrophy. Similarly, in epilepsies, if diagnosed on a few symptoms alone, distinction would often be impossible even among the broad categories of focal and generalised, idiopathic and symptomatic epilepsies that all manifest with seizures.[20] Despite the occasional occurrence of 'overlap syndromes', syndromic classification allows the scientific analysis of the underlying disease processes and their specific clinicopathological features and genetics, and provides a framework for clinical trials aimed at optimising treatment.[23]

Some parts of the current ILAE classification[19,24] remain contentious and some syndromes are ill or broadly defined and require further clarification.[20–22] There are patients whose clinical and EEG features do not appear to fit neatly into any recognised category or erroneously appear to evolve from one syndrome to another. Some may represent new or 'overlap' syndromes, others may be unusual or atypical forms of known syndromes or cases where clinical history is misleading. However, many syndromes are common, well characterised and easily diagnosed.[20] An epilepsy syndrome can be diagnosed in most, even first-seizure, patients.[25] In one study, a generalised or focal epilepsy syndrome was clinically diagnosed in about half (47%) the patients. The addition of EEG data enabled a diagnosis for about three-quarters (77%) of the patients.[25]

Parents and patients often use the wide information provided on the internet to formulate their own opinion about diagnosis and management. They are entitled and should be encouraged to do so, in order to develop their awareness as part of their partnership with their healthcare professionals. Ultimately, they are the decision-makers.

Epilepsy or epilepsies?

The danger from a unified diagnosis of 'epilepsy' or a symptom diagnosis of 'seizures' is exemplified by common epileptic syndromes such as benign childhood focal seizures, juvenile myoclonic epilepsy (JME) and hippocampal epilepsy, which comprise more than a third of all epilepsies. They are entirely different in presentation, causes, investigative procedures, short- and long-term treatment strategies, and prognosis.

Benign childhood focal seizures are specific for children, manifest with focal seizures that may be solitary, remit within a few years of onset and may or may not require a short course of AED treatment, usually with carbamezapine.

JME is a lifelong idiopathic generalised epilepsy (IGE) syndrome that mainly manifests with myoclonic jerks and primarily GTCSs on awakening. Management of JME differs from standard medical practice for 'the treatment of epilepsy' in several important respects. Recommendations not to treat after the first seizure are usually inappropriate, many AEDs such as carbamazepine and phenytoin worsen JME, and withdrawal of appropriate AEDs after 2–3 years of being seizure free is inappropriate because relapses are inevitable.

Hippocampal epilepsy is a focal epileptic disorder of defined pathology that can be documented *in vivo* with high-resolution MRI in almost all patients. AED treatment may be ineffective, whereas neurosurgical treatment offers excellent and sustained benefit.

Even the most sceptical physicians, among those who doubt the clinical or practical significance of the syndromic diagnosis of epilepsies, have to accept that benign childhood focal epilepsies, JME and hippocampal epilepsy have nothing in common other than the fact that they may all be complicated by GTCSs, which are primarily GTCSs in JME and secondarily GTCSs in benign childhood focal epilepsies and hippocampal epilepsy. Furthermore, the short- and long-term treatment strategies are entirely different for each disorder: benign childhood focal seizures may or may not require medication for a few years, appropriate AED treatment is lifelong in JME, and neuro-

surgery may be life saving for patients with hippocampal type epilepsy. What is an effective drug for one type (carbamazepine for focal seizures) may be contra-indicated for another type of epilepsy (carbamazepine monotherapy in JME).

It should not be difficult to distinguish an intelligent child with benign focal seizures or childhood absence epilepsy from a child with Kozhevnikov–Rasmussen, Lennox–Gastaut, Down or Sturge–Weber syndrome, or a child with severe post-traumatic cerebral damage, brain anoxia or progressive myoclonic epilepsy of Unverricht or Lafora disease. Diagnosis of all these children as simply having epilepsy just because they have seizures offers no more benefit than a diagnosis of a febrile illness irrespective of cause, which may be a mild viral illness, bacterial meningitis or malignancy. Describing all these children as simply having epilepsy just because they have seizures is medically as unacceptable as a diagnosis of muscle atrophy, irrespective of whether it is localised or generalised, post-traumatic or genetically determined, static, reversible or progressive, or whether the underlying cause is in the muscle, nerve or spinal cord, and is treatable or untreatable.

The treatment of epilepsies will change, but their correct diagnosis will always be the golden rule. We should discourage RCTs that lump all patients with any type of seizures as a 'universe of epilepsy' or recommendations such as 'start with valproate and if this does not work change it to carbamazepine' or 'an EEG is not needed after the first seizure because treatment is after the second seizure' (not even specifying the type of seizure and the need to enquire specifically about minor fits).

Significant progress is expected if emphasis is directed at 'how to diagnose the epilepsies' rather than the current theme of 'how to treat epilepsy'.

Inappropriate generalisations in terminology, diagnosis and treatment is the single most important factor in the mismanagement in epilepsies.

The ILAE classification of epileptic seizures and epileptic syndromes

Outstanding achievements in the scientific and social aspects of epilepsies in the last 100 years should be largely attributed to the leaders and committee members of the ILAE. Two publications this year marked the 100th anniversary of the ILAE and Epilepsia, its official journal. Both publications are masterfully written by eminent epileptologists and ILAE protagonists. They are essential reading because they are part of the history of every one of us involved in the diagnosis and management of epilepsies.

The book *International League Against Epilepsy 1909–2009: A Centenary History*[26] is a painstaking and comprehensive history of the ILAE, including numerous illustrations of our past and present mentors. The March 2009 edition of Epilepsia, titled *History of epilepsy 1909–2009*, provides an excellent outline of 10 different aspects of epilepsy during this period, including the clinical concept of epilepsy, EEG, brain imaging, drug treatment and surgery.[27]

The ILAE standardised classification and terminology for epileptic seizures and syndromes provides a fundamental framework for organising and differentiating the epilepsies. This categorisation is essential in clinical practice, randomised controlled trials (RCTs) of AEDs and other therapies, epidemiology and research into these disorders. The efforts of the ILAE to devise classifications of the epilepsies has greatly improved communication among epileptologists and influenced both basic and clinical research.

The Classification of Epileptic Seizures (1981)[28] and Classification of Epilepsies and Epileptic Syndromes (1989)[19] are still the current valid formal ILAE classifications.

These classifications were made through lengthy and thorough assessments of the clinical, EEG, imaging, neurosurgical, neuropathological and other data then available. The Commissions explained their procedures and their reasoning behind their decisions at length. Further, they provided a brief definition of each epileptic seizure[28] and epileptic syndrome.[19] A dictionary of epilepsies had been published earlier in 1973.[29]

Subsequent advances in the clinical-EEG manifestations of epileptic seizures and syndromes, videoEEG information, functional and structural imaging, investigative procedures and genetics mandated a thorough and realistic revision of these classifications. Since 1997, members of the ILAE Task Force and the Commission on Classification and Terminology have invested tremendous work and time to incorporate these advances and introduce scientific principles and standards into the classification of the epilepsies – a challenging and difficult task. The subsequent recommendations and reports[24,30,31] given below are not a replacement for the 1981 Classification of Epileptic Seizures[28] and the 1989 Classification of Epilepsies.[19]

Recommended sources of ILAE information and classification

A recommended source of information is the ILAE website (www.ilae-epilepsy.org). The ILAE glossary and most epileptic seizures and epileptic syndromes can be found at www.ilae-epilepsy.org/Visitors/Centre/ctf/index.cfm. The newest report of the ILAE Commission on Classification and Terminology is posted at http://www.ilae-epilepsy.org/Visitors/Centre/ctf/ctfoverview.cfm and the ILAE member comments on this are available at http://www.ilae-epilepsy.org/Visitors/Centre/ctf/ctfcomments.cfm. The currently valid reports of the Classification of Epileptic Seizures (1981)[28] Epileptic Syndromes (1989)[19] are available free of charge on the Epilepsia website.

The ILAE Task Force on Classification and Terminology (Chair: Jerome Engel, Jr. 1997–2005) produced a report in 2001 as A Proposed Diagnostic

Proposed ILAE Task Force diagnostic scheme for people with epileptic seizures and with epilepsy[24]

Axis 1 involves a detailed description of ictal phenomenology using the glossary of descriptive ictal terminology. This can be extremely valuable for older patients with focal epilepsy who are being evaluated for surgical resection, but is not likely to be necessary in infants and young children, so it is optional

Axis 2 is the diagnosis of specific seizure type(s) that are detailed in Chapter 2

Axis 3 is the diagnosis of a specific syndrome as detailed in Chapter 5 and all other relevant chapters in this book. About half of these syndromes occur in infancy and early childhood, most of which are noncontroversial

Axis 4 is an aetiological diagnosis of 'diseases frequently associated with epileptic seizures' (see Chapter 17) or with epilepsy syndromes when possible, genetic defects (see Chapter 14) or specific pathological substrates for symptomatic focal epilepsies (see Chapter 15)

Axis 5 is an optional assessment of impairment taken from the WHO International Classification of Functioning, Disability and Health (ICIDH-2) classification. This axis is intended for application in older patients (see chapter 7, page 219)

Table 1.1 *Reproduced with permission from Engel (2000).*[24]

Scheme for People with Epileptic Seizures and with Epilepsy,[24] and this was updated and revised in 2006.[30] A glossary of descriptive terminology for ictal semiology has also been published.[3]

Table 1.1 shows the proposed ILAE diagnostic scheme to be used in the description of individual patients with epileptic seizures, syndromes and diseases for diagnostic studies and therapeutic strategies.[24] It takes into consideration the following:

- some patients cannot be given a recognised syndromic diagnosis
- seizure types and syndromes change as new information is obtained
- complete and detailed descriptions of ictal phenomenology are not always necessary
- multiple classification schemes can, and should, be designed for specific purposes (e.g. communication and teaching, therapeutic trials, epidemiological investigations, selection of surgical candidates, basic research, genetic characterisations).

The subsequent ILAE Commission on Classification and Terminology (Chair: Anne Berg, 2005–2009) have made their report, "Revised terminology and concepts for organization of the Epilepsies", available online on the ILAE website.[31] This report is an important document for consideration and reflection as it contains the thoughts of the leading authorities in the epilepsies. The authors should also be commended for their openness by establishing a forum for constructive debate with invitation for comments from ILAE member national chapters. Therefore, the report is not at its final form and it may be premature to discuss it at any length in this revision of the Guide (see page 15). Also, this is not a new classification: "rather we have provided new terminology and concepts which better reflect the current understanding of these issues. A guiding principle has been to strive for clarity and simplicity so that terms refer to single qualities and are not a mixture of different concepts and dimensions".[31] My own comments in response to the Commission's invitation can be found at http://www.ilae-epilepsy.org/Visitors/Centre/ctf/ctfcomments.cfm.

These newer ILAE proposals concentrate mainly on terminological and taxonomic issues. A significant drawback of these reports is that recognized epileptic seizures and epileptic seizures are listed by name only. There is no definition or brief description of what each of these should be in accordance with the advances made since 1981.

The attempts to provide a new classification for epileptic seizures and syndromes is to be continued by the newly appointed ILAE Commission on Classification and Terminology (Chair: Ingrid E. Scheffer, 2009–2011).

On classifications: concepts, clarifications and difficulties in reaching a consensus in the classification of epileptic seizures and syndromes

The different methodologies, approaches, targets and philosophies on classifications and their relevance to epilepsies have been authoritatively discussed in a multiauthor editorial in Epilepsia (January 2003) entitled Cabbages and Kings in the classification of seizures and the epilepsies.[32,33] More recently, a series of important essays appeared in Epilepsy Research (2007) that provides an excellent insight into what has been achieved so far and what is expected from future developments and proposals.[34–36]

Gardeners and botanists

Classifications in epileptological literature are often compared to the classification of plants for botanists and gardeners.[28,32] The botanists, like all scientists, need a systematic taxonomy based on scientific principles, whereas the gardeners, like all practising physicians, need a practical scheme that they can use in their daily work.

> There are two ways of investigating diseases, and two kinds of classification corresponding thereto, the empirical and the scientific. The former is to be illustrated by the way in which a gardener classifies plants, the latter by the way in which a botanist classifies them. The former is, strictly speaking, only an arrangement. The gardener arranges his plants as they are fit for food, for ornament, etc. One of his classifications of ornamental plants is into trees, shrubs, and flowers. His object is the direct application of knowledge to utilitarian purposes. It is, so to speak, practical. The other kind of classification (the classification properly socalled) is rather for the better organization of existing knowledge, and for discovering the relations of new facts; its principles are methodical guides to further investigation. It is of great utilitarian value, but not directly.
>
> John Hughlings Jackson (1874)[37]

In this sense, the currently valid classification of epileptic seizures (1981)[28] and epileptic syndromes (1989)[19] should be considered as pragmatic tools for gardeners, in accordance with which the ILAE Commission[28] quotes Jackson:

> Plainly enough, such an arrangement goes by what is most superficial or striking. The advantages of it are obvious. It facilitates the identification and the application of knowledge to utilitarian purposes, but it must not be trusted as a natural classification. However much of it may be further elaborated, it makes not even an approach to a scientific classification.
>
> John Hughlings Jackson (1874)[37]

The quest for a scientific classification of epilepsies useful for botanists has been a key point of attention in the newer ILAE reports.[24,30,31] Such a classification, applying the methods used in biology to determine separate species, is a noble and legitimate target but it appears to be very elusive.

> Phylogenetic systematics could provide an initial model worth studying in this context. While the classification of species cannot be directly applied to the classification of epilepsy syndromes, three general points can be appreciated. (1) In evolutionary biology, there is an operationalized definition of the end point (a species). There is no such definition of a syndrome. (2) There are rules and criteria for the type of evidence and how it is evaluated to determine whether an entity does or does not represent a separate species. There are currently no such rules or criteria for epilepsy syndromes. (3) There is an underlying model (evolution) that generates the diversity among species. With the possible and only partial exception of the idiopathic generalized epilepsies, there are no models to explain the diversity among the epilepsies.[35]

Therefore, and in view of the difficulties with finding a scientifically correct classification for botanists in epilepsies, the new ILAE proposals and reports mainly focus on terminological changes, aiming to "characterize seizures and epilepsies in dimensions that should represent useful, natural classes".[31] This may require significant compromises that they may not serve either the botanists or the gardeners.

> Finally, although new approaches need to be investigated, we should not suddenly abandon the work that has been done up until now. Not only did it inaugurate the field, but it also represents the observations of extraordinarily astute individuals who, in all likelihood have identified some very solid, biologically real entities, which, as they are put to the test will hold up under scrutiny. The evidence in support of this is the utility of the current syndromic classification especially for epilepsy in infancy and childhood. While we would like to do even better, we need to avoid doing worse. Ideally, the botanists' scientific classification and a gardeners' pragmatic arrangement are not incompatible, but there may be points when they seem worlds apart. For any endeavor, such as this, but especially one that represents such a major departure from previous practice, it will be essential to remain open-minded and self-critical at every stage. We will inevitably make mistakes despite our best efforts not to. A willingness and ability to recognize those errors and respond to them accordingly is essential. This is the essence of scientific inquiry.[35]

Author's clarifications on the ILAE terminology and classifications

The intentions of this book from its first edition were to promote and disseminate knowledge based on the ILAE classifications. This required a significant effort to study and understand these classifications, including their minor details. In doing so, I also made and continue to make some suggestions on how these can be improved by pointing out matters that may be unclear or appear conflicting within the same text, purpose, principle or reasoning. The aim was and always is to inform readers and to assist the ILAE Commissions in their noble and difficult goal of achieving their best for the benefit of patients with epilepsies and health care professionals. These suggestions, reasoning and documentations can be found in nearly all the chapters that follow. They should be considered as part of a healthy debate and not as a sterile criticism. Key points that I wish to emphasise here are:

- That deep rooted terms in epileptology (generalised epileptic syndromes, complex focal seizures, benign epileptic syndromes) and medicine (disease, idiopathic, cryptogenic) have been misunderstood or misused is correct but the answer to this would be to better define and clarify their meaning instead of eliminating them. New terms introduced to replace them may not be easier to comprehend or to apply and are equally vulnerable to misunderstanding and misuse. Terms need to be redefined when new information arrives, not abandoned or replaced every time that something new comes to light.
- That epileptogenicity and its evolution have significant differences from neonates to the elderly is well known. However, age at onset is an unsafe criterion to accept as the primary organisational factor for the electro-clinical syndromes. It creates significant problems and frequently defies previous efforts for a relatively homogeneous categorisation of epilepsies, which is often achievable. Syndromes that are likely to be linked together on vast electro-clinical (and often genetic) evidence are separated and intermixed with a number of heterogeneous epilepsies in this age-related sequence. Further, some electroclinical syndromes have a small range of age of onset (and indeed months or few years before complete remission), while in other syndromes the range of onset expands for many decades.
- That the differences between generalised and focal (partial) seizures are not as sharp as was initially thought is not new and was certainly known by the authors of the 1981 and 1989 seizure and syndrome classifications (see also Chapter 2, page 31–32). Similarities and overlaps between the pathophysiological or genetic aspects of generalised and focal seizures/syndromes are significant but this should not distract us from the fact that their differences are of much greater magnitude. It is by emphasising their differences that the possibility of therapeutic disasters such as prescribing carbamazepine in absence seizures has been minimised. Abandoning the term generalised epileptic syndromes is an example of how existing evidence may be interpreted in diametrically different ways; it is reversing the previous, also unsatisfactory, ILAE proposal that juvenile myoclonic epilepsy, juvenile absence epilepsy and idiopathic generalized epilepsy with GTCS only are a syndrome of IGE of adolescence.[38] Abandoning generalized epilepsies also creates the paradox that syndromes such as "epilepsy with generalized tonic-clonic seizures only" are not classified as generalised epilepsy though by name it manifests exclusively with GTCS. The same applies to childhood absence epilepsy and other IGEs that may be evidenced only with generalised seizures.

We should also not lose sight of that fact that we still are very much behind in precisely defining universally recognized epileptic seizures such as typical absence seizures and syndromes such as childhood absence epilepsy that are still cited, sometimes erroneously, as per their original brief definitions of the 1981 and 1989 classifications.[39,40]

Splitters and lumpers

In the past significant emphasis was given to the differences between two main schools of thought in the classification and clinical management of epilepsies: splitters and lumpers. This may now be of historical interest only and serve as an illustrative example of how time and resources can be lost in debating straightforward matters such as the usefulness of the syndromic diagnosis of epilepsies (see pages 8–10).

The 'splitters' try to identify specific epileptic syndromes while recognising the existence of borderline cases. The 'lumpers' do not recognise specific syndromes within the spectrum of epilepsies.

Related to differentiation is the debate about lumping together what may or may not be similar forms of epilepsy or splitting apart groups that may represent minor variations of the same form of epilepsy. Ideally any method for classifying the epilepsies should require identification and measurement of all potentially relevant characteristics (be they phenotypic characteristics, gene mutations, etc.) and appropriate analyses to determine which characteristics truly define and differentiate between 'syndromes'. Implicitly, one must be prepared to split before one can lump. Thus we must always be on guard against unwittingly lumping because we are unaware of certain characteristics on which we should have split.[41]

Epidemiology of epilepsies

Epileptic seizures affect 1–2% of the population and 4% of children[42] in those developed countries where they have been studied.[43] Incidence and prevalence rates vary largely according to how 'epilepsy' is defined and whether neonatal, febrile and single or provoked seizures are included. Cases can be missed because people sometimes conceal their condition, do not consult physicians or discontinue treatment. Despite methodological shortcomings, it appears that in developed countries, 6–7% of children will suffer at least one or more epileptic seizures (provoked or unprovoked) and this is probably double in resource-poor countries (7–15% of children).

Incidence and prevalence of epilepsies

The incidence and prevalence of epilepsy (Figure 1.4) are different measures of a disease's occurrence. Incidence refers to the number of newly diagnosed patients with at least two unprovoked seizures in 1 year per 100,000 people. Prevalence refers to the number of patients with active epilepsy at any given time (prevalence date) per 1000 people. A short-lived disease such as rolandic epilepsy can have a high annual incidence but a low prevalence. Conversely, a lifelong disease such as Lennox–Gastaut syndrome has a low annual incidence but a high prevalence.

The incidence rate of epilepsy is age related. The highest incidence rate (ranging from 100 to 233 per 100,000) is observed in children younger than 1 year, with a peak in the first week of life. Subsequently, this declines in early childhood to around 60/100,000, plateaus in adolescents and adults to around 30–40/100,000 and rises again in elderly people to 100–170/100,000 after the age of 65 years.

Higher incidence rates have been found in resource-poor countries. An apparent decline of the incidence of epilepsies in recent studies may be attributed to better diagnosis, improved prenatal care and decreased exposure of children to risk factors, such as severe head trauma and CNS infections.

Cumulative incidence is much higher than incidence data because this is the cumulative risk of

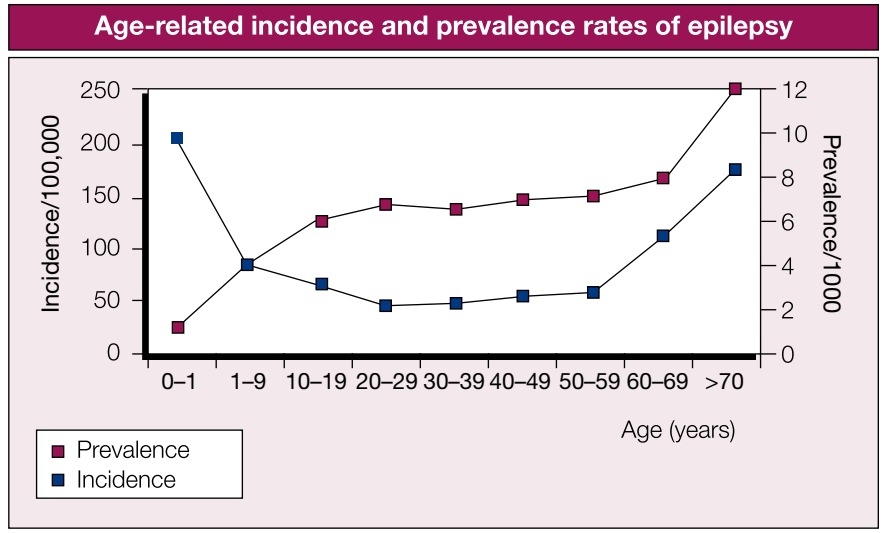

Figure 1.4 *Reproduced with permission from Jallon (2006).*[43]

incidence over many years. This is estimated to be 0.8% of active epilepsy by age 14 or 15 years. In Rochester, Minnesota, the incidence up to age 20 years is 4% for all convulsive disorders, 1% for active epilepsy and 2% for all non-febrile seizures.[44]

The prevalence rate increases with age (2.3/1000 at age 7 years to 4–6/1000 at age 10–15 years). Rates tend to be higher in boys than in girls (sex ratio of boys to girls: 1.2–1.5). Higher rates from 8/1000 (Ecuador) to more than 50/1000 (Panama) have been reported in some studies conducted in resource-poor countries, not only in relation to some methodological problems but also in relation to some specific risk factors such as neurocysticercosis in Latin America and non-Muslim countries in Africa.

Taking into account the mean values of incidence and prevalence, we could expect that, in Europe, about 0.9 million children and adolescents would have active epilepsy (prevalence 4.5–5.0/1000), with 130,000 new cases per year (incidence rate 70/100,000).[45] The corresponding numbers in the USA (incidence and prevalence are similar to those of Europe) are 1.4 million with active epilepsy and 210,000 new cases per year. Focal epilepsies are more frequent (about 70%) than generalised epilepsies (Figure 1.5).

Mortality and epilepsies

Epilepsy is associated with an increased risk of mortality.[46–52] The standardised mortality ratio (SMR), i.e. the ratio of the number of deaths in a population with epilepsy to that in a reference-matched population, is two to three times greater than that in the general population.[46,47] This excess is mainly related to associated or underlying disease and less often directly attributable to epilepsy, as with sudden unexpected death (SUDEP), which mainly occurs in the context of a generalized tonic clonic seizure. The SMR is more elevated in patients with symptomatic epilepsies. SUDEP incidence varies and is less than 1/1000 person-years among prevalent cases in the community and approximately 1/250 person-years in specialist centres.[51] In children, the SMR is six-times greater than in a reference-matched population. However, death from epilepsy is uncommon in children without a neurological disorder that is sufficiently severe to cause functional neurological deficit. In addition, in children, SUDEP is rare (1–2/10,000 patient-years).[52] A "must-read" review on SUDEP by Lina Nashef and Philippe Ryvlin has just been published.[53]

Normal children with epilepsy do not have an increased risk of death compared with the general population.[52]

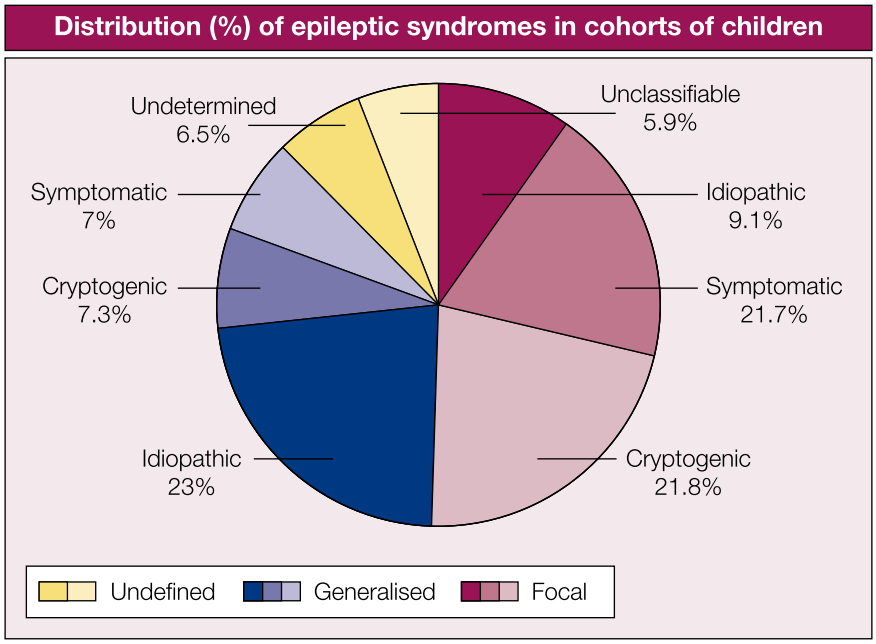

Figure 1.5 *Reproduced with permission from Jallon (2006).*[43]

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two

Epileptic seizures and their classification

Epileptic seizures are numerous and diverse in their presentation, pathophysiology, age relationships, prevalence and triggering factors (Tables 2.1–2.3).

The definition of epileptic seizures

Epileptic seizures are transient paroxysmal events, characterised by clinical symptoms, signs or both, which are generated by abnormal excessive and synchronous electrical discharges of brain networks. The most recent formal definition of epileptic seizures reflects consensus discussions held by representatives of the ILAE and the IBE (2005).[1]

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[1]

Other ILAE definitions are:

Epileptic seizure: Manifestation(s) of epileptic (excessive and/or hypersynchronous), usually self-limited activity of neurones in the brain.[2]

Epileptic seizure: A clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurones in the brain. The clinical manifestation consists of a sudden and transitory abnormal phenomena, which may include alterations of consciousness, or motor, sensory, autonomic or psychic events perceived by the patient or an observer.[3,4]

All three essential elements of the definition of an epileptic seizure should be present before it is decided that a paroxysmal event is an epileptic seizure and not something else:[1]

1. transient, with an onset and termination of usually brief duration
2. clinical manifestations
3. ictogenesis due to abnormal enhanced synchrony in the brain

Mode of onset and termination: An epileptic seizure is 'transient', demarcated in time, with a start and finish of usually brief duration. In practice, onset and termination are assessed by clinical and EEG changes. However, it should be realised that an ictal electrical discharge may start in a set of neurones and networks before it becomes evident on surface EEG (either in the same or different brain locations) and clinical manifestations appear. Furthermore, clinical changes may be more apparent than EEG changes or vice versa and there may be a significant time lag between their onsets (on video EEG), with the EEG changes often appearing first (Figures 1.2, 12.3, 12.5). There are plenty of illustrative cases in this book emphasising that some epileptic seizures, such as hypermotor seizures, may manifest with severe clinical symptoms and/or signs but without visible changes in surface EEG (Figure 15.8).

Conversely severe ictal EEG abnormalities may be associated only with subtle clinical manifestations that may not be apparent to the observer (Figure 15.4) and/or the patient, such as phantom absences. These facts are even more striking when one attempts to determine precisely the onset of clinical and EEG ictal events.

See also onset of focal versus generalised seizures on pages 33 and 57.

Termination of an epileptic seizure is often less evident than is the onset, because EEG and clinical post-ictal abnormalities can blur its end. The duration of a seizure varies significantly from seconds or minutes (usually 1–3 min) to lengthy periods of status epilepticus, when self-sustaining processes prevail over self-terminating mechanisms (see chapter 3, page 65).

Clinical manifestations: Clinical symptoms and signs are an essential part of defining an epileptic seizure. 'Ictal-like' EEG-only patterns are not defined as epileptic seizures.

Subclinical and/or electrographic seizures

'EEG only' ictal patterns that resemble those seen during epileptic seizures, but not perceived subjectively or objectively either by the patient or by the observer, are not defined as epileptic seizures.[1] They are called 'subclinical' or 'electrographic' seizures, which manifest with paroxysmal rhythmic epileptiform discharges that evolve in time and space in the absence of objective and subjective clinical manifestations. However, it is often difficult to determine the lack of subtle clinical manifestations during 'ictal-like' EEG paroxysms and their boundaries with truly ictal seizures (see for example phantom absence seizures or electrographic seizures in neonates and comatose patients).

An epileptogenic discharge may start in or invade any cortical or subcortical brain area and network. Therefore any type of function controlled by the affected brain regions may be disturbed, producing abnormal symptoms and signs that may be sensory, motor, autonomic, cognitive, behavioural, mnemonic or psychological and/or affect alertness, awareness and responsiveness. An epileptic seizure may affect only one or many brain functions with a varying degree of severity and a shifting sequence. Symptoms may be entirely subjective or objective or both. They may be so mild that they are barely perceived by the patient, observer or recording device or very severe and massive.

Seizure semiology depends on location of onset in the brain, patterns of propagation, maturity of the brain, confounding disease processes, sleep–wake cycle, medications and a variety of other factors.[1]

Detailed specification of subjective and objective clinical phenomena during an epileptic seizure is difficult because of the wide range of possible manifestations.[1] Tables 2.1, 2.2 and 2.3 show the classification of seizures according to their predominant symptoms and localisations.

Motor manifestations may be clonic, tonic, myoclonic, dystonic, atonic or hypermotor and may be limited to a small group of muscles or involve the entire voluntary musculature.

Sensory manifestations can affect the somatosensory, auditory, visual, olfactory, gustatory or vestibular senses. Again, they may be entirely localised or widely spread, and may occur alone or in combination with other sensory or other manifestations.

Autonomic manifestations of any type are often encountered in seizures, whether focal or generalised, in adults or children, and they are implicated in occurrences of sudden death. They are sometimes the most difficult symptoms and signs to detect without, for example, ictal ECG or polygraphic recordings (see neonates and figures 1.2; 8.1; 12.5). They usually appear together with symptoms from other modalities but they may also occur alone for brief or lengthy periods (see autonomic status epilepticus in Panayiotopoulos syndrome, page 347).

Effects on cognition, perception, attention, emotion, memory, execution, praxis, speech, consciousness, awareness, responsiveness, behaviour, psychology and other related functions are common, may occur alone or in combination, and may appear as the first ictal symptom or occur later in the course of a seizure. These symptoms are often referred with various terms that need to be clarified. 'Complex internal

sensations',[1] 'dreamy states', 'psychic or mental symptoms', 'intellectual aura' and 'experiential phenomena' are the terms most commonly used to denote symptoms of seizures that uniquely relate to the patient's personality, identity, experience, emotion, thought and memory. These terms are not necessarily synonymous, because they are used in the relevant literature to encompass either limited or much wider ictal manifestations (see Chapter 15 page 438). Dyscognitive is a term that is widely used to denote impairment of cognition, which is the process of knowing, including aspects such as awareness, perception, reasoning and judgement (see chapter 3 page 78). "Memory distortions can be either negative or positive, in the sense of interruption of memory formation or retrieval as a negative symptom, or intrusion of inappropriate memories as a positive symptom."[1] "Emotional state is difficult to specify but must be considered in the definition, because some seizures manifest as fear, elation, satisfaction, anxiety or other subjective sensations that cannot be ascribed to the primary senses".[1] For 'impairment of consciousness', see blue box on this page.

Ictogenesis: This is the most difficult element of the definition of an epileptic seizure to assess in practice because the electrical discharge may not be visible even in long EEG recordings and some patients may have consistently normal EEGs. "Nevertheless, the definition assumes that such an abnormal electrical discharge could be ascertained under ideal circumstances....Without the electrical discharge criteria, many other clinical events that are not epileptic seizures would meet the other definition criteria".[1] Consider for example the galaxy of clinical imitators of epileptic seizures in listed chapter 4, such as migraine with aura, that may be clinically near-identical to epileptic seizures but without a causative relation to ictogenesis. Further, "definition of an epileptic seizure becomes operationally difficult without ascribing it to the brain. Trigeminal neuralgia, for example, can result from an abnormal enhanced synchrony of neurones in the trigeminal ganglion or the fifth cranial nerve, but would not be considered an epileptic seizure. Nor would hyperactive spinal reflexes resulting in an excessive discharge of anterior horn cells and tonic stiffening of a limb".[1]

The book *Epileptic Seizures*, edited by Hans Luders and Soheyl Noachtar, is highly recommended for its in-depth insight into pathophysiology and clinical semiology.[9]

Impairment of consciousness, unresponsiveness, awareness

There is no precise definition of 'consciousness' and therefore 'impairment of consciousness' cannot be exactly defined either. Components of consciousness include perception, cognition, memory, affect, and voluntary motility. In epileptic seizures 'loss or impairment of consciousness' often reveals that only some components of consciousness are impaired. Responsiveness and awareness are frequently disturbed during ictal 'impairment of consciousness' but to a varying degree of severity, and in some seizures the patient may be entirely responsive but unaware (amnesic) of the events or vice versa. Further, unresponsiveness may be due to aphasia, inability to perform voluntary movements, ictal or postictal amnesia (sometimes with preservation of memory during the ictus itself), or to diversion of attention by a hallucinated experience.[5,6]

See also 'altered content of consciousness' in fully alert patients with absence status epilepticus (page 73).

Impaired consciousness according to the 1981 ILAE report is the inability to respond normally to exogenous stimuli by virtue of altered awareness and/or responsiveness. Aberrations of behaviour (automatisms) may occur in patients with impaired consciousness.[7]

The precise brain mechanisms for control of consciousness are not fully understood but emerging data show that conscious information processing depends on the activation of certain networks in the brain and that the impairment of consciousness is related to abnormal activity in these systems.[8]

Other useful or ILAE seizure-related terminology

Aura: A subjective ictal phenomenon that, in a given patient, may precede an observable seizure; if alone, it constitutes a sensory seizure.[2]

Prodrome: A preictal phenomenon, i.e. a subjective or objective clinical alteration (e.g. unlocalised sensation or agitation), that heralds the onset of an epileptic seizure but does not form part of it.[2]

Ictus: A sudden neurological occurrence, such as a stroke or an epileptic seizure.[2]

Ictal: The seizure period or events due to a seizure.

Inter-ictal: The interval between seizures.[2]

Post-ictal: A transient clinical abnormality of CNS function that appears or becomes accentuated when clinical signs of the ictus have ended.[2]

Single or isolated seizure: One or more epileptic seizures occurring in a 24 hour period.[3,4]

Symptomatogenic zone: the brain region that corresponds with the ictal symptoms and signs of an epileptic seizure as detected by clinical means. Ictal symptoms may happen long after the onset of the electrical discharges and may appear from areas that are different from the epileptogenic zone.

Epileptogenic zone or focus: the brain region that corresponds with the onset of ictogenesis as detected with surface and more accurately invasive EEG (see also page 224). This frequently extends beyond the structural lesion visualised on neuroimaging (called *epileptogenic lesion*) or the epileptogenic cortical area generating inter-ictal spikes (called *irritative zone*).

Important clinical notes

Prodrome should not be confused with aura

Aura is not synonymous with prodrome; aura is a seizure itself, and is brief, lasting seconds or minutes. Prodrome is a non-epileptic symptom preceding the onset of an epileptic seizure by several hours (page 99).[10]

Classification of epileptic seizures

Epileptic seizures in accordance with the 1981 ILAE classification[11]

The currently valid ILAE *Classification of Epileptic Seizures* was made in 1981.[11] This is an updated version of the classification proposed by Gastaut in 1970,[12] with a full description of each seizure in his classic book[13] and the WHO dictionary of epilepsies.[10]

The 1981 ILAE seizure classification is based on clinical and EEG (ictal and inter-ictal) manifestations (Tables 2.1 and 2.2). Seizures are principally divided into the following types:

I. *Partial (focal or local) seizures* (with great variation in clinical expression and severity).

II. *Generalised seizures (tonic, clonic or tonic–clonic, myoclonic and typical or atypical absences).*

III. *Unclassified epileptic seizures*, which cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto described categories. This includes some neonatal seizures, e.g. rhythmic eye movements, chewing and swimming movements.[11]

IV. *Prolonged or repetitive seizures (status epilepticus).*

'Focal seizures' are synonymous and exchangeable with, but preferred to, 'partial seizures'.[14]

The dichotomy between focal and generalised seizures was considered to be necessary 'because an abnormal paroxysmal discharge of cerebral neurones may be localised (partial seizures) or simultaneously affect the whole cerebral cortex from onset to termination (generalised seizures)'.[11]

See page 31 for the recent debate on this dichotomy.

ILAE classification of partial (focal, local) seizures

Clinical seizure type	EEG seizure type	EEG inter-ictal expression
A. Simple partial seizures (consciousness not impaired)	Local contralateral discharge starting over the corresponding area of cortical representation (not always recorded on the scalp)	Local contralateral discharge
1. With motor signs a. Focal motor without march b. Focal motor with march (jacksonian) c. Versive d. Postural e. Phonatory (vocalisation or arrest of speech)		
2. With somatosensory or special-sensory symptoms (simple hallucinations, e.g. tingling, light flashes, buzzing) a. Somatosensory b. Visual c. Auditory d. Olfactory e. Gustatory f. Vertiginous		
3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection and pupillary dilation)		
4. With psychic symptoms (disturbance of higher cerebral function). These symptoms rarely occur without impairment of consciousness and are much more commonly experienced as complex partial seizures a. Dysphasic b. Dysmnesic (e.g. déjà vu) c. Cognitive (e.g. dreamy states, distortions of time sense) d. Affective (e.g. fear, anger) e. Illusions (e.g. macropsia) f. Structured hallucinations (e.g. music, scenes)		
B. Complex partial seizures (with impairment of consciousness; may sometimes begin with simple symptomatology)	Unilateral or, frequently, bilateral discharge, diffuse or focal in temporal or frontotemporal regions	Unilateral or bilateral, generally asynchronous focus; usually in the temporal or frontal regions
1. Simple partial onset followed by impairment of consciousness a. With simple partial features (A1 to A4) followed by impaired consciousness b. With automatisms		
2. With impairment of consciousness at onset a. With impairment of consciousness only b. With automatisms		
C. Partial seizures evolving to secondarily generalised seizures (this may be generalised tonic–clonic, tonic or clonic) (above discharges become secondarily and rapidly generalised)		
1. Simple partial seizures (A) evolving to generalised seizure		
2. Complex partial (B) evolving to generalised seizure		
3. Simple partial seizures evolving to complex partial seizures evolving to generalised seizure		

Table 2.1 *Adapted with permission from the Commission of Classification and Terminology of the ILAE (1981).*[11]

ILAE classification of generalised seizures (convulsive and non-convulsive)

Clinical seizure type	EEG seizure type	EEG inter-ictal expression
A1. Absence seizures a. Impairment of consciousness only b. With mild clonic components c. With atonic components d. With tonic components e. With automatisms f. With autonomic components *(b–f may be used alone or in combination)*	Usually regular and symmetrical 3 Hz, but may be 2–4 Hz spike–slow-wave complexes and may have polyspike–slow-wave complexes. Abnormalities are bilateral	Background activity usually normal, although paroxysmal activity (such as spikes or spike–slow-wave complexes) may occur. This activity is usually regular and symmetrical
A2. Atypical absence seizures May have: a. Changes in tone that are more pronounced than in A1 b. Onset and/or cessation that is not abrupt	EEG more heterogeneous, may include irregular spike–wave complexes, fast activity or other paroxysmal actions. Abnormalities are bilateral but often irregular and asymmetrical	Background usually abnormal paroxysmal activity (such as spikes or spike–slow-wave complexes) frequently irregular and symmetrical
B. Myoclonic seizures Myoclonic jerks (single or multiple)	Polyspike and wave or sometimes spike and wave or sharp and slow waves	Same as ictal
C. Clonic seizures	Fast activity (⩾10 cycles/s) and slow waves or occasional spike–wave patterns	Spike and wave or polyspike and wave discharges
D. Tonic seizures	Low-voltage, fast activity or a fast rhythm 9–10 cycles/s, decreasing in frequency and increasing in amplitude during tonic phase. Interrupted by slow waves during clonic phase	Polyspike and wave or spike and wave or, sometimes, sharp- and slow-wave discharges
E. Tonic–clonic seizures	Rhythm at ⩾10 cycles/s decreasing in frequency and increasing in amplitude during tonic phase. Interrupted by slow waves during clonic phase	Polyspike and waves or spike and wave or, sometimes, sharp- and slow-wave discharges
F. Atonic seizures (astatic)	Polyspikes and wave or flattening or low-voltage fast activity	Polyspikes and slow wave
Combinations of the above may occur, e.g. B and F, B and D		

Table 2.2 *Adapted with permission from the Commission of Classification and Terminology of the ILAE (1981).*[11]

Partial (or focal) seizures (Table 2.1)

> Partial (focal) seizures are those in which, in general, the first clinical and EEG changes indicate initial activation of a system of neurones limited to a part of one cerebral hemisphere.[11]

Partial seizures are further subclassified chiefly on the basis of (1) whether or not consciousness is impaired during the attack and (2) whether or not progression to generalised convulsions occurs.

A. *Simple partial seizures (when consciousness is not impaired).*

B. *Complex partial seizures (when consciousness is impaired).* Impairment of consciousness may be the first clinical sign or simple partial seizures may evolve into complex partial seizures.

A partial seizure may not terminate, but instead progress to a generalised motor seizure.

C. *Partial seizures (simple or complex) evolving to secondarily generalised (tonic–clonic or tonic or clonic) seizures.*

Generalised seizures (Table 2.2)

> Generalised seizures are those in which the first clinical changes indicate initial involvement of both hemispheres. Consciousness may be impaired and this impairment may be the initial manifestation. Motor manifestations are bilateral. The ictal EEG patterns initially are bilateral and presumably reflect neuronal discharge, which is widespread in both hemispheres.[11]

Generalised seizures may be convulsive or non-convulsive and vary considerably: mild or severe myoclonic jerks, inconspicuous or severe typical and atypical absences and generalised clonic, tonic or tonic–clonic convulsions.[11]

In this[11] and the newer[7,14] ILAE epileptic seizure classifications, there is a main "distinction between seizures that are generalized from the beginning and those that are partial or focal at onset and become generalized secondarily",[11] with significant differences in their epileptogenesis, clinical and EEG features, aetiology and management.

Important note

The terminology of primarily and secondarily generalised seizures

The terms primarily and secondarily GTCSs should not be confused with the now obsolete terms of primary (= idiopathic) and secondary (= symptomatic or cryptogenic) epilepsy, which either have not been used or have been rightly abandoned by the ILAE and most physicians. These terms are also not used in the current ILAE glossary.[2] Idiopathic (from the Greek words *idios* = self, own and personal, and *pathic* = suffer; see also pathology and pathological)[16] usually refers to genetically determined aetiology.[7] In the USA idiopathic is traditionally considered to signify cases of unknown aetiology and pathogenesis, which is the reason why American physicians prefer the term 'primary' to 'idiopathic'.[17] Of the dictionary definitions of 'primary', the following are relevant to its use in the classification of epilepsies:

1. Preceding all others in time: earliest, first, initial, maiden, original, pioneer, prime, primordial. This definition would apply to primarily GTCSs (PGTCSs).
2. Not derived from something else: original, prime, primitive. This definition would apply to idiopathic GTCSs.

In ILAE classifications and guidelines, as well as other formal recommendations, the frequency and inconsistency with which the words primary and primarily, secondary and secondarily are used are confusing; for instance, why use 'primary reading epilepsy' instead of 'idiopathic reading epilepsy'?

A major issue is that the term 'primary GTCS', which etymologically means and implies 'idiopathic GTCS', is in fact used for GTCSs of idiopathic, symptomatic and cryptogenic epilepsies, particularly in randomised controlled trials of AEDs (see pages 190–193).[18]

Another issue to clarify is that the PI and SmPC of an AED may indicate that it is licensed for focal epileptic seizures with or without "secondary generalisation", meaning secondarily GTCS only. Tonic, clonic or absence seizures and possibly epileptic spasms may also result from secondarily generalisation (Table 2.1 and 2.3).

1. *Generalised-onset seizures.* They are often called primarily or primary generalised seizures, although this is not a formal term used in the ILAE nomen-

clature. 'Generalised-onset seizures' are synonymous with 'generalised epileptic seizures' in the ILAE classifications.

2. *Focal-onset generalised seizures (is synonymous to 'secondarily generalised seizures' used in the ILAE terminology).* They are partial (focal) at onset but do not remain localised. They spread and trigger a generalised epileptic seizure.

A significant and continuing problem of confusion may result from the inappropriate use of the terms 'primary' or 'secondary' for the characterisation of epileptic seizures and epileptic syndromes (see important note in chapter 5 page 140).[15] In idiopathic generalised epileptic syndromes, seizures are likely to be of generalised onset, whereas in cryptogenic and symptomatic syndromes, generalised seizures are likely to be of focal onset (see important note on page 27).

The ILAE classification of generalised-onset seizures is presented in Table 2.2 with the following broad categories:[11]

A1. absence seizures
A2. atypical absence seizures
B. myoclonic seizures
C. clonic seizures
D. tonic seizures
E. tonic–clonic seizures
F. atonic seizures (astatic).

Seizure classification in the new ILAE Task Force reports[7,14]

Table 2.3 lists the various types of epileptic seizures approved in the recent ILAE report,[7,14] which varies little from the original ILAE seizure classification.[11]

Significant changes in the ILAE Task Force reports are:

I. The old term 'focal' is reintroduced to replace 'partial' and 'localisation-related' epileptic seizures, which is an understandable and welcomed change.

However, this new scheme abandons the division of focal seizures into 'simple' (without impairment of consciousness) and 'complex' (with impairment of consciousness).[7] The reason given is that this 'inappropriately created the impression that impairment of consciousness had certain mechanistic implications related to limbic system involvement' (Figure 2.1) and that 'complex partial seizures' has been erroneously used as a synonym of 'temporal lobe epilepsy'.[7] Although these are correct, there are significant practical reasons (medicolegal cases, driving and job-related performance) for distinguishing seizures with or without impairment of consciousness. Therefore, I keep using the terms 'simple' and 'complex' focal seizures in this book, while emphasising that (1) ictal impairment of consciousness is a symptom of either neocortical or limbic seizures and (2) complex focal seizures may originate from any cerebral lobe and therefore they are not synonymous with temporal lobe epilepsy.

The newest ILAE report proposes to abandon the terms simple and complex partial seizures and their distinction.[19] An added argument is that "the distinction based on impairment of consciousness... was impossible to define in a precise scientific manner".[19] However, 'impairment of consciousness' is also a defining symptom of other seizures such as absence seizures. Therefore, it needs to be defined and clarified (see important clinical note on page 23) even if 'complex partial seizures' are eliminated from our glossary.

II. The scheme introduced the terms 'self-limited seizure types' for brief seizures and 'continuous seizure types' for status epilepticus.[7] These terms were unlikely to find any support and they were not used in the first edition of this book. Also, 'continuous seizure types' is etymologically incorrect because 'status epilepticus' is sometimes self-limited (see examples of absence, autonomic or febrile status epilepticus) and often discontinuous (see examples of myoclonic or complex focal status epilepticus). The terms 'self-limited' and 'continuous' seizure are both rightly abandoned in the new ILAE report.

III. The ILAE Task Force has also introduced the term 'epileptic seizure type', which 'represents a unique diagnostic entity or natural class which ought to be defined on the basis of a distinct pathophysiology and anatomical substrate'.[14]

Epileptic seizures

I. Generalised onset

A. Seizures with tonic and/or clonic manifestations
1. Tonic–clonic seizures
2. Clonic seizures
3. Tonic seizures

B. Absences
1. Typical absences
2. Atypical absences
3. Myoclonic absences

C. Myoclonic seizure types
1. Myoclonic seizures
2. Myoclonic–astatic seizures
3. Eyelid myoclonia

D. Epileptic spasms

E. Atonic seizures

II. Focal onset (partial)

A. Local
1. Neocortical
   a. without local spread
      i. focal clonic seizures
      ii. focal myoclonic seizures
      iii. inhibitory motor seizures
      iv. focal sensory seizures with elementary symptoms
      v. aphasic seizures
   b. with local spread
      i. jacksonian march seizures
      ii. focal (asymmetrical) tonic seizures
      iii. focal sensory seizures with experiential symptoms
2. Hippocampal and parahippocampal

B. With ipsilateral propagation to:
1. Neocortical areas (includes hemiclonic seizures)
2. Limbic areas (includes gelastic seizures)

C. With contralateral spread to:
1. Neocortical areas (hyperkinetic seizures)
2. Limbic areas (dyscognitive seizures with or without automatisms [psychomotor])

D. Secondarily generalised
1. Tonic–clonic seizures
2. Absence seizures
3. Epileptic spasms (unverified)

III. Neonatal seizures

Table 2.3 *Reproduced with permission from Engel (2006).*[14]

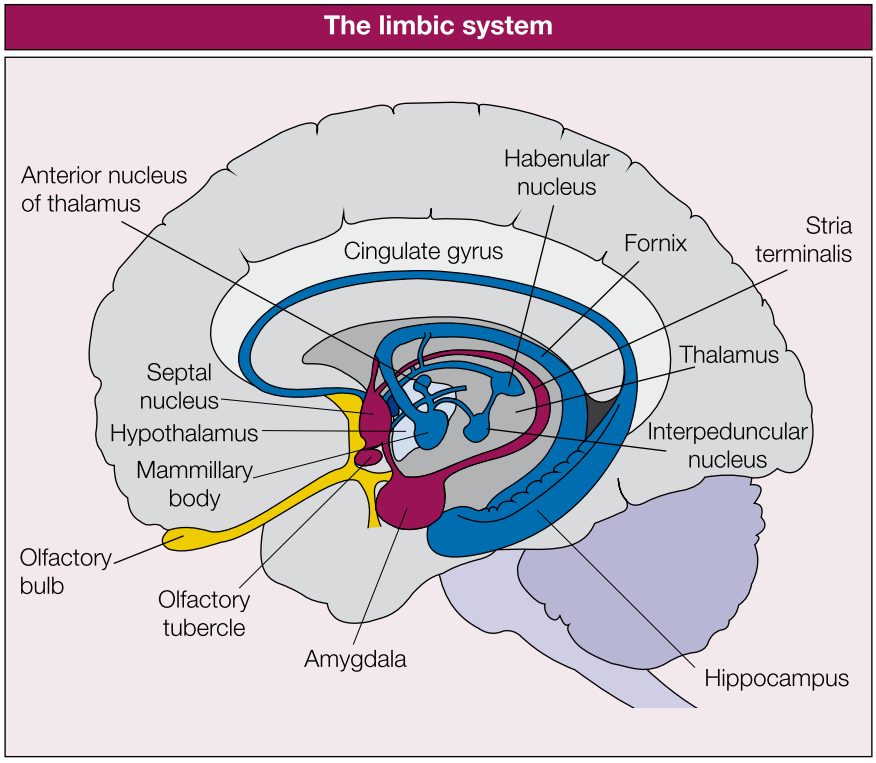

Figure 2.1

The following criteria were used to select specific seizure types as possibly unique diagnostic entities, for further hypothesis testing:

- *Pathophysiological mechanisms:* Including electrophysiological features, neural networks, neurotransmitter evidence if known (e.g. increased excitation and decreased inhibition for generalised tonic–clonic and some neocortical seizures versus increased excitation and increased inhibition, leading to hypersynchronisation for absences and some hippocampal seizures).
- *Neuronal substrates:* For these purposes, the neocortex is considered a single substrate regardless of exact location and function subserved, unless specific pathophysiological mechanisms differ. Thus, focal clonic movements caused by an epileptogenic abnormality in precentral cortex are not, in any essential way, different from unformed visual hallucinations caused by the same type of epileptogenic abnormality in the calcarine cortex if the pathophysiological mechanisms are the same, just as electrical stimulation induced after discharge of the neocortex represents the same epileptogenic mechanism, regardless of the area of neocortex stimulated and the behavioural signs and symptoms elicited. Other brain structures and networks should be included (e.g. thalamic reticular nucleus for absence seizures versus brain stem for GTCSs).
- *Response to AEDs:* Selective responsiveness to or exacerbation associated with specific drugs can suggest a specific mechanism of seizure generation.
- *Ictal EEG patterns:* Specific ictal EEG patterns can be necessary diagnostic features of specific seizure types (e.g. 3 Hz for absences). These should reflect specific pathophysiological mechanisms and anatomical substrates.
- *Propagation patterns and post-ictal features:* Patterns of propagation, or lack of propagation, and post-ictal features, or lack of them, help to define pathophysiological mechanisms and anatomical substrates (e.g. typical absences have no post-ictal dysfunction; contralateral propagation is

slow for hippocampal seizures versus fast for neocortical seizures; some seizures are strictly local, others more widespread).

The newest ILAE report makes no reference to "epileptic seizure type".[19] Therefore, it is assumed that this is no longer considered to be a diagnostic entity or natural class.

Debate on the distinction between generalised and focal seizures

The dichotomy between generalised and focal seizures is rightly maintained in all ILAE classifications and their distinction has immense practical implications for the evaluation and management of patients. However, there has recently been significant debate on whether the differences between generalised and focal (partial) seizures are as sharp as was initially thought. This is well clarified in the newest ILAE report, which maintains the dichotomy between generalised and focal seizures.[19]

Generalised epileptic seizures are now considered to originate at some point within, and rapidly engage, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. Although individual seizure onsets can appear localised, the location and lateralisation are not consistent from one seizure to another. Generalised seizures can be asymmetric. [19]

Focal epileptic seizures are now considered to originate primarily within networks limited to one cerebral hemisphere. These may be discretely localised or more widely distributed. Some lesions in subcortical structures may produce focal seizures (e.g. hypothalamic hamartomas). For each seizure type, ictal onset is consistent from one seizure to another with preferential propagation patterns, which can involve the contralateral hemisphere. In some cases, however, there is more than one epileptogenic network, and more than one seizure type, but each individual seizure type has a consistent site of onset. This also applies to cases in which focal seizures may arise independently in either hemisphere (e.g, bilateral mesial temporal lobe epilepsy or benign epilepsy with centrotemporal spikes).[19]

Focal seizures does not necessarily imply that the epileptogenic region is limited to a small circumscribed area, nor does generalised seizures imply that the entire brain is involved in initiation of the epileptogenic process.[14]

Important clarification

In all previous and new ILAE classification the dichotomy between focal and generalised epileptic seizures is maintained. A significant deviation has occurred in the newest ILAE report in that although the distinction is maintained for epileptic seizures, it is stated that "for epilepsies, recent electro-clinical, imaging and genetic data do not support such a simple dichotomy".[19] Abolishing the distinction between focal and generalised epileptic syndromes creates significant problems of clinical and diagnostic significance, as detailed in Chapter 1, page 15.

The ILAE Task Force in justifying the decision to maintain the distinction between generalised and focal seizures states:

> Although the dichotomy of focal (partial) vs. generalized has been criticized, and we have recommended in an earlier report that these terms should eventually be discarded because no seizures or syndromes are truly generalized, nor is it likely that many, if any, seizures or syndromes are due to a discretely focal epileptogenic process, the Core Group has recognized the value of distinguishing epileptic seizures that begin in a part of one hemisphere, from those that appear to begin in both hemispheres at the same time. The Core Group, however, has been unable to come up with simple terms to describe these two situations. Given the prevalent usage, and the therapeutic implications, of the terms 'focal' and 'generalized,' we have decided to retain them, with the understanding that the former does not necessarily imply that the epileptogenic region is limited to a small circumscribed area, nor does the latter imply that the entire brain is involved in initiation of the epileptogenic process.[14]

The comments of Peter Wolf should also be considered:[17]

> The definition of generalised is very simple and straightforward. There are, however, serious problems with the term which the two subsequent commissions did not pay sufficient attention to. When generalised seizures are defined as those where the first changes indicate bilateral involvement, the concept of secondary generalisation which also is included in the 1981 seizure classification becomes meaningless, and a contradiction in itself. Then, in an unexplained way, secondary generalisation is not considered in the same way as bilateral spread of seizure activity which would seem logical. In complex partial seizures there is often bilateral involvement, but this seizure type is not considered as generalised but as partial. Both localisation-related and 'generalised' idiopathic epilepsies are about to be understood as related variants of system disorders of the brain, with an ictogenesis making pathological use of existing functional anatomic networks.[17]

The explanations given above for the use and boundaries of the terms generalised and focal epileptic seizures would be more than sufficient and the same applies to the distinction between generalised and focal epileptic syndromes (see important clarification in blue box on page 32 and chapter 1, page 15). It would be premature and confusing to discard or change these terms to something else that we may have to abandon again when new information emerges.Both pathophysiological and clinical factors render it important to retain the distinction between the focal and generalised epileptic seizures and syndromes.

All seizures "start somewhere", but there are significant pathophysiological, clinical, EEG and therapeutic differences between focal and generalised seizures:

- Pathophysiologically, generalised seizures start within specific regions that rapidly engage bilaterally distributed networks while focal seizures begin in other brain areas that engage localised and unilateral network of epileptogenicity.
- Clinically, focal seizures start with symptoms and signs that can be ascribed to specific brain locations while generalised seizures do not (unless they are secondarily generalised).
- EEG, interictal and ictal patterns are predominantly different between focal and generalised seizures as illustrated on many occasions in this book
- Pharmacologically, certain AEDs beneficial for focal seizures may have deleterious effects on generalised seizures

The main types of generalised and focal seizures are described below.

Generalised epileptic seizures

Generalised tonic–clonic seizures[10,20]

A GTCS is the most dramatic seizure type. It is a symptom of many idiopathic, cryptogenic or symptomatic epilepsies. GTCSs occur in all ages except neonates.[21] Examples of GTCSs in children include most febrile seizures and GTCSs in idiopathic generalised epilepsies (IGEs), such as juvenile myoclonic epilepsy (JME). Almost all focal epilepsies manifest with secondarily (focal-onset) GTCSs (SGTCSs).

The ILAE[2] glossary provides the following definitions for GTCSs.

Generalised tonic–clonic seizure (synonym: bilateral tonic–clonic seizure [formerly 'grand mal' seizure]). Noun; bilateral symmetrical tonic contraction, then bilateral clonic contractions of somatic muscles usually associated with autonomic phenomena.[2]

Generalised-onset tonic–clonic seizures (= PGTCSs) are generalised from the onset without warning other than by a series of myoclonic jerks or absences that often herald GTCSs (Figure 2.2). This contrasts with SGTCSs of focal epilepsies in which seizures of focal onset do not remain localised but spread and trigger a GTCS (Figure 12.3).[25]

Secondarily generalised tonic–clonic seizures are often preceded by an aura, motor sensory or other symptoms of focal seizures.

The differentiation of PGTCSs from SGTCSs is of immense clinical significance and is usually easy using clinical, EEG and MRI findings (Table 2.4). In addition, single photon emission CT (SPECT) shows increased thalamic cerebral flow only after PGTCSs.[24]

Investigation of symptoms and precipitating factors immediately before the onset of a GTCS is a crucial part of the history taking, with significant diagnostic and management implications.

Epidemiology of GTCS

PGTCSs are the most serious type of seizures in IGE. Their prevalence, frequency and prognosis markedly depend on the syndrome of IGE (see chapter 13).

SGTCSs occur in around 90% of patients with focal epilepsies with marked variability in their occurrence, frequency, severity and prognosis (see for example chapters 12, 14 and 15).

Clinical manifestations

A GTCS, whether a PGTCS or SGTCS, manifests with:

- loss of consciousness from onset to the late phase of recovery
- generalised tonic–clonic convulsions
- significant autonomic disturbances.

The depiction of GTCSs in this chapter is largely taken from the classic text of Gastaut and Broughton,[7] which has not been surpassed (Figure 2.3). More recent contributions have been made with video-EEG analyses of PGTCSs and SGTCSs.

Ictal events preceding the onset of a GTCS

These differ between the PGTCSs and SGTCSs; e.g. clusters of myoclonic jerks or absences or absence status epilepticus precede and herald PGTCSs in IGEs, whereas SGTCSs develop from focal seizures.

Onset of GTCS proper

At the start of a GTCS, the eyes immediately open and remain open during the whole period of the attack (Figure 2.4). A GTCS may start with asymmetrical lateral tonic deviation of the head and eyes. This is of little practical diagnostic significance because it may occur in both PGTCSs and SGTCSs, and may be contralateral or ipsilateral to the epileptic focus in SGTCSs. Brief symmetrical or asymmetrical clonic movements may also occur at the start of a PGTCS or SGTCS, and immediately before the tonic phase. Asymmetrical clonic jerks are more common in SGTCSs and may last for 3–21 s.[25] However, lateralisation of SGTCSs is more likely when head turning is forceful and prolonged, usually in a clonic motion with the chin pointing upwards, and eye version to the same side as the head version allows.[26] The 'sign 4' (extension of the elbow on the side contralateral to the epileptogenic focus and with elbow flexion of the ipsilateral side; Figure 2.5) may also be of lateralising significance when it occurs at the onset of a GTCS.[27]

Tonic phase of GTCSs

The tonic phase is a 10–20 s sustained contraction of all skeletal muscles, producing a succession of characteristic body postures. It usually consists of an initial brief phase of tonic flexion forwards, followed by a longer one of tonic extension backwards. In tonic flexion, the arms are in elevation, abduction and external rotation, with semiflexion of the elbows; the body is dorsiflexed, and the lower limbs are less involved, but there may be flexion, abduction and external rotation of the thighs and legs. This converts into tonic ventriflexion of the neck and trunk with extension of the limbs. The tonic extension phase is heralded by forced closure of the previously widely open mouth, which often causes tongue biting. The 'epileptic cry', a high, pinched, loud scream occurring at this stage, is caused by the tonic contraction of thoracic abdominal muscles, which forcibly emit air across the tightly closed vocal cords. The semiflexed arms slowly lower in adduction until the forearms are crossed in front of the chest. Their subsequent posture is of extension and pronation at the elbow, with the fists clenched and wrists extended, or with the fingers extended and wrists flexed. The legs are in extension,

Video-EEG recording of a 23-year-old woman with IGE: numerous typical absences occurred on awakening and one progressed to a GTCS

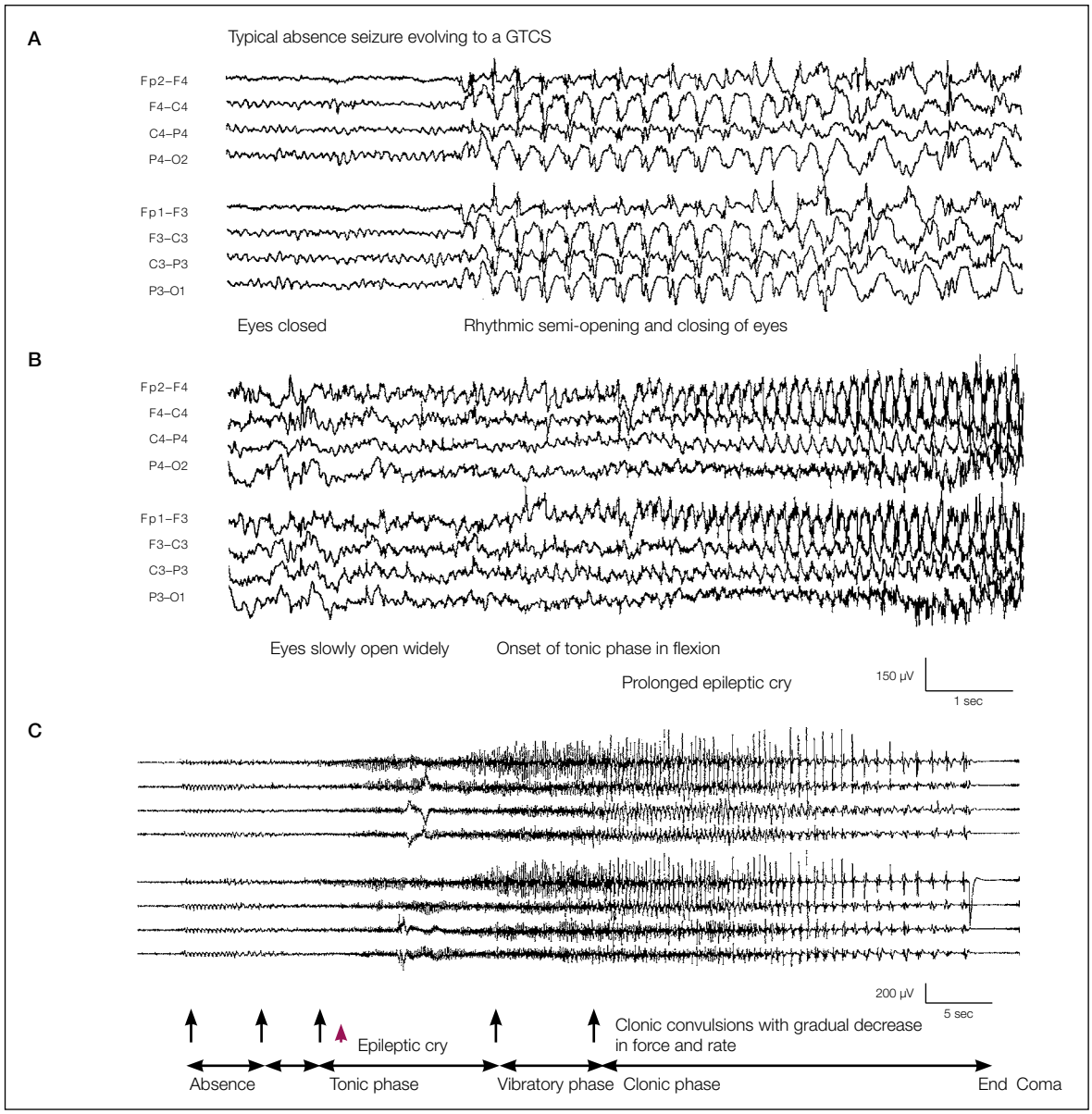

Figure 2.2 Video-EEG recording of a 23-year-old woman with IGE. Numerous typical absences occurred on awakening, and one progressed to a GTCS (see details in Panayiotopoulos[22]). (**A**,**B**) Continuous recording from onset of the absence seizure to just before the onset of the vibratory phase of the GTCS. (**C**) The various phases of the whole seizure from onset to termination (duration approximately 1 min).
Modified with permission from Panayiotopoulos (2000).[22]

adduction and external rotation. Feet and big toes are also in extension (spontaneous Babinski sign). Tonic contraction of the diaphragm and chest wall muscles appears to be responsible for the cyanosis that results from inadequate alveolar ventilation. The tonic phase may be brief for 1–3 s, or last longer for 20 s.

Differentiation of primarily versus secondarily GTCS

	Primarily GTCS	Secondarily GTCS
GTCS in patients who also have other clinically evident seizures	About 90%	About 90%
Typical absences	About 40%	None
Myoclonic jerks	About 60%	None
Focal seizures	None	About 90%
GTCS in patients without other clinically evident seizures*	About 10%	About 10%
Precipitating factors	>60%	<10%
Consistently on awakening	Common	Uncommon
Family history of similar epilepsies	Common	Uncommon
EEG in untreated patients		
Generalised discharges	About 80%	Exceptional
Focal abnormalities alone	About 10%	About 60%
Generalised discharges and focal abnormalities	About 30%	Exceptional
High-resolution brain imaging		
Focal abnormalities	Exceptional	About 60%
Normal	By definition	About 40%

Table 2.4 *It is these patients, who make up about 10% of each category, that constitute the main problem in the differential diagnosis between primarily and secondarily GTCS. However, other features, such as precipitating factors, circadian distribution, EEG and brain imaging, are often of diagnostic significance.

Intermediate transitory (vibratory) phase of GTCSs

The tonic phase ends gradually with fine clonus (vibratory tremor) initially superimposing on dominant tonic rigidity. The clonus is of waxing amplitude and waning frequency from 8 Hz down to 4 Hz. Distal muscles are affected before the proximal and facial masticatory muscles.

Clonic phase of GTCSs

This is characterised by continuously repetitive, massive, symmetrical and synchronous flexor clonic convulsions of the facial, trunk and limb musculature. They last for 30 s to 1–2 min with progressively decreasing force, amplitude and frequency (to 1 Hz). They may finally restrict only in the facial muscles or end with a massive clonic convulsion. The tongue is often bitten repeatedly during this clonic phase and each convulsion may produce an epileptic cry. Towards the end of the clonic phase, the clonic convulsions may become asynchronous and asymmetrical, and side-to-side head and eye movements may also occur. Contraction of the bladder sphincter blocks urinary incontinence until the end of the clonic phase.

Recovery phase of GTCSs

Immediate post-ictal phase of GTCSs (comatose or stertorous phase): Recovery starts with the cessation of clonic convulsions, although the patient remains in a coma, is unresponsive and markedly hypotonic. Respiration is restored with a deep inspiration, followed by usually noisy deep breathing associated with the secretion of frothy and bloodstained saliva. Urinary incontinence occurs only at this stage (Figure 2.4). Faecal incontinence or ejaculation is rare. Skin resistance and blood pressure return progressively to pre-seizure levels; the patient becomes pale.

Then, 5–8 s later, there may be a new phase of tonic contraction that mainly affects the facial and masticatory muscles: teeth are tightly clenched, and the limbs and trunk (when involved) take a decerebrate-like posture. Autonomic abnormalities include mydriasis, tachycardia, sometimes with marked cardiac arrhythmia, and intense tachypnoea. This state is associated with hypometabolism predominating in cortical structures.[46] It is of variable duration, from seconds to 3 or 4 min, or it may not occur. The patient remains unconscious throughout

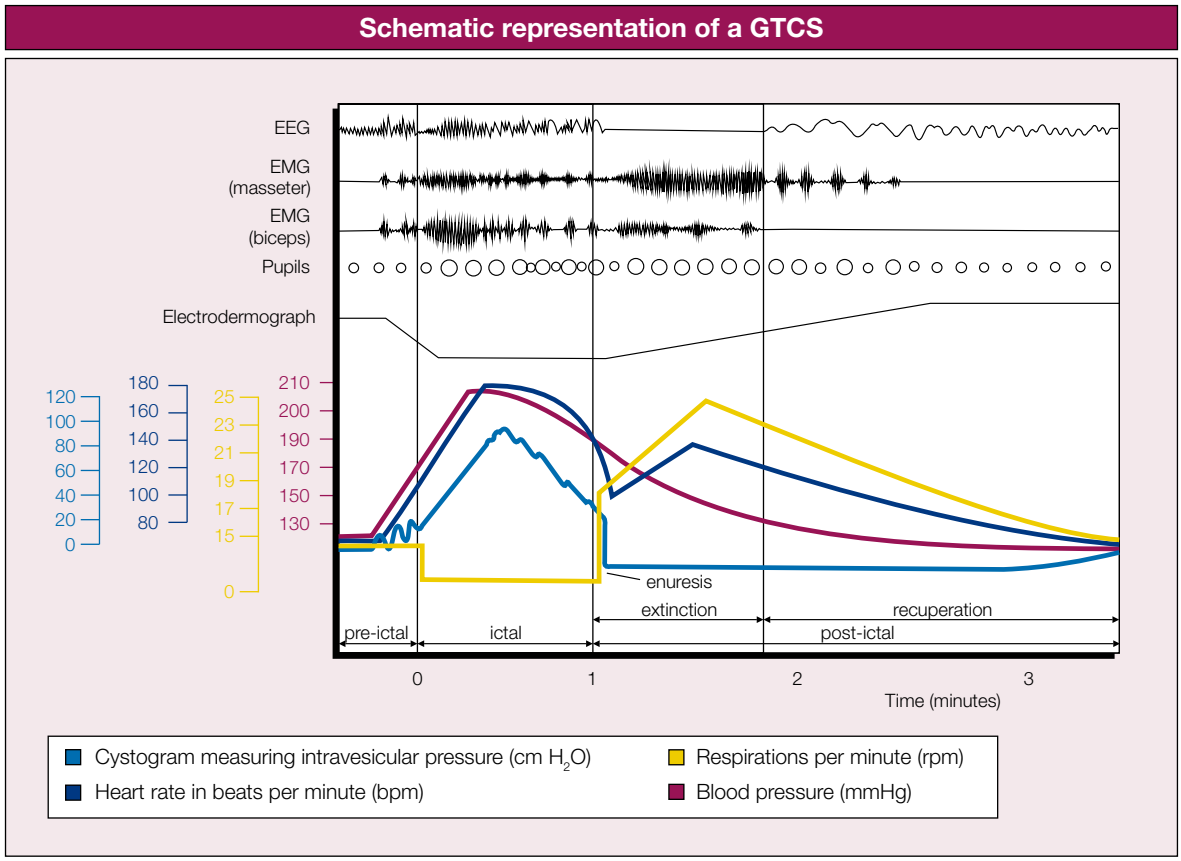

Figure 2.3 *Modified with permission from the classic monograph of Gastaut and Broughton (1972).*[10]

this post-ictal state. Pupillary and cutaneous reflexes are absent, deep tendon reflexes are often exaggerated and the Babinski sign is elicited in half the patients. Unilateral pyramidal signs indicate SGTCSs of contralateral cortical onset.

Late post-ictal phase of GTCSs: This period of recovery is characterised by a gradual return to normality. Autonomic nervous system function normalises and pupillary, cutaneous and tendon reflexes reappear, but muscle atonia persists. Reactivity to pain stimuli returns. Cognitive functions also return to normal, but confusion and automatisms may initially be marked (post-ictal epileptic automatisms). The patient is extremely tired and drowsy and goes into a deep and lengthy sleep if left undisturbed. On awakening the patient feels exhausted, usually complaining of severe throbbing headache and with complete retrograde amnesia. The usual duration of the late post-ictal phase (not including the sleep period) is 2–10 min.

Upon full recovery, the patients are totally amnesic of what happened during the GTCS and most of the post-ictal state. However, they are aware that something happened to them mainly because of the memory gap, aching muscles and traumas.

Autonomic changes of GTCS

Significant autonomic changes occur from the onset of a GTCS; they reach their peak at the end of the tonic phase and progressively improve with the onset of the clonic phase. Some continue in the immediate post-ictal phase and return to baseline normal function in the late post-ictal phase (see Figure 2.3 for their sequence). Apnoea is prolonged,

Onset and sequence of a GTCS

Pre-ictal: In this example the patient is relaxing in bed and eyes are closed

Initial stage of tonic phase in flexion

The eyes open immediately after the onset and remain open during the whole period of a GTCS. They usually close post-ictally. Asymmetrical postures may occur both in PGTCS and SGTCS

Second stage of tonic phase in extension

Immediate post-ictal stage with urinary incontinence

Urinary incontinence occurs in the immediate post-ictal stage and not during the convulsions

Figure 2.4

starting immediately after the epileptic cry, and lasts throughout the entire tonic and clonic phases and, occasionally, into the initial post-ictal period. Heart rate and blood pressure increase markedly to double their pre-seizure values (Figure 2.3). Bladder (intravesicular) pressure increases sixfold, but urinary incontinence is prevented during the convulsions because of tonic contraction of the bladder sphincter muscles.

Urinary incontinence occurs only in the immediate post-ictal phase (Figure 2.4) because of relaxation of the urinary sphincter muscles. It does not occur earlier in the attack.

> It may be doubted whether they [the loss of urine and faeces] are due to epileptic spasm; they may occur after the fit and be due to loss of control.
>
> John Hughlings Jackson (1878)[3]

Pupils dilate in the tonic phase and become unresponsive to light. Hippus (rhythmic pupillary contraction and dilatation) occurs in the clonic phase. Unvarying pupil dilatation occurs again in the immediate post-ictal phase. Skin-colour changes are profound. Cyanosis caused by apnoea-induced hypoxia is apparent in the convulsive stages, whereas pallor becomes apparent in the immediate post-ictal phase. Piloerection is common. Glandular hypersecretion produces marked sweating, hypersalivation and tracheobronchial secretions.

Post-ictal metabolic and hormonal changes[28]

Post-ictal metabolic and hormonal changes occurring immediately after a GTCS last for approximately 1 hour. The most consistent changes are lactic acidosis and the elevation of prolactin and serum creatine kinase levels. Rise of prolactin peaks 20 min post-ictally to 5–30 times the baseline levels and remains significantly elevated for 1 hour.[29]

Important note

Serum prolactin levels are normal in GTC status epilepticus.[29]

Variants of GTCS

It should be emphasised that GTCSs often vary in severity, duration of the tonic and clonic phases, and duration and symptoms of the recovery period. Either the clonic or tonic phase may predominate,

The 'sign 4' position

Figure 2.5

recovery may be very slow or relatively fast, and post-ictal symptoms may be severe or relatively mild. The tonic phase may be brief followed by lengthy clonic convulsions. In children the tonic phase may be longer than the clonic phase. These variants of GTCS are sometimes difficult to differentiate from a genuine tonic or clonic seizure.[10]

Complications of GTCSs[28]

The complications of a GTCS are either from a direct effect of the GTCS manifestations on the body or by accidents occurring as a result. Trauma of differing types and severity is the most likely complication. Skin lesions, aspiration pneumonia, pulmonary oedema and death may occur.

Oral lacerations involving the tongue, lip and cheek occur probably in one out of ten GTCSs.[20] These are more often unilateral than bilateral.

> Placing an object in the patient's mouth to prevent tongue biting is erroneous and causes more harm than good. Mouth closure is so forceful that it can amputate a finger placed between the teeth or break the teeth if the object is metallic.

Craniocerebral trauma is caused by falls. Severe burns may occur while cooking or when falling into a fire. *Stress fractures* as a direct consequence of a GTCS without direct trauma occur in 0.3% of cases and are more common in elderly people. They mainly affect the thoracic and lumbar vertebrae and are usually asymptomatic. More serious fractures may occur. Vertebral compression and other fractures are the main complications during epilepsy monitoring when AEDs are withdrawn.

> An astute orthopaedic surgeon referred a young patient to me with recurrent dislocation of the shoulder during sleep. He was not known to have epileptic seizures but EEG confirmed the diagnosis of IGE.

Skin abrasions and lacerations are caused by external trauma during a GTCS. Skin petechial haemorrhages over the face, neck and chest, as well as conjunctival haemorrhage, are due to capillary bleeding.

Aspiration pneumonia is an uncommon (around 4 of 1600 patients)[30] but potentially life-threatening complication caused by the aspiration of saliva, tracheobronchial secretions or vomiting. It occurs in the post-ictal rather than the ictal phase (when oral secretions are not usually increased and there is cessation of respiratory movements) of a GTCS. The risk for aspiration pneumonia is higher in institutionalised patients and those with swallowing difficulties, increased oral secretions,[30] lowered resistance to infection or depressed airway reflexes from drug or alcohol abuse.

> Positioning the patient in a lateral decubitus position in the immediate post-ictal phase significantly decreases the risk of aspiration.[30]

Pulmonary oedema is rare, but potentially life threatening if untreated. It is usually misdiagnosed as aspiration pneumonia. Its exact pathophysiology is unknown. Pulmonary oedema usually resolves rapidly with oxygen, independent of diuretic use. It is associated with high mortality mainly of older patients.

Death: Accidental (falls, drowning) and non-accidental deaths (aspiration, pulmonary oedema, cardiac arrhythmias, cardiac asystole) may occur during and immediately after a GTCS. Furthermore, the risk of sudden unexplained death in epilepsy (SUDEP) is significantly higher in patients with GTCS than in patients with other types of seizure.[31]

Ictal EEG of GTCSs[10,28]

In routine EEGs the electrical signature of GTCSs is usually masked by muscle artefacts in all derivations, except those from the vertex. Accurate EEG description has been mainly derived from patients who were pharmacologically paralysed at the time of the GTCS.[10]

The ictal EEG discharges of GTCSs are diffuse and generalised with approximately synchronous and symmetrical amplitude on the corresponding areas of both sides.

The patterns of PGTCSs and SGTCSs are virtually indistinguishable from the onset of the tonic phase to the end of the seizure. GTCSs during sleep have EEG patterns that are virtually identical to those of a diurnal attack; they interrupt the electrical activity of the ongoing sleep.

Tonic phase: The ictal EEG onset of the GTCSs is marked by a brief (1–3 s) period of flattening or with low-voltage fast rhythmic activity at about 20 Hz or fast spiking. This gradually becomes more synchronised, increases in amplitude and slows in frequency to a sustained 10 Hz rhythm ('epileptic recruiting rhythm' is the preferred term of Gastaut). See Figure 2.2.

Intermediate phase and clonic phase: Slow waves of increasing amplitude and decreasing frequency superimpose and gradually rhythmically interrupt the 10 Hz fast rhythms of the tonic phase. Finally, the EEG assumes a pattern of repetitive, high-amplitude polyspike–slow-wave complexes that increase in amplitude and slow down to 1 Hz. The clonic convulsions correspond to the polyspikes, whereas the periodic muscle atonia corresponds to the slow waves. See Figures 2.2 and 12.3.

The post-ictal period is characterised by diffuse background suppression (flat or isoelectric EEG) or a burst-suppression or triphasic wave pattern of several seconds to 2 or 3 min (longer in children). This is followed by diffuse slow waves that gradually increase in frequency and amplitude. The periods of coma and confusion and the return to normality correlate fairly well with dominant delta activity, theta activity and the return of a normal alpha rhythm after several minutes. See Figures 2.2 and 12.3.

Surface electromyography (EMG) shows sustained and continuous muscle contraction at around 50 Hz, which corresponds to the tonic phase of GTCSs and is concurrent with the EEG recruiting rhythms. This is followed by repetitive EMG bursts–EMG paucity at the frequency of the slow waves of the intermediate phase and spike–wave complexes of the clonic phase. The EMG bursts correspond to the clonic convulsions. Each slow wave is associated with decrease, then abolition, of muscle tone. See Figure 2.2.

The variants of tonic–clonic seizures have the EEG patterns expected based on clinical grounds. Those with relatively prolonged tonic or clonic phases have correspondingly longer periods of recruiting rhythm or polyspike–wave discharges.

Aetiology of GTCS

Any structural or functional brain abnormality can generate a GTCS, which may be a one-off event or a cause of epilepsy with recurrent GTCSs. GTCSs occur:

- in nearly all types of focal or generalised epileptic syndromes (idiopathic, symptomatic and cryptogenic)
- are the most common type of 'situation-related epileptic seizures', acute symptomatic seizures and often occur in 'diseases frequently associated with epileptic seizures or syndromes'.

GTCSs in epileptic syndromes

PGTCSs are the most serious seizure type of IGEs, and SGTCSs are the most serious seizure type of focal (idiopathic, symptomatic or cryptogenic) epilepsies.

GTCSs in 'situation-related epileptic seizures' and acute symptomatic seizures

PGTCSs and SGTCSs are the most common types among the situation-related epileptic seizures,[13] such as febrile seizures (see Chapter 5), which are a separate category of acute symptomatic seizures.

Acute (provoked, occasional, reactive) symptomatic seizures are epileptic seizures that occur in close temporal association with a transient CNS insult or transient systemic disturbance.[32,33]

These seizures are presumed to be an acute manifestation of the insult. The definition of 'close' varies with the insult.[32,22]

Most of the acute symptomatic seizures are PGTCSs or SGTCSs, and their major causes are:

- structural CNS lesions due to any type of infection, brain trauma, cerebrovascular disease, primary or metastatic CNS tumour
- metabolic or toxic systemic dysfunction, such as acute toxic insults due to poisoning or drug overdose, alcohol or drug withdrawal, eclampsia, metabolic disorders or an electrolyte imbalance (such as uraemia, hyponatraemia, hypocalcaemia, ketoacidosis and hypoglycaemia).

In certain brain disorders, such as encephalopathies, there is a combination of metabolic dysfunction and structural abnormalities.

Each type of acute symptomatic seizure has age, gender and time period patterns that reflect the occurrence of the underlying cause. Meningitis, encephalitis, dehydration and toxic encephalopathy predominate in children. Stroke, brain haemorrhage, infection, trauma and degenerative disease, such as dementia, are the main causes in the elderly.[34]

The aetiological spectrum of acute symptomatic seizures in resource-poor countries (CNS infections, dehydration and acute diarrhoea account for a significant number of cases) is different[35] from that described in developed countries (cerebrovascular disorders predominate).

Pathophysiology

The pathophysiology of GTCSs is not precisely known, as also indicated by the ILAE Core Group report,[14] which raises more questions than answers:

GTCSs involve brain stem, possibly prefrontal, and basal ganglia mechanisms. Ictal initiation of primarily bilateral events are predominantly disinhibitory, but other mechanisms are responsible for ictal evolution to the clonic phase, involving gradual periodic introduction of seizure-suppressing mechanisms. Several discrete types might be identified – future investigation is needed to determine which of these types represent unique phenomena:

- reactive GTCSs (acutely provoked seizures)
- GTCSs of idiopathic epilepsies
- GTCSs of symptomatic epilepsies
- GTCSs evolving from myoclonic seizures (e.g. clonic–tonic–clonic seizures in JME and epilepsy with myoclonic–astatic seizures)
- GTCSs evolving from absence seizures.

And several questions can be raised:

Do patients with idiopathic focal epilepsies have primarily as well as secondarily seizures? Some data suggest that GTCSs in benign childhood epilepsy with centrotemporal spikes are secondarily, although some patients with this condition may have PGTCSs as well.

What are clonic–tonic–clonic seizures? Are GTCSs that evolve from myoclonic seizures the only form, or are there also true clonic–tonic–clonic seizures (as may be seen in forms of progressive myoclonus epilepsy)?

How should we regard hemi-seizures that manifest unilaterally in the immature brain owing to poor myelinisation of the corpus callosum? In this case, the disorder is bilateral, but the onset is clearly unilateral. Do these only occur in infants, or do they also occur in children and adults? In some infants, hemi-seizures have focal onset.

Some experimental evidence suggests that the mechanisms of ictal initiation could be different for some or even all of these subtypes of GTCSs, and that there may even be more than one mechanism of initiation within each of the subtypes.[14]

The pathophysiology of the various stages of GTCSs

Gastaut attributed 'the entire GTCS to be a diffuse subcortical reticular discharge which leads to activation of inhibitory systems and, at the end of the seizure, to a transient post-ictal state of cortical depression'.[10]

Theories of the synchronous and bilateral nature of generalised discharges associated with absence seizures and GTCSs (Figure 2.6)

The centrencephalic, corticoreticular and cortical theories that have been proposed explain the synchronous and bilateral nature of the generalised discharges associated with absence seizures, GTCSs and loss of consciousness. The analysis of these theories by their main protagonists can be found in the classic book *The Physiopathogenesis of the Epilepsies*.[36] See also more recent reviews in the literature.[37,38]

Animal and human data suggest that the various types of generalised epileptic seizures involve selective networks (while sparing others) that engage in abnormally synchronous and high-frequency neuronal oscillation.

The pathophysiology of absence seizures is better understood than that for any other type of generalised seizures (Figure 2.6).[38–41] It appears that the generalised discharges of spikes and waves associated with absence are generated and sustained by highly synchronised abnormal oscillations between thalamic and cortical networks, which mainly involve neocortical pyramidal cells of predominantly mesial frontal cerebral cortex, the reticular thalamic nucleus and the relay nuclei of the thalamus. Neither the cortex

nor the thalamus alone can sustain these discharges, indicating that both structures are involved in their generation. However, their primary neurocellular and neurochemical abnormality is still debated, with evidence and arguments for the primary role of either the cortex[42] or the thalamus.[43] More recently, it has been suggested that seizure activity from an epileptic focus within the perioral region of the somatosensory cortex generalises rapidly over the cortex. During the first cycles of the seizure, the cortex drives the thalamus, whereas thereafter the cortex and thalamus drive each other, thus amplifying and maintaining the rhythmic discharge.[37]

The basic intrinsic neuronal mechanisms involve low-threshold T-type calcium currents. $GABA_B$ receptors play the most prominent role by eliciting the long-standing hyperpolarisation needed to drive low-threshold calcium channels for the initiation of sustained burst firing. Thus, the generation of absences is due to a predominance of inhibitory activity (mainly $GABA_B$), in contrast to generalised or focal convulsive seizures in which an excess of excitatory activity is present.[44]

The pathophysiology of GTCSs is different to that of absence seizures, but there may be a similar interplay of oscillations in networks intensely involving, not the whole brain homogeneously, but rather the focal bilateral regions most intensely, especially the frontal and parietal association cortex, thalamus, basal ganglia and brain stem.[40,51,52] Some other cortical regions appear to be relatively spared, or at least less intensely involved.[47] The cerebellum may also play a role in GTCS termination and post-ictal suppression.[53]

In mammals, there are two sets of convulsive seizure circuitry: the forebrain and brain-stem seizure circuitry. In humans, focal seizures correspond with

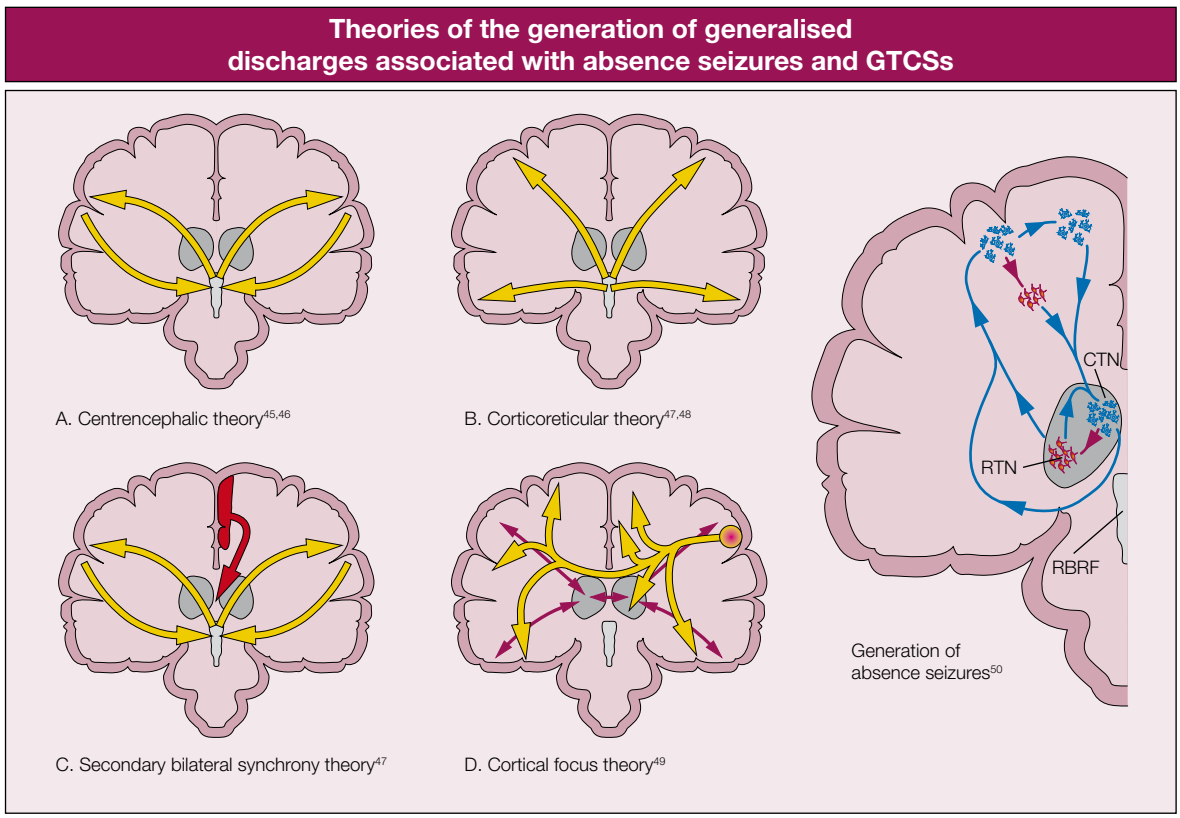

Figure 2.6 CTN, corticothalamic neurones; RTN, reticular thalamic nucleus; RBRF, rostral brain-stem reticular formation.

those of the forebrain circuitry, GTCSs with those of the brain-stem circuitry and SGTCSs with forebrain seizures that secondarily evoke brain-stem seizures.[54] The clinical and electrophysiological manifestations of GTCSs (including initiation, continuation and termination) in humans closely resemble generalised brain-stem seizures in genetically epilepsy-prone rats (GEPR) and *Papio papio*.[54]

Advanced functional neuroimaging techniques have been used in the study of spontaneous GTCSs of patients with epilepsy[51,55] or GTCSs induced by electrotherapy in psychiatric patients.[51] On the basis of their findings, Blumenfeld, *et al*[51] proposed a model in which GTCSs involve the cortical regions of seizure onset and selective bilateral regions of seizure propagation. Corresponding subcortical networks are also involved, whereas other cortical regions may be relatively spared or even inhibited during seizures. The behavioural manifestations of GTCSs can be explained by selective abnormal regional cortical excitation and inhibition, together with the involvement of brain-stem networks.[51]

Generalised tonic seizures

Generalised tonic seizures are convulsive attacks of sustained muscular contractions only, without clonic components. They usually last a few seconds (>2 s to 10 s) but sometimes minutes and thus they are of longer duration than myoclonic jerks (under a tenth of a second) and epileptic spasms (0.2–2 s). The tonic seizures differ from the tonic convulsions of GTCS, which occur in continuity with the subsequent clonic convulsions. In addition, the mechanism responsible is probably different to that of the tonic phase of GTCS.

Prevalence is high, because generalised tonic seizures frequently occur in a variety of common epileptic syndromes affecting neonates, infants and children.

Aetiology: The aetiology of generalised tonic seizures is mainly symptomatic.

Clinical manifestations

Tonic seizures usually have an abrupt onset, may be symmetrical or asymmetrical, and may be inconspicuous or violent. Concurrent autonomic manifestations including apnoea may be prominent. Consciousness is impaired. Focal and asymmetric signs of head or eye deviation may occur. In Lennox–Gastaut syndrome, tonic seizures occur more often during slow non-rapid eye movement (REM) sleep (hundreds of times in some patients) than in states of wakefulness; they do not occur during REM sleep.

Tonic seizures are descriptively classified as:

Axial tonic seizures affect the facial, neck, trunk, paraspinal, respiratory and abdominal muscles, either alone or in combination. Symptoms include raising the head from a pillow, elevation of the eyebrows, opening of the eyes, upward deviation of the eyeballs, opening of the mouth and stretching of the lips to a fixed smile. An 'epileptic cry' is common at the onset of attacks.

Axorhizomelic tonic seizures are axial seizures that also involve the proximal (rhizomelic) muscles of the upper and less often the lower limbs. Elevation and abduction or adduction of the upper limbs and shoulders occur together with the other symptoms of axial tonic seizures.

Global tonic seizures are axorhizomelic seizures that also involve the distal part of the limbs. The arms are forced upwards, abducted and semiflexed with clenched fists. The lower limbs are forced into triple flexion at the hip, knee and ankle or into extension. Global tonic seizures often cause forceful falls and injuries.

Tonic seizures are precipitated/facilitated by sleep. Startle-induced tonic seizures may be of focal origin.

Aetiology

The aetiology of generalised tonic seizures is mainly symptomatic. Tonic seizures are the most common type of seizure (80–100%) in Lennox-Gastaut syndrome. They are exceptional or do not occur in epilepsy with myoclonic–astatic seizures or IGE.

Diagnostic tests

Interictal EEG is grossly abnormal with frequent runs of fast rhythms and spikes mainly in non-REM sleep and also slow spike–wave discharges.

Ictal EEG comprises low-voltage accelerating fast paroxysmal activity that may be: (a) very rapid (20 ± 5 Hz) and progressively increasing in amplitude from low to 50–100 μV; and (b) rhythmic discharge

of around 10 Hz similar to that of the tonic phase of GTCS. Generalised tonic seizures usually correlate with the burst component of the burst-suppression pattern. *Brain imaging and other tests* are necessary, because most tonic seizures are symptomatic.

Differential diagnosis

Generalised tonic seizures should be differentiated from epileptic spasms, myoclonic attacks, other seizures manifesting with combined tonic, clonic and other symptoms, and focal tonic seizures. Conditions that may mimic tonic seizures include hyperekplexia, dystonia and repetitive sleep starts in neurologically impaired patients, and benign non-epileptic myoclonus in infancy.

Management

Treatment with any AED is often disappointing (see Lennox-Gastaut syndrome). Callosotomy may be the last resort.

Generalised clonic seizures

Generalised clonic seizures, by definition, manifest with bilateral rhythmic clonic convulsions only. Their duration varies from minutes to hours but each clonic event lasts < 100 ms at a rate of 1–3 Hz (Figure 12.3). The generalised clonic seizures differ from the clonic convulsions of GTCS, which occur in continuity with the preceding tonic convulsions. They also differ from other types of seizure that manifest with tonic components mixed with myoclonus (e.g. eyelid myoclonia) or absence (e.g. myoclonic absence seizures in which the myoclonic component is rhythmic at 2.5–4.5 Hz, is clonic rather than myoclonic and has a tonic component). The mechanisms responsible for generalised clonic seizures (rhythmic excitatory discharges) are probably different from those in the clonic phase of GTCS (phasing in of seizure-suppressing mechanisms). Clonic seizures should also be distinguished from myoclonic seizures; clonic seizures are rhythmic at 1–5 Hz, whereas myoclonic seizures are singular or irregular recurrent events. Thus, the ILAE defines clonic seizures as 'rhythmic myoclonus' at a frequency of about 2–3 Hz.[11]

According to the ILAE Task Force,14 generalised clonic seizures are: "fast rhythmic events (1–2 Hz), associated, or not, with impaired consciousness" and proposes that their "mechanisms are different from those of the clonic phase of GTCS. In the latter, the clonic phase represents the phasing in of seizure-suppressing mechanisms, whereas in clonic seizures, the repetitive discharges appear to be due primarily to rhythmic excitatory discharges."[14]

Prevalence: Isolated generalised clonic seizures (without the preceding tonic phase of GTCS, or the clonic-absence or clonic/tonic complex) are rare. They are reported in neonates and infants (but are often of focal onset), progressive myoclonic epilepsies (but may be myoclonic jerks with rhythmic or pseudo-rhythmic occurrence) and hemiconvulsions (which are not generalised seizures).

Clinical manifestations

Clonic seizures may cause:

- repetitive rhythmic flexion and extension
- repetitive rhythmic contraction and relaxation of the affected muscles.

In neonates and infants, generalised clonic seizures may appear as more or less rhythmically repeated, bilateral clonic contractions, distributed more or less regularly throughout the entire body and associated with loss of consciousness and massive autonomic symptoms and signs. Clonic seizures are associated with the loss, or severe impairment, of consciousness. Exceptionally, bilateral clonic convulsions of the upper extremities may occur without clouding of consciousness; however, in these cases, there are no EEG generalised spike–wave discharges and the seizures originate in the supplementary motor area. Also, some children with benign myoclonic epilepsy of infancy may have generalised clonic seizures exclusively during sleep or on awakening, which are prolonged (up to 15–20 min) and can cause cyanosis without loss of consciousness.

Aetiology

The aetiology is usually symptomatic. Generalised clonic seizures alone are not specific to any syndrome.

Diagnostic tests

Interictal EEG can range from normal to grossly abnormal.

Ictal EEG: Each clonic convulsion corresponds to a generalised discharge of spike and multiple spikes or, more rarely, a mixture of rapid rhythms and slow waves.

Brain imaging and other tests are needed to detect the underlying pathology.

Differential diagnosis

The main problem is to differentiate clonic seizures from myoclonic seizures and from seizures manifesting with clonic convulsions in continuity or together with tonic, absence and myoclonic manifestations. In early childhood and the epileptic encephalopathies, GTCS may appear only as generalised clonic convulsions, in which the preceding tonic phase is brief and inconspicuous.

Management

Pure generalised clonic seizures probably require AEDs that are suitable for generalised seizures. Phenobarbital may be preferred in neonates.

Epileptic spasms[56,57]

Synonyms: infantile spasms, salaam spasms.

Epileptic spasms are seizures that may be generalised, focal, or of unclear onset.[19]

Epileptic spasms are sudden and brief bilateral tonic contractions of the axial and proximal limb muscles with abrupt onset and termination (Figure 10.1). They usually last for around 1 s (range 0.2–2 s) and thus they are of longer duration than myoclonic jerks (<0.1 s) but of shorter duration than tonic seizures (usually 2–10 s) (Figure 2.8).

Prevalence of epileptic spasms must be higher than that of West syndrome (which is around 0.5/1000 babies), because they also have other aetiologies.

Clinical manifestations

The most common and characteristic form of epileptic spasms is with West syndrome but epileptic spasms may also occur in older children with epileptic encephalopathies (see Chapter 10).

Epileptic spasms are usually symmetrical and may involve widespread muscle groups or only the neck (bobbing of the head or grimacing), abdomen (mild bending) or shoulders (a shrug-like movement). Lateralising features may occur. Subtle epileptic spasms may appear as episodes of yawning, gasping, facial grimacing, isolated eye movements and transient focal motor activity. The more common form manifests with moderate flexion of the hips, the upper trunk and the head. The arms are almost always involved, being abducted, elevated and in a semi-flexed position. The force is usually violent but may also be mild or intermediate. Falls are common. Alteration and pauses of respiration during the spasms are common (60%) while changes in heart rate are rare. The end of the attack is often followed by a cry or laughter. Post-ictally, there may be a brief (< 90 s) arrest of motion and responsiveness. On rare occasions, this 'arrest' constitutes the entire seizure. Epileptic spasms usually occur in clusters, often on awakening.

Spasms may be flexor, more often flexor-extensor and less frequently extensor (see West syndrome page 276).

Epileptic spasms are precipitated by the half-awake state before sleep or after waking, sudden loud noises, tactile stimulation and feeding, but not by light.

Aetiology

Epileptic spasms may be idiopathic or cryptogenic, but is mainly symptomatic. Epileptic spasms are seen in West syndrome and young children with epileptic encephalopathies. Reversible causes include drugs such as theophylline and ketotifen.

Diagnostic tests

Interictal EEG shows hypsarrhythmia, modified hypsarrhythmia or the slow waves of the epileptic encephalopathies.

The ictal EEG is heterogeneous. The most common pattern is an electrodecremental event. A high amplitude, biphasic, slow wave or spike and wave activity may occur.[58,59]

Brain imaging and other tests are usually necessary.

Differential diagnosis

Includes exaggerated startle responses, 'colic and abdominal pain', non-epileptic episodic disorders, gastro-oesophageal reflux and benign myoclonus of early infancy or Fejerman syndrome (See Chapter 4).

Management

Treatment comprises vigabatrin, adrenocorticortricotrophic hormone and corticosteroids. See also West syndrome (Chapter 10, page 283).

Myoclonus

There is no generally accepted, precise definition of 'myoclonus' and there is a long-standing source of confusion and debate about the term and concept of epileptic and non-epileptic 'myoclonus'.[60–62] 'Myoclonus' is a descriptive term for heterogeneous phenomena such as 'sudden brief jerk caused by involuntary muscle activity', 'quick muscle regular or irregular jerks', 'a sudden brief, shock-like muscle contraction arising from the central nervous system', and 'abrupt, jerky, involuntary movements unassociated with loss of consciousness'.

Myoclonus is probably best defined as sudden jerks typically lasting 10–50 ms, with the duration of movements rarely longer than 100 ms (Figure 2.7).[63]

The ILAE definition for myoclonus[2,14] is:

> *Myoclonic (adj.); myoclonus (noun):* sudden, brief (<100 ms), involuntary, single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).[2]

Description of myoclonus

Myoclonic jerks are shock-like, irregular and often arrhythmic, unidirectional, clonic, twitching movements that are singular or occur in irregular clusters. They are of variable amplitude, force, location, duration, precipitating factors and circadian distribution.

Myoclonic jerks may be:

- focal, segmental, multifocal or generalised
- mild, causing minor and inconspicuous flickering, or massive with traumatic falls
- rhythmic, arrhythmic or oscillatory (often resembling a very fast tremor)
- spontaneous, reflex (photic, acoustic, somatosensory, reading) or action (movement or intention to move) induced
- related to sleep, awakening or alert stages
- brief bursts or repetitive and continuous for hours and sometimes for days.

Classification of myoclonus[62–66]

Myoclonus may be:

- a normal (physiological) phenomenon such as hiccups (singultus) or hypnagogic jerks (sleep starts)
- an abnormal (epileptic or non-epileptic) symptom of a wide range of different disorders with regard to aetiology, semiology, nosology, pathophysiology and prognosis.

The two main classification systems of myoclonus are based on aetiology (Table 2.5) and physiology (Table 2.6).

Epileptic myoclonus

There are various definitions of what epileptic myoclonus is: 'myoclonus is termed epileptic when it occurs in combination with cortical epileptiform discharges. In some cases, the latter may be demonstrated only by the technique of back-averaging'[64] or 'myoclonus is epileptic, when generated in the cortex, and non-epileptic, when generated in subcortical structures'. Others prefer indirect definitions such as 'epileptic myoclonus is the presence of myoclonus in the setting of epilepsy'[62] or 'myoclonic seizures are epileptic seizures in which the motor as well as the main manifestation is myoclonus'.[62]

I propose the following definition of epileptic myoclonus, which is in compliance with the current ILAE definition of an epileptic seizure:

> Epileptic myoclonus is a transient (<100 ms) involuntary single or multiple muscle jerk due to abnormal excessive or synchronous neuronal activity in the brain.[1]

Myoclonic seizures are briefer than tonic seizures and epileptic spasms (Figure 2.7). According to the recent ILAE report:[14]

Myoclonus versus clonic, tonic, atonic seizures and epileptic spasms

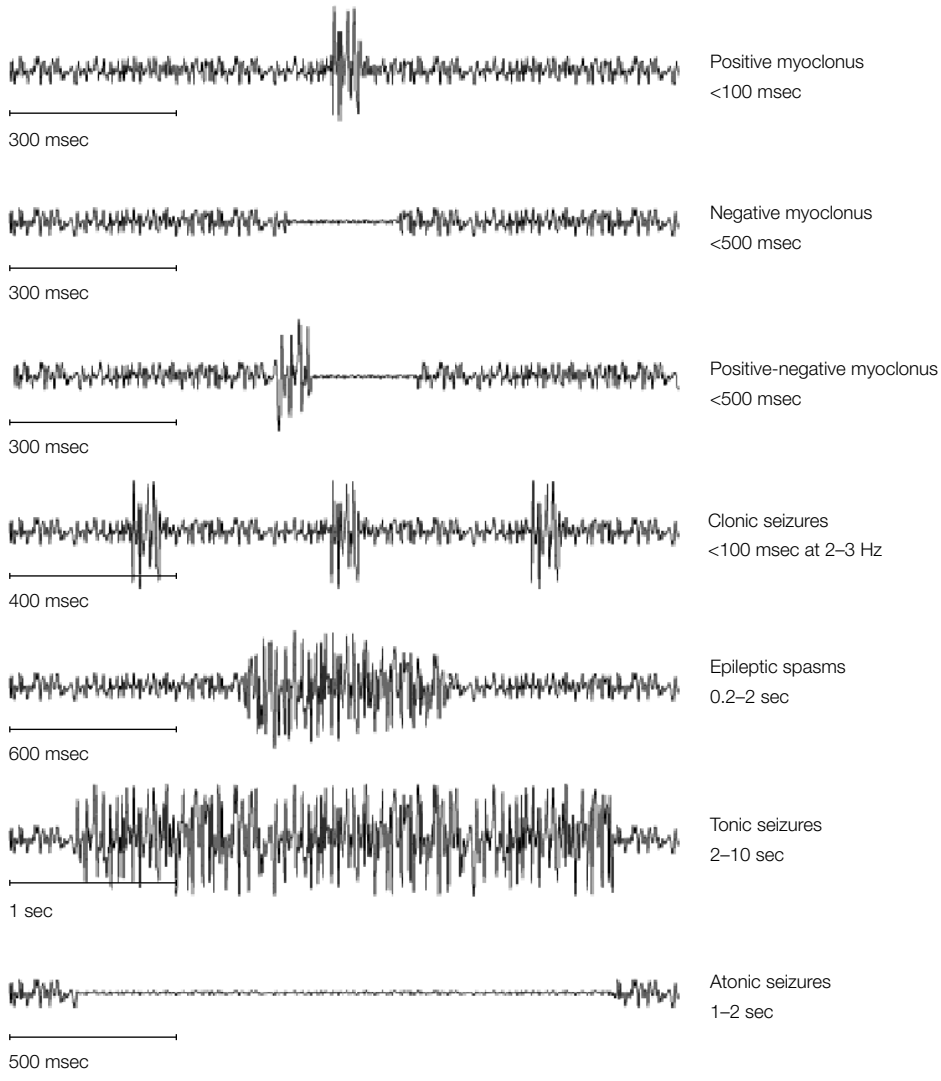

Figure 2.7 Illustrative EMG presentation of positive and negative myoclonus, clonic, tonic and atonic seizures and epileptic spasms.
Reproduced with permission from Panayiotopoulos (2006).[23]

The distinction between myoclonic seizures and clonic seizures is not clear. Classically, clonic seizures are rapid rhythmically-recurrent events, whereas myoclonic seizures are single, or irregularly recurrent events. The prototype of generalized myoclonic seizures are those occurring with JME. These are typically bilateral and symmetrical, but localized reflex myoclonus can also occur. The slowly rhythmic events of subacute sclerosing panencephalitis (SSPE) used to be considered epileptic myoclonus but are more accurately epileptic spasms, those with biPEDs (bilaterally synchronous periodic lateriliziing epileptiform discharges) in comatose patients also are not necessarily epileptic, and their cause is usually not clearly defined. Differential

diagnosis between myoclonic and clonic seizures can be difficult because a single jerk can be a fragment of a clonic seizure.

Working groups will be convened to specifically evaluate myoclonic epileptic phenomena, including negative myoclonus and atonic seizures, compare them with non-epileptic myoclonic phenomena, and develop uniform criteria and terminology for these diagnoses.[14]

The epileptic myoclonus may be:

- generalised such as myoclonic jerks in JME (Figure 2.8)
- segmental such as eyelid myoclonia in Jeavons syndrome
- focal such as epilepsia partialis continua (EPC) of Kozhevnikov or jaw myoclonus of idiopathic reading epilepsy
- the only manifestation of an epileptic seizure, as in the above examples
- one component of an epileptic attack combining in continuity with another type of seizure such as myoclonic–atonic seizures, myoclonic absence seizures, myoclonic tonic–clonic seizures.

Epileptic myoclonus is commonly accompanied by generalised EEG discharges of mainly polyspikes, as in the generalised epilepsies. However, the ictal EEG may show focal abnormalities only (idiopathic reading epilepsy) or be entirely normal, requiring documentation with jerk-locked back-averaging techniques.

The cause of epileptic myoclonus may be idiopathic, cryptogenic or symptomatic.

Epileptic negative myoclonus[2,64,68]

Most myoclonic jerks are caused by abrupt muscle contraction (*positive myoclonus*), but similar jerks are sometimes caused by sudden cessation of muscle contraction associated with a silent period in the ongoing EMG activity (*negative myoclonus*).

Aetiological classification of myoclonus, including its multiple and heterogeneous causes[62,65]

- Physiological myoclonus (normal myoclonus)
- Essential myoclonus (idiopathic and often of autosomal dominant inheritance)
- Epileptic myoclonus
- Symptomatic myoclonus

Symptomatic causes are more common and include post-hypoxia, toxic–metabolic disorders, reactions to drugs, storage disease and neurodegenerative disorders

Table 2.5

Physiological classification of myoclonus based on presumed locations of its generators[63,66]

- Cortical
- Subcortical*
- Spinal
- Peripheral

Table 2.6 *Some authorities also consider thalamocortical and reticular reflex myoclonus as belonging in this classification (see page 46).

Epileptic negative myoclonus, focal or generalised, is a motor symptom characterised by abrupt and brief (<500 ms) stoppage of muscular activity, not preceded by any enhancement of EMG activity (Figure 2.7).[68]

Negative myoclonus of cortical origin may be associated with an EEG spike or spike–wave complex but it is often difficult to establish exactly the temporal and spatial relationship between the EMG silent period and the associated EEG spike on conventional EEG/EMG recordings.

Epileptic negative myoclonus may originate from various brain areas, including the premotor cortex and the motor cortex, probably depending on aetiology.[64] It occurs in heterogeneous epileptic disorders of idiopathic, cryptogenic and mainly symptomatic origin. Patients may manifest with positive and negative myoclonus in various proportions, either independently or in combination.[63] When both forms of myoclonus occur in combination, the abrupt increase in muscle discharge (positive myoclonus) often precedes the onset of the silent period (negative myoclonus), but occasionally follows its offset.[63] In these cases it is often difficult to determine precisely whether the EEG spike is directly related to the activated or inhibited EMG phase.

Violent myoclonic jerks of the hands associated with typical EEG manifestations

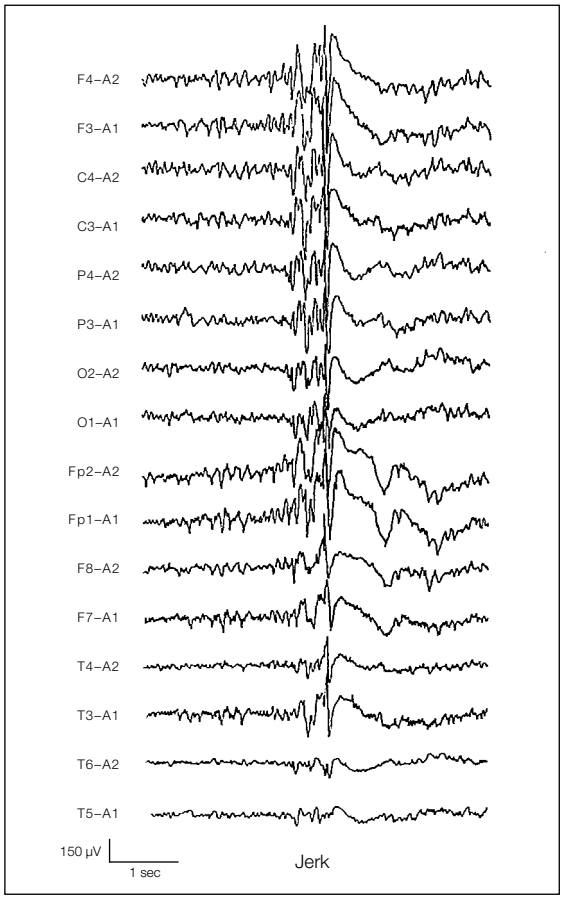

Figure 2.8 *Figure reproduced with permission from Panayiotopoulos,* et al *(1994).*[67]

ILAE classification of epileptic myoclonus

The ILAE classifies myoclonic seizures among generalised epileptic seizures (that simultaneously affect both cerebral hemispheres):[11] '*myoclonic seizures:* includes massive bilateral myoclonus, eyelid myoclonia, myoclonic–atonic seizures, myoclonic absence seizures, negative myoclonus'. Also, in tonic–clonic seizures they 'include variations beginning with a clonic or myoclonic phase'.[11] However, it is also recognised that other types of myoclonus are focal; for example, EPC or reading epilepsy.[7]

The new ILAE report[11] gives the following description for some types of myoclonic-related epileptic seizures:

Myoclonic–atonic seizures: These are characterised by a myoclonic–atonic sequence. Symmetrical myoclonic jerks of the arms or irregular twitching of the face precedes the more or less pronounced loss of tone.[2,69,70]

Myoclonic–astatic seizures: These seizures occur typically in epilepsy with myoclonic–astatic seizures. There is a question about whether the astatic component is an atonic seizure.[14]

Eyelid myoclonia: The degree to which these recurrent events (5 or 6 Hz) are associated with impairment of consciousness has not been adequately documented, but should be. In some patients they can be provoked by eye closure. Nonetheless, the seizure type does exist as a unique entity.[14] See, however, Chapter 16, page 514.

Pathophysiological categorisation of epileptic myoclonus

The ILAE Commission on Pediatric Epilepsy categorised epileptic myoclonus, pathophysiologically, into:[64]

- cortical myoclonus
  - spontaneous cortical myoclonus[63]
  - reflex cortical myoclonus[63]
  - EPC[63]
- thalamocortical myoclonus
- reticular reflex myoclonus
- negative myoclonus.

Cortical myoclonus may be focal or multifocal. Patients with cortical myoclonus commonly have both positive and negative myoclonus, together or independently. Cortical myoclonus is usually more severe than myoclonus of other categories, and patients with cortical myoclonus often develop generalised convulsive seizures.

Myoclonus in progressive encephalopathies is of the cortical type, and EPC is a distinct form of cortical myoclonus.

Thalamocortical myoclonus occurs in:

- IGEs such as benign myoclonic epilepsy of infancy and JME[71]
- myoclonic absence seizures where a combination of positive and negative myoclonus exists; the muscle jerk is associated with the positive component of a spike that precedes its negative transient, whereas negative myoclonus follows the spike by 100 ms, and its onset is before the onset of the slow wave
- Dravet syndrome
- myoclonic–astatic epilepsy.

Myoclonus and epileptic syndromes[64]

Epileptic myoclonus is a common symptom in the following epileptic syndromes:

- IGEs (see Chapter 13)[71,72]
- idiopathic focal epilepsies:[72] idiopathic reading epilepsy is a characteristic syndrome with focal jaw myoclonus (see Chapter 17)
- in idiopathic focal epilepsies such as rolandic epilepsy and Panayiotopoulos syndrome, positive and negative myoclonus may occur in either atypical evolutions or be induced by carbamazepine (see Chapter 12).[73,74] In these situations, atypical myoclonic status epilepticus may occur and consists of continuous unilateral or bilateral contractions of the mouth, tongue or eyelids, positive or negative subtle perioral or other myoclonia, dysarthria, anarthria or speech arrest, difficulties in swallowing, buccofacial apraxia and hypersalivation
- epileptic encephalopathies and congenital non-progressive encephalopathy of various causes (see Chapter 10)[64]
- progressive myoclonic epilepsies (see Chapter 17)[63,64]
- EPC (see Chapter 15).

Atonic seizures[69,70,75,76]

Atonic seizure: A sudden loss or diminution of muscle tone without an apparent preceding myoclonic or tonic event, lasting approximately 1 or 2 s, involving the head, trunk, jaw or limb musculature (Figure 2.7).[2]

Atonic seizures are not synonymous with astatic seizures, which are defined as follows:

Astatic seizure (synonym: drop attack): A loss of erect posture that results from an atonic, myoclonic or tonic mechanism.[2,69]

Thus, an atonic seizure could also be called an astatic seizure, but not all astatic seizures are atonic as they may also be myoclonic or tonic-astatic. Furthermore, atonic seizures are not akinetic seizures. In akinetic seizures there is an inability to perform voluntary movements that is not caused by loss of consciousness (as, for example, in absence seizures) or by loss of muscle tone (as in atonic seizures).

Atonic seizures often occur in continuation with a preceding myoclonic seizure, so-called myoclonic–atonic seizures (see page 49).

Some atonic seizures may manifest solely with atonic symptoms. In others, there is a brief myoclonic or tonic component preceding the atonic manifestations. When these events are very short, they have been referred to as negative myoclonus. Also, a number of seizure types, such as typical and atypical absences, often manifest with atonic symptoms.[14]

Atonic seizures often occur in epilepsies with onset before the age of 5 years and predominate in 'epilepsy with myoclonic–astatic seizures' or epileptic encephalopathies such as Lennox–Gastaut syndrome.

Clinical manifestations[77]

The manifestations of atonic seizures range from falls to only head nodding. Recovery is usually immediate, occurring within 1–2 s.

In falls from the standing position, the patient suddenly flexes at the waist and knees, followed by further knee flexion, and then drops straight down and lands on the buttocks. When sitting, the patient falls forward or backward depending on the position of the centre of gravity. Consciousness is usually intact. However, longer atonic seizures with loss of consciousness do occur; the patient falls down and remains mute and motionless.

Aetiology

Aetiology may be idiopathic, cryptogenic and symptomatic. They predominate in 'epilepsy with myoclonic–atonic seizures' or epileptic encephalopathies such as Lennox–Gastaut syndrome. Atonic seizures also result from acquired central nervous system insults, including those of childhood cancer with uncontrolled seizures.

Diagnostic tests

Interictal EEG is usually very abnormal, as in the epileptic encephalopathies. Ictal EEG reveals brief generalised 2–3 Hz spikes/polyspikes and slow waves. Atonic seizures associate with the slow wave and show sudden interruptions of EMG acivity in the affected musculature (EMG silence). Brain imaging and other testing is as for the epileptic encephalopathies.

Differential diagnosis

The main difficulty is in differentiating atonic seizures from other types of seizure that may cause falls. This often requires polygraphic neurophysiological techniques.

Management

Atonic seizures are very difficult to control. AED treatment usually involves rational polytherapy and may include any agent suitable for generalised epilepsies. Corpus callosotomy may be the only choice for devastating atonic seizures with traumatic falls.

Typical absence seizures[39,71,78]

Typical absences (previously known as petit mal) are brief (lasting seconds) generalised epileptic seizures of abrupt onset and abrupt termination. They have two essential components:

1. a clinical component manifesting with impairment of consciousness (absence)
2. an EEG component manifesting with generalised spike–slow-wave discharges of 3 or 4 Hz (>2.5 Hz).[11,78]

The absence seizures are fundamentally different and pharmacologically unique compared with any other type of seizure, which also makes their treatment different.[78]

> The term 'typical' is used not to characterise them as 'classic', but to differentiate them from 'atypical' absence seizures.

The clinical and EEG manifestations of typical absences are extensive and syndrome related (Figure 2.9).

Impairment of consciousness may be severe, moderate, mild or inconspicuous (and special cognitive testing may be required to detect it). It is often associated with other concomitant symptoms, such as myoclonia, automatisms or autonomic disturbances. Myoclonia may be rhythmic or random, mild or severe, regional (mouth or eyes) or widespread (head, limbs and trunk).

Typical absences are predominantly spontaneous, although they are precipitated by hyperventilation in around 90% of untreated patients. Other specific modes of precipitation include photic, pattern, video games and thinking (reflex absences).

The ictal EEG consists of generalised discharges with repetitive and rhythmic 3 or 4 Hz single or multiple spike–slow-wave complexes. These generalised spike–wave discharges (GSWD) may be brief (sometimes <3 s) or long (≥30 s), and continuous

Examples from video-EEG-recorded generalised discharges of 3-Hz spikes or polyspikes and waves of typical absence seizures

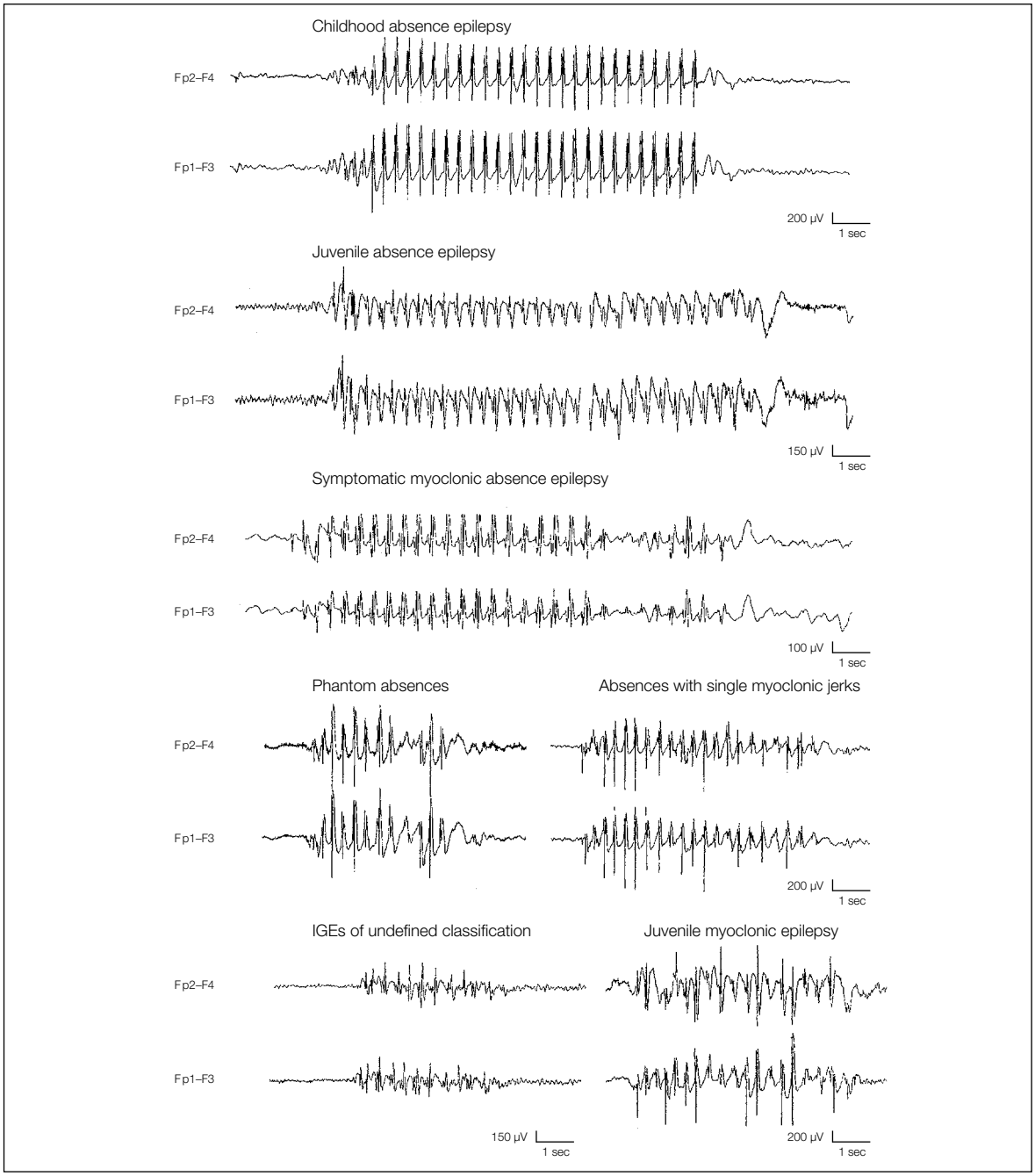

Figure 2.9 These seven patients had different syndromes of idiopathic and symptomatic absence epilepsies. Note that the GSWD may be brief or prolonged, with or without polyspikes and of regular or irregular sequence. Also, note that the intradischarge frequency of the spike–wave complexes may show marked diversity. Although there are significant variations between different syndromes, the GSWD is not itself pathognomonic of any syndrome. The syndromic diagnosis requires homogenous clustering of symptoms and signs.

or fragmented. The intradischarge frequency of the spike–wave may be relatively constant or may vary.

Typical absence seizures in IGE syndromes: Typical absences are severe in childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE), but mild or inconspicuous in other syndromes, such as JME. They may occur alone or in combination with other types of generalised seizures. IGEs with absences may remit with age or be lifelong.

Typical absence status epilepticus occurs in about a third of patients who have typical absence seizures.[79]

Clinical manifestations[11,39,78]

The clinical manifestations of typical absence seizures vary significantly between patients. Impairment of consciousness may be the only clinical symptom, but it is often combined with other manifestations.

Typical absences are categorised as:

- simple absences with impairment of consciousness only
- complex absences when impairment of consciousness combines with other ictal motor manifestations.

Complex absences are far more frequent than simple absences in children. Simple absences are more common in adults. The same patient may have both simple and complex absences.

Absence with impairment of consciousness only: The classic[80] and ILAE[11] descriptions refer to absence seizures with severe impairment of consciousness, such as CAE and JAE:

> Transient loss of consciousness without conspicuous convulsions. A patient stops for a moment whatever he or she is doing, very often turns pale, may drop whatever is in the hand… There may be a slight stoop forward, or a slight quivering of the eyelids… The attack usually lasts only a few seconds. The return of the consciousness may be sudden and the patient after the momentary lapse, may be in just the same state as before the attack, may even continue a sentence or action which was commenced before it came on, and suspended during the occurrence.[80]

The hallmark of severe absence seizures is a sudden onset and interruption of ongoing activities, often with a blank stare. If the patient is speaking, speech is slowed or interrupted; if walking, he or she stands transfixed. Usually the patient will be unresponsive when spoken to. Attacks are often aborted by auditory or sensory stimulation.

In less severe absences, the patient may not stop his or her activities, although reaction time and speech may slow down.

In their mildest form, absences may be inconspicuous to the patient and imperceptible to the observer (*phantom absences*), as disclosed by video-EEG recordings showing errors and delays during breath counting or other cognitive tests during hyperventilation.

Absence with clonic or myoclonic components: During the absence, as described above, clonic motor manifestations, rhythmic or arrhythmic and singular or repetitive, are particularly frequent at the onset. They may be continuous. They may also occur at any other stage of the seizure. The most common manifestations are clonic jerking of the eyelids, eyebrows and eyeballs, together or independently, as well as random or repetitive eye closures. Fast flickering of the eyelids is probably the most common ictal clinical manifestation, and may occur during brief GSWD without discernible impairment of consciousness. Myoclonias at the corner of the mouth and jerking of the jaw are less common. Myoclonic jerks of the head, body and limbs may be singular or rhythmical and repetitive, and they may be mild or violent. In some patients with absence seizures, single myoclonic jerks of the head and, less often, of the limbs may occur during the progression of ictus.

In the so-called *myoclonic absences*, the myoclonic components of these seizures are rhythmic (2.5–4.5 Hz) clonic rather than myoclonic and have a tonic component. "The seizure type should be called something else, but there is no agreement on another name at this time."[14]

Absence with atonic components: Diminution of muscle tone is usual when absences are severe. This manifests with drooping of the head and, occasionally, slumping of the trunk, dropping of the arms and relaxation of the grip. Rarely, tone is sufficiently diminished to cause falls.

Absence with tonic components: Tonic seizures alone do not occur in IGEs. However, tonic muscular contractions are common concomitant manifestations during typical absence seizures. They mainly affect facial and neck muscles symmetrically or asymmetrically. The eyes and head may be drawn backwards (retropulsion) or to one side, and the trunk may arch.

Absence with automatisms: Automatisms are common in typical absences when consciousness is sufficiently impaired, and they are more likely to occur 4–6 s after the onset of GSWD. They do not occur in mild absence seizures irrespective of duration, as, for example, in absence status epilepticus. Automatisms of typical absence seizures are simple and void of behavioural changes. They vary in location and character from seizure to seizure. Perioral automatisms, such as lip licking, smacking, swallowing or 'mute' speech movements, are the most common. Scratching, fumbling with clothes and other limb automatisms are also common. Automatisms can be evoked; passive movements, postural repositioning or other stimuli can change their pattern and distribution.[81]

Absence with autonomic components: Autonomic components consist of pallor and, less frequently, flushing, sweating, dilatation of the pupils and urinary incontinence.

Absences with focal motor components, hallucinations and other manifestations of neocortical or limbic symptomatology: During a typical absence seizure, patients frequently manifest with concomitant focal motor components (tonic or clonic) imitating focal motor seizures. Hallucinations and other manifestations such as concurrent epigastric sensations[82] may occur; these are, in particular, more apparent during absence status epilepticus.[78]

Electroencephalography

The ictal EEG is characteristic with regular and symmetrical 3 or 4 Hz GSWD (Figure 2.9). The intradischarge spike–wave frequency varies from onset to termination. It is usually faster and unstable in the *opening phase* (first 1 s), becomes more regular and stable in the *initial phase* (first 3 s), and slows down towards the *terminal phase* (last 3 s).[81] The intradischarge relationship between spike/polyspike and slow wave frequently varies. The GSWD are often of higher amplitude in the anterior regions.

Duration of the discharges commonly varies from 3 s to 30 s.

The background inter-ictal EEG is usually normal. Paroxysmal activity (such as spikes or spike–wave complexes) may occur. Focal spike abnormalities and asymmetrical onset of the ictal 3 to 4 Hz spike–wave discharges are common.

Pathophysiology of absence seizures

See page 41 and Figure 2.6 for the pathophysiology of absence seizures.

The ILAE Task Force Core Group[14] considers that:

> Although the pyknoleptic manifestations of typical absences in CAE have been suggested to differ by shorter duration from the longer-duration, less frequent absences of JAE, based upon what we currently know, it seems likely that they do not represent two mechanisms, but merely the evolution of a single mechanism as the brain matures. Phantom absences also are likely to be a result of brain maturation. A working group will be convened to study whether absences of CAE and JAE represent two seizure types or a spectrum of the same seizure type, and to better define associated motor components.[14]

Diagnosing absences and differential diagnosis

The brief duration of absence seizures, with abrupt onset and abrupt termination of ictal symptoms, daily frequency and almost invariable provocation by hyperventilation, makes the diagnosis easy.

The differential diagnosis of typical absence seizures with severe impairment of consciousness in children is relatively straightforward. The absences may be missed if mild or void of myoclonic components. Automatisms, such as lip smacking or licking, swallowing, fumbling or aimless walking, are common and should not be taken as evidence

Differential diagnosis of typical absences from complex focal seizures

	Typical absences	Complex focal seizures
Clinical criteria		
Duration <30 s	As a rule	Exceptional
Duration >1 min	Exceptional	As a rule
Non-convulsive status epilepticus	Frequent	Rare
Daily frequency	As a rule	Rare
Simple automatisms	Frequent	Frequent
Complex behavioural automatisms	Exceptional	Frequent
Simple and complex hallucinations or illusions	Exceptional	Frequent
Bilateral facial myoclonic jerks or eyelid closures	Frequent	Exceptional
Evolving to other focal seizure manifestations	Never	Frequent
Sudden onset and termination	As a rule	Frequent
Post-ictal symptoms	Never	Frequent
Reproduced by hyperventilation	As a rule	Exceptional
Elicited by photic stimulation	Frequent	Exceptional
EEG criteria		
Ictal generalised 3 to 4 Hz spike and wave	Exclusive	Never
Inter-ictal generalised discharges	Frequent	Exceptional
Inter-ictal focal abnormalities of slow waves	Rare	Frequent
Normal EEG in untreated state	Exceptional	Frequent

Table 2.7 The primary differences are shown in red.

of complex partial (focal) seizures, which require entirely different management.

The EEG or, ideally, video-EEG can confirm the diagnosis of typical absence seizures in more than 90% of untreated patients, mainly during hyperventilation. If not, the diagnosis of absences should be questioned.

The differentiation of typical absences from complex focal seizures may be more difficult when the motor components of the absence are asymmetrical and in adults in whom absences are often misdiagnosed as temporal lobe seizures (Table 2.7).[83]

Atypical absence seizures[10,84]

Atypical absences are generalised epileptic seizures of inconspicuous start and termination with the following:

- clinical symptoms of mild-to-severe impairment of consciousness (absence), often significant changes in tone with hypotonia and atonia, mild tonic or autonomic alterations
- EEG discharges of slow spike–wave (1–2.5 Hz), which are often irregular and heterogeneous and may be mixed with fast rhythms.[11,78,84] They also innvade limbic areas.[85]

Their duration, determined by EEG changes rather than clinical manifestations, ranges from 5–10 s to minutes. A patient may have few or numerous atypical absences each day.

Atypical absences occur only in the context of mainly severe symptomatic or cryptogenic epilepsies of children with learning difficulties, who also suffer from frequent seizures of other types. They are common in Lennox–Gastaut syndrome, epileptic encephalopathy

with continuous spike and waves during sleep, and epilepsy with myoclonic–astatic seizures.

The differentiation of typical from atypical absence seizures is shown in Table 2.8:

- patients with atypical absences usually have learning disabilities and also suffer from frequent seizures of other types, such as atonic, tonic and myoclonic seizures
- in atypical absences, onset and termination are not as abrupt as in typical absences, and changes in tone are more pronounced
- the ictal EEG of atypical absence has slow (<2.5 Hz) GSWD. These are heterogeneous, often asymmetrical, and may include irregular spike–wave complexes and other paroxysmal activity. Background inter-ictal EEG is usually abnormal.

Clinical tip

In practical terms, a child suspected of typical absences should be asked to overbreathe for 3 min, counting his or her breaths while standing with hands extended in front. Hyperventilation will provoke an absence in more than 90% of those with typical absences. This procedure should preferably be videotaped to document the clinical manifestations. It may reveal features favouring a specific epileptic syndrome and, therefore, may determine the long-term prognosis and management. Video-EEG documentation may be particularly useful if absences prove resistant to treatment, if other seizures develop or for future genetic counselling. Focal spike abnormalities and asymmetrical onset of the ictal GSWD are common and may be a cause of misdiagnosis, particularly in resistant cases. If video-EEG is not available, documentation of absences using a camcorder or modern digital means of recording is recommended.

Main differences between atypical and typical absence seizures

Clinical and EEG features	Atypical absences	Typical absences
Onset and termination	Usually gradual	Abrupt
Responsiveness	Decreased but not abolished	Varies from mild to severe
Changes in tone	Usually pronounced	Usually mild
Duration	Usually long sometimes for minutes	Usually brief; exceptionally >30–40 s
Post-ictal recovery	Cognitive impairment may persist	Immediately
Inter-ictal EEG	Background often abnormal with frequent discharges of various types and combinations	Background usually normal sometimes with typical IGE discharges
Ictal EEG	Slow (<2.5 Hz) spike and wave	Fast (>2.5 Hz) spike and slow wave
Normal neurological and mental state	Exceptional	As a rule
Other types of seizure	Commonly atonic and tonic seizures of symptomatic generalised epilepsies	Depend on IGE syndrome (myoclonic jerks, GTCS or both)
Prognosis	Commonly bad	Commonly good

Table 2.8

Focal epileptic seizures[9–11,86–88]

Focal epileptic seizures emanate from an epileptogenic focus anywhere within cortical and sometimes subcortical brain regions, leading to localisable and asymmetric semiology. 'Epileptogenic focus' or zone refers to a specific network within a circumscribed brain area, from which seizures are initiated; it can range in size from small to large or be widely distributed within one cerebral hemisphere (see page 24). This also applies when focal seizures arise independently in either hemisphere because of regional epileptogenicity, as for example in rolandic epilepsy (see below and chapter 12). Focal seizures may remain entirely localised within the initial epileptogenic focus or propagate and spread to involve (a) networks in other localisations within the same and/or contralateral hemisphere and (b) widespread networks of larger parts of the brain that are involved in the initiation of generalised seizures (secondarily or focal-onset generalised seizures.

Ictal symptoms, particularly at onset, are determined by localisation and not aetiology.

In practice, onset of focal seizures is determined by clinical and EEG manifestations (see page 22). Brain localisation can be identified from (a) an insightful clinical history and (b) skilful assessment of interictal and ictal EEG changes. This is often easy but in other cases can prove very difficult. Furthermore, (a) clinical manifestations may be very subtle in the presence of marked EEG changes and vice versa; (b) the syptomatogenic zone may not be concordant with the epileptogenic zone; and (c) onset of ictogenesis may be from clinically silent localisations.

Let us consider benign childhood focal seizures, which are also a good example of regional epileptogenicity (see also Chapter 12).[89]

- Interictal EEGs are disproportionally severe in relation to clinical manifestations
- Epileptogenicity involves bilateral regional cortical areas which are bi-rolandic in rolandic epilepsy, bi-occipital in idiopathic childhood occipital epilepsy of Gastaut (ICOE-G) and multifocal (bi-frontal, bi-parietal, bi-occipital and bi-temporal) in Panayiotopoulos syndrome (PS).
- Ictal EEG always starts from a localised area of the corresponding region of epileptogenicity; this may be on the right on one occasion or on the left on another occasion in the same patient
- Ictal clinical symptoms may appear shortly after the EEG onsets in rolandic and ICOE-G seizures or after a significant delay in PS.
- The symptomatogenic zone appears to correspond to the epileptogenic zone in rolandic epilepsy (sensory-motor symptomatology of the rolandic cortex) and the ICOE-G (occipital lobe symptomatology), while the autonomic clinical manifestations of PS are likely to be generated by variable and widely spread epileptogenic foci acting upon a temporarily hyperexcitable central autonomic network.
- Ictal clinical symptoms may be subtle and entirely localised (elementary visual hallucinations of ICOE-G, hemifacial sensory-motor symptoms of rolandic epilepsy), or may spread to involve other brain regions within the same or contralateral hemisphere, occasionally initiating a secondarily GTCS.
- Symptomatic focal epileptic seizures may manifest with identical clinical semiology, as exemplified by the visual seizures of ICOE-G and other occipital epilepsies of structural cause.

Focal epileptic seizures and syndromes have been extensively reviewed with regard to clinical manifestations, diagnostic procedures and management in a two-volume issue of "The educational kit on epilepsies". This publication includes numerous EEG and brain imaging illustrations as well as live video-EEG recordings of patients with focal seizures.[87,88]

ILAE terminology and classification of focal seizures

The terminology and classification of focal seizures of the ILAE proposals has been described above and it is given in tables 2.1 and 2.3.

The ILAE Core Group considers that:[14]

(I). The anatomical substrates of a substantial number of focal seizure manifestations has now been sufficiently established to include this information in their description (see Table 2.3).

(II). As focal seizures represent dynamic events that usually involve propagation, and clinical manifestations can reflect discharges at the site of ictal onset, and/or sites of propagation, the organisation of focal seizures in their report takes into account the various patterns of ictal propagation (see Table 2.3).

(III). A number of factors will need to be investigated in order to develop more definitive criteria for distinguishing between different types of focal seizures. These include:

- Factors that might distinguish between focal seizures due to discretely localised lesions, as occur with focal symptomatic epilepsy, and focal seizures due to more distributed network disturbances, as might occur with some focal idiopathic epilepsies (e.g. those responsible for the transverse dipole of the centrotemporal spikes of rolandic epilepsy), or even in IGEs.
- Maturational factors.
- Modes of precipitation, as in reflex seizures.
- Pathology, i.e. focal seizures due to various malformations of cortical development may be different from each other and from those due to other lesions.
- Pathophysiological mechanisms (see pathophysiology below).[14]

The ILAE Core Group[14] provides the following information for the focal seizures listed in Table 2.3 with regard to the factors influencing seizure-induced progressive disturbances in neuronal function and structure at the site of, and downstream from, ictal onset:

Focal onset (partial) seizures

A. Local

1. Neocortical

a. Without local spread

i. *Focal clonic seizures* are brief focal motor events that are distinguished from focal myoclonic seizures by their rhythmic repetition. Localisation to the primary motor cortex is implied.

ii. *Focal myoclonic seizures* most likely consist of many types. These events, including multifocal myoclonus, will be discussed by the ILAE working group on myoclonus. There is no unanimity of opinion as to whether the myoclonic events in progressive myoclonic epilepsy, which have no EEG correlate, are epileptic. At least in Lafora disease, there is evidence to suggest a cortical site of initiation.

iii. *Inhibitory motor seizures* are not a unique seizure type. The clinical manifestation merely represents the function of the involved cortex, just as focal motor seizures and unformed visual hallucinations reflect seizures in precentral gyrus and calcarine cortex.

iv. *Focal sensory seizures with elementary* (visual, somatosensory, vestibular, olfactory, gustatory or auditory) symptoms manifest themselves as a variety of sensory phenomena that can be produced by activation of primary sensory cortices.

v. *Aphasic seizures* can consist of inability to speak when Broca's area is principally involved, or more complex disturbances of speech production or reception when other language cortical areas are principally involved.

b. With local spread

i. *Jacksonian march seizures* refers to the clinical manifestations of the slow ephaptic propagation of epileptic discharge along the motor cortex, although similar progression can sometimes be seen in other primary cortical areas as well.

ii. *Focal (asymmetrical) tonic seizures* can be associated with seizure origin from practically anywhere in the neocortex. In their purest form, focal tonic seizures are seen in the explosive motor seizures of supplementary motor area origin.

iii. *Focal sensory seizures with experiential symptoms* are those with complex, usually

formed, distorted and/or multimodal, sensory symptoms implying seizure initiation in association cortices, such as the temporo-parieto-occipital junction, with connections to multiple sensory areas.

2. *Hippocampal and parahippocampal* seizures almost always require local spread for clinical manifestation, which may involve insula, amygdala, hypothalamus and other limbic structures (Figure 2.1). Autonomic features such as a sensation of epigastric rising is common, as well as emotional experiences such as fear, dysmnesias, focal sensory seizures with olfactory or gustatory symptoms, and vague bilateral sensory phenomena such as tingling.

B. With ipsilateral propagation to:

1. *Neocortical areas (includes hemiclonic seizures)*
   a. Same manifestations as A.1.a and A.1.b.
   b. *Hemiclonic seizures* occur early in development before myelinisation of the corpus callosum and do not necessarily have localising value. They can alternately affect both hemispheres, as in Dravet syndrome and ischaemic encephalopathy, or only one hemisphere in the case of focal disturbances.
2. *Limbic areas*
   a. Same manifestations as A.2.
   b. *Gelastic seizures* are clearly unique ictal events when they are initiated in relation to structural abnormalities of the hypothalamus, which are usually hamartomas. The mechanism is unknown, but initiation, at least, is distinct from gelastic seizures arising from other areas, such as mesial temporal lobe and cingulate.

C. With contralateral spread to:

1. *Neocortical areas (hyperkinetic seizures):* also referred to by some as *hypermotor seizures*, involve bilateral forceful limb movements, sometimes with vocalisations. Frontal lobes are implicated in these behaviours.
2. *Limbic areas: dyscognitive seizures with or without automatisms (psychomotor)* are not exactly synonymous with the current term 'complex partial seizures', which were defined on the basis of impaired consciousness only and do not necessarily involve limbic areas. This new term, as well as the term 'psychomotor', conforms more to the original intent of the term 'complex partial seizures' in the 1970 *ILAE Classification of Epileptic Seizures*. It is implied that mesial temporal limbic areas and their immediate connections are involved in the clinical manifestations, although seizures may have been initiated elsewhere.

D. Secondarily generalised

1. *Tonic–clonic seizures* that are secondarily generalised probably consist of multiple types and may involve different pathophysiological mechanisms and anatomical substrates, at least initially, than GTCSs with generalised onset.
2. *Absence seizures* can rarely represent propagation from localised cortical areas, usually in the frontal lobe. There may be a continuum between these events and generalised atypical absences.
3. *Although epileptic spasms* can occur in infants with focal lesions, the mechanism by which these generalised events are generated is unknown.

Epidemiology

In population-based studies, focal seizures predominate with a median incidence of 30.4 cases/100,000 population/year compared with an incidence of generalised seizures of 19.6 cases/100,000 population/ year. Also, focal seizures predominate in prevalence studies 55–60% (adults) and 36–66% (children).

Clinical manifestations

The clinical manifestations of focal epileptic seizures are detailed in chapters 11, 12, 14 and 15, within focal epileptic syndromes and according to their site of origin and aetiology. It should also be noted that semiology, particularly at onset, is determined by localisation and not by cause.

Aetiology

This may be symptomatic (21.7% of all epilepsies), cryptogenic (21.8%) or idiopathic (9.1%) (Figure 1.5). In children it is much more common for focal epileptic seizures to be idiopathic than symptomatic.

In the elderly, nearly all newly identified epileptic seizures are focal from a symptomatic cause.

Pathophysiology[14,90–92]

Focal epileptogenesis is a multistep process. An initial precipitating injury may predispose to the development of the first seizure. During the latent phase, structural and functional changes occur that may ultimately lead to spontaneously recurrent epileptic seizures in some patients over the course of days to years. At each step of the process, biological and age- or gender-specific factors, and genetic, epigenetic or comorbid conditions, may interfere and modify the course of epileptogenesis.[90]

Neocortical[91] and limbic (mainly hippocampal)[92] seizures have some important differences in their pathophysiology. This reflects anatomical, functional and phylogenetic disparities between them, as well as all other factors involved in ictogenesis from elements within the neurones, synapses, interconnections and their modifications by age, exogenous and endogenous influences and causes of disease. These are beyond the remit of this clinical book.

As the ILAE Task Force emphasised:[14]

"Hypersynchronous ictal onsets most commonly occur in hippocampus while low voltage fast ictal onsets, most commonly occur in the neocortex. These electrophysiological features clearly reflect different pathophysiological mechanisms of seizure initiation, which may not be absolutely correlated with location, and there may be other ictal onset patterns indicative of other initiating mechanisms that have not yet been well described.[14] Also there are differences in neurophysiological properties and anatomical connections unique to specific areas of cortex, e.g. those that cause brief and clustered seizures with little or no postictal disturbances and nocturnal predilection typical of some frontal areas, compared with longer, less frequent events with profound postictal disturbances in other areas, and those that cause fast distant propagation from some areas and localised, slower propagation in others."[14]

Diagnostic procedures

EEG and neuroimaging remain the cornerstones of investigation in the focal epilepsies, as detailed in chapter 7 and in the discussion of the individual focal epileptic syndromes. In view of the high incidence of symptomatic epilepsies, a high resolution structural MRI scan on a scanner with a field strength of at least 1.5 Tesla should now be considered standard practice. Other appropriate tests have been described in page 4 and these include molecular testing when genetic focal epilepsies are suspected (Chapter 14). More elaborate diagnostic procedures including functional neuroimaging, advanced MRI technologies, invasive EEG and magnetoencephalography are used to investigate patients with focal epileptic seizures that may benefit from neurosurgical interventions (page 222).

Prognosis

This largely depends on aetiology and syndromic diagnosis. It varies from purely benign and age-limited (see examples in chapter 12) to very severe and progressive (Chapter 15).

Management

When focal epileptic seizures have been unequivocally diagnosed, the decision of whether they need treatment depends on the underlying aetiology and syndrome and on factors relating to the individual. AED is the mainstay of treatment when the risk of recurrence is high. Currently there are more AEDs for the treatment of focal than generalised epilepsies (see Tables 7.1 and 7.12). These should be used according to the principles detailed in chapter 7 and chapter 15.

Surgical treatment is a life saving option for many patients with pharmaco-resistant focal epilepsy and this should be recommended as soon as possible (Page 222).

Socio-psychological support is part of good clinical practice in the management of all epilepsies.

Reflex epileptic seizures

Reflex epileptic seizures and related syndromes are detailed in Chapter 16.

They are consistently precipitated by environmental or internal stimuli and are differentiated from spontaneous epileptic attacks in which precipitating factors cannot be identified. In individual patients, the precipitating stimuli are usually limited to a single specific stimulus or a limited number of closely related stimuli.

Reflex seizures have a prevalence of 4–7% among patients with epilepsies and may be of the same types as the spontaneous focal or generalised seizures:

- generalised, primarily or secondarily
- focal, simple or complex.

Visually induced seizures and epilepsies are the most common among reflex epilepsies.

In response to the same specific stimulus, the same patient may have absences, myoclonic jerks and GTCSs alone, or in various combinations. Usually, absences and myoclonic jerks precede the occurrence of GTCSs. Patients may have reflex and spontaneous seizures.

Focal seizures are exclusively seen in certain types of reflex focal epilepsy, such as visual seizures of photosensitive occipital lobe epilepsy or complex focal temporal lobe seizures of musicogenic epilepsy.

The role of the EEG is fundamental in establishing the precipitating stimulus in reflex epilepsies, because it allows subclinico-EEGs, or minor clinical ictal events, to be reproduced on demand by application of the appropriate stimulus.

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three

Status epilepticus

Status epilepticus (SE) is a broad term comprising all types of epileptic seizures that fail to stop at their usual time course and that last for over 30 min (Table 3.1).[1]

The duration of an epileptic seizure is the result of a balance between pathophysiologically determined self-initiating, self-sustaining and self-terminating mechanisms. Any seizure that fails to stop at its usual time course becomes unlikely to stop spontaneously and enters into SE because its self-sustaining processes are unopposed by self-terminating mechanisms.

All types of seizure listed in Table 2.1 can enter into SE. Tonic–clonic SE represents a severe form of SE, whereas absence SE is at the opposite mild extreme.

The classical monograph by Shorvon on all types of SE in all ages is highly recommended reading.[2] Nonconvulsive status epilepticus is the theme of a newly published multi-author book edited by Kaplan and Drisdane.[3] The proceedings of the first London colloquium on status epilepticus were published in 2008 in Epilepsia.[4] Animal models of SE are exhaustively covered in the recent book edited by Pitkänen, Schwartzkroin and Moshé.[5] A number of expert multi-author recent reviews of SE have also been published.[6–11] The diagnostic assessment of the child with SE has been the subject of an evidence-based review of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.[12] The European Federation of Neurological Societies has issued a guideline on the management of SE[13]; see also the consensus statement on the drug treatment of status epilepticus in Europe.[14]

Definition and classification

The definition and classification of SE has been the subject of significant and still unresolved debate within and outside the ILAE. In part, this reflects the varied entities included in the term of SE.

The following are proposed definitions of SE:

> A condition characterised by epileptic seizures that are sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition.
>
> WHO (1973)[15]

> A seizure (that) persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur.
>
> ILAE Commission (1981)[16]

> A seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without inter-ictal resumption of baseline central nervous system function.
>
> ILAE glossary (2001)[17]

> A condition in which epileptic activity persists for 30 minutes or more, causing a wide spectrum of clinical symptoms, and with a highly variable patho-physiological, anatomical and aetiological basis.
>
> Shorvon (1994)[2]

My definition would be:

> An epileptic seizure that exceeds its usual time course and becomes unlikely to end spontaneously because self-sustaining processes prevail over self-terminating mechanisms.

Status epilepticus

ILAE Task Force 2001	ILAE Task Force 2006
Continuous seizure types	**I. Epilepsia partialis continua (EPC)**
Generalised status epilepticus	A. As occurs with Rasmussen syndrome
A. Generalised tonic–clonic status epilepticus	B. As occurs with focal lesions
B. Clonic status epilepticus	C. As a component of inborn errors of metabolism
C. Absence status epilepticus	**II. Supplementary motor area (SMA) status epilepticus**
D. Tonic status epilepticus	**III. Aura continua**
E. Myoclonic status epilepticus	**IV. Dyscognitive focal (psychomotor, complex partial) status epilepticus**
Focal status epilepticus	A. Mesial temporal status epilepticus
A. Epilepsia partialis continua of Kozhevnikov	B. Neocortical status epilepticus
B. Aura continua	**V. Tonic–clonic status epilepticus**
C. Limbic status epilepticus (psychomotor status)	**VI. Absence status epilepticus**
D. Hemiconvulsive status with hemiparesis	A. Typical and atypical absence status epilepticus
	B. Myoclonic absence status epilepticus
	VII. Myoclonic status epilepticus
	VIII. Tonic status epilepticus
	IX. Subtle status epilepticus

Table 3.1 *Adapted with permission from Engel (2001)[20] and Engel (2006)[1] of the ILAE Task Force on Classification and Terminology. See also www.ilae-epilepsy.org/Visitors/Centre/ctf/seizure_types.cfm.*

In this definition I consider that SE may not terminate either because self-sustaining processes accelerate or become stronger over self-terminating processes, or that the natural homeostatic seizure-suppressing mechanisms responsible for seizure termination are not activated or are weak. This is different to the view of the ILAE Core Group that 'SE mechanistically represents the failure of the natural homeostatic seizure-suppressing mechanisms responsible for seizure termination'.[1]

There are two main reasons for debate on SE. First, the time length of the transitional point from a seizure to the onset of SE is unknown. This is likely to be different in epileptic seizures that are customarily short for seconds such as in typical absence seizures, or long for minutes such as in the autonomic seizures of Panayiotopoulos syndrome. Second, the pathophysiology of SE, its effect on the brain and the risk to the patient differs significantly among different types of SE. Generalised tonic–clonic SE (GTC-SE), for example, is known to cause significant duration-related neuronal damage, systemic and metabolic disturbances, and endangers the patient's life. The 30-min duration required in the operational definition of SE is meant to demarcate the point at which compensatory mechanisms that prevent brain damage break down in GTC-SE. Conversely, absence SE may not cause any significant disturbances, although it often ends with a GTCS.

Traditionally, SE has been divided into:

- convulsive SE
- non-convulsive SE.

However, this is not correct. Non-convulsive SE is a term that has been rightly discarded in the new ILAE diagnostic scheme, because it encompasses heterogeneous conditions, which may be focal such as limbic SE, or generalised such as absence SE.[1,18] Furthermore, *convulsive* elements and particularly myoclonic jerks are common and may predominate

in generalised *non-convulsive* SE as, for example, in eyelid or perioral SE. If the term 'non-convulsive' is used, the distinction between 'focal non-convulsive SE' and 'generalised non-convulsive SE' should be made for clinical and management purposes.

Generalised convulsive epileptic seizures are broadly divided into:

- primarily or secondarily generalised tonic–clonic seizures (GTCSs)
- primarily or secondarily generalised clonic seizures
- primarily or secondarily tonic seizures
- generalised myoclonic seizures.

Similarly, convulsive SE reflects the above seizure classification:

- primarily or secondarily GTC-SE
- primarily or secondarily clonic SE
- primarily or secondarily tonic SE
- generalised myoclonic SE.

Furthermore, to comply with seizure and syndrome classification, convulsive SE may be 'situation related'[19] and 'not requiring the diagnosis of epilepsy',[20] such as febrile convulsive SE, or caused by the introduction or withdrawal of certain drugs, intoxication or electrolyte or metabolic disturbances. Acute symptomatic convulsive SE may also be caused by severe brain anoxia or other brain damage.

Convulsive SE, whether primarily or secondarily and irrespective of cause, appear to have the same pathophysiology, effect on brain and body, and management requirements for termination. The treatment of convulsive and non-convulsive SE is the same irrespective of cause.[21–26]

Author's note: See important note on page 27 for an explanation of the problems associated with the term 'primary GTCS' instead of 'generalised-onset GTCS'.

The 2001 ILAE diagnostic scheme[20] considered SE to be a 'continuous seizure' (Table 3.1) with two main categories:

- generalised SE
- focal SE.

The new 2006 report of the ILAE Core Group[1] rightly abolishes this previously preferred term 'continuous seizure' (SE may also stop spontaneously or be discontinuous; there was nothing wrong with the term 'status epilepticus'), it provides a list of types of SE and avoids characterising them as focal or generalised. This list is provided in Table 3.1.

In regard to the pathophysiology of SE, the ILAE[1] considers that the mechanisms involved in the initiation and spread of the various types of SE are emerging, although they are still speculative.[27] In general, they are similar to those of self-limited epileptic seizures, but additional factors that need to be considered in determining criteria for classification include:

- different mechanisms that can prevent seizure termination, e.g. mechanisms that prevent active inhibition, desynchronisation of hypersynchronous discharges and depolarisation block
- progressive features that contribute to subsequent functional and structural brain disturbances
- maturational factors.[1]

Generalised tonic–clonic status epilepticus

A GTC seizure becomes a GTC-SE when it enters into a self-perpetuating, self-sustaining process that fails to terminate spontaneously. When exactly this transition occurs has not yet been precisely determined.

GTC-SE consists of continuing GTCSs or a series of GTCSs between which consciousness is not regained and that lasts at least 30 min. The duration of at least 30 min is arbitrary and is set because usually after this time compensatory mechanisms break down, and brain damage and pharmacoresistance occur.[24,27] However, converging evidence indicates that a GTCS of more than 5–10 min is already an early stage of GTC-SE and has the same pathophysiology, risks and management requirements as longer GTCSs of up

to 30 min.[28] For this reason, rescue therapy should start 5 min after the initiation of a GTCS, accepting that a few of these GTCSs would have stopped spontaneously without the use of medication.[27–30] The modified proposed definition for GTC-SE is:

> Generalised, convulsive SE in adults and older children (>5 years old) refers to 5 min or less of (1) continuous seizures or (2) two or more discrete seizures between which there is incomplete recovery of consciousness.[28]

GTC-SE can be an acute symptomatic event, primarily GTC-SE in idiopathic or symptomatic generalised epilepsies, and commonly secondarily GTC-SE in focal epilepsies.[1] Occasionally, the manifestations of GTC-SE can be unilateral.[1]

The convulsions of GTCSs are usually violent but their intensity lessens and fades with time, transforming to a continuous tonic state. This is followed by irregular continuous jerking, which may becomes subtle and consists of only small-amplitude clonic or myoclonic twitching of the face, hands or feet, or nystagmoid eye jerks. Some patients continue with electrographic GTC-SE without conspicuous repetitive motor activity (electroclinical or electromechanical dissociation). Subtle GTC-SE is more likely to last longer than overt GTC-SE. Comatose patients often have subtle GTC-SE from onset.[31]

The ictal EEG[32,33] follows five patterns, which occur in a predictable sequence during the course of GTC-SE:

1. distinct typical features of a GTCS with generalised low amplitude, fast activity in the tonic phase followed by repetitive generalised polyspike–wave discharges (GPSWD) of the clonic phase with a repetition rate gradually slowing from 4 Hz to 1 Hz or less (see page 39 and Figures 2.2 and 12.3)
2. merging seizures with EEG rhythms of waxing and waning amplitude and frequency
3. continuous ictal activity
4. continuous ictal activity punctuated by low voltage 'flat periods'
5. pseudoperiodic lateralised epileptiform discharges (PLEDs) on a 'flat' background.[33]

Subtle SE refers to an end stage of prolonged GTC-SE characterised by focal or multifocal myoclonic movements, coma and PLEDs against a slow, low-voltage background on EEG. The myoclonic movements reflect severe brain damage caused by prolonged SE and may not be epileptic in nature.[1]

Physiological stages of GTC-SE[2,13,34–41]

The stages of GTC-SE reflect pathophysiology, brain and body effects, risks and management. The transition from one stage to another is not clearly demarcated in time and these probably constitute a continuum.

The physiological changes of GTC-SE can be divided into two phases. In the initial phase 1 (compensatory phase), compensatory mechanisms prevent cerebral damage. This is followed after about 30 min by phase 2 (refractory phase) where compensatory mechanisms break down with an increasing risk of brain damage as the status progresses.

Compensatory phase

The compensatory phase of GTC-SE probably begins after 5–7 min from the onset of a GTCS (*impending GTC-SE*) and lasts for around 30 min. In this phase, systemic, autonomic and cerebral physiological changes are prominent (Figure 2.3) but homeostatic compensatory mechanisms are adequate to meet the metabolic demands and prevent brain damage from hypoxia or metabolic aberrations.[2,24]

The major physiological changes are related to the greatly increased cerebral blood flow and metabolism, massive autonomic activity and cardiovascular changes (Figure 2.3 and Chapter 2). Significant sympathetic nervous system overdrive results in an increase in heart rate, blood pressure and glucose levels. Arterial pH sometimes decreases to less than 7 (in 25% of patients) mainly because of lactic acidosis and partly due to respiratory acidosis (rise of carbon dioxide tension). The core body temperature steadily rises and prolonged hyperthermia of above 40°C may ensue. Other sympathetic autonomic changes involve profound sweating, hypersalivation, mydriasis and

bronchial or other hypersecretion. Homeostatic mechanisms to compensate for these changes involve a massive increase in cerebral blood flow with maintained delivery of glucose to active cerebral tissue. The blood–brain barrier and neuronal integrity are intact with little risk of brain damage. However, cardiac arrhythmias, hypotension and cardiovascular compromise may cause pulmonary oedema.

Treatment at this stage is usually successful and prevents associated morbidity and mortality of GTC-SE.

Impending GTC-SE is the earliest part of the compensatory phase of GTC-SE. It is defined as either continuous or intermittent GTCSs lasting less than 5 min, without full recovery of consciousness between seizures.[27,29,30] This definition attempts to recognise:

- the transitional/transformation period from an isolated GTCS to GTC-SE, or in other words the period that self-terminating mechanisms fail to stop a GTCS that then enters the self-sustaining processes of GTC-SE.[27,29,30]
- that patients with a GCTS of greater than 5-min duration should receive rescue treatment, accepting that a few would have had a GTCS that would have stopped spontaneously without treatment.

The reason for using the 5-min criterion is that self-terminating GTCSs last between 1 and 4 min in children (in adults 53–62 s ± SD 14 s) and do not require emergency 'rescue' treatment.[27,29,30] Conversely, approximately 95% of GTCSs that are still ongoing at 7 min will continue for at least 30 min.[42] Therefore, it is likely that a seizure that lasts 5–7 min is pathophysiologically similar to one that lasts 30 min and could be considered to be SE, thus requiring treatment to prevent intractable SE and its consequences (i.e. brain damage and epileptogenesis).[27,29,30]

Refractory stage of GTC-SE (established GTC-SE)

The refractory stage or established GTC-SE starts approximately 30 min after the onset of the compensatory phase,[2,24] although this time may vary.[28]

During this stage, the greatly increased cerebral metabolic demands cannot be fully met, resulting in hypoxia and altered cerebral and systemic metabolic patterns. Autonomic changes persist and cardiorespiratory functions may progressively fail to maintain homeostasis. These changes do not necessarily occur in all cases. Their type and extent depends on aetiology, clinical circumstances and the methods of treatment employed.

Cerebral autoregulation fails. Cerebral blood flow becomes dependent on systemic blood pressure and there is a depletion of energy states and a reduction of brain oxygen, glucose and lactate. Intracranial hypertension and cerebral oedema ensue.

Systemic and metabolic changes involve hypoglycaemia, hyponatraemia, hypokalaemia or hyperkalaemia, metabolic and respiratory acidosis, hepatic and renal dysfunction, consumptive or disseminated intravascular coagulopathy, multi-organ failure, rhabdomyolysis, myoglobulinuria and leucocytosis.

Autonomic and cardiovascular changes involve systemic hypoxia, falling blood pressure and cardiac output, respiratory and cardiac impairment (pulmonary oedema, pulmonary embolism, respiratory collapse, cardiac failure, dysrhythmia), and hyperpyrexia.

In more than 10% of patients treated for GTC-SE, clinical manifestations stop or only become subtle while electrical seizures continue.[43] During prolonged GTC-SE both the convulsions and the EEG features become less florid (subtle GTC-SE), although the prognosis is worse than in any other stage of GTC-SE.[33]

Pharmacoresistance in GTC-SE

Pharmacoresistance develops during GTC-SE. It is progressive and time-dependent. The efficacy of benzodiazepines decreases by 20 times within the first 30 min of GTC-SE,[44] while phenytoin and phenobarbital both lose potency more slowly; they never become totally ineffective but high, sometimes toxic, doses are required. By contrast, *N*-methyl-D-aspartate (NMDA) blockers remain highly efficient at stopping GTC-SE, even when administered late in its course.[27]

Cerebral damage and epileptogenesis[9]

The cerebral damage in GTC-SE is either:

- indirect, i.e. by systemic and metabolic disturbances such as hypoxia, hypoglycaemia or intracranial hypertension
- direct, i.e. due to the excitotoxic effect of electrical seizure discharges, which result in a calcium influx into neurones, and a cascade of events that result in necrosis and apoptosis.

Direct cerebral damage is the more common of the two.[27,39,40]

Epileptogenesis is common after many types of GTC-SE in several animal species and at different ages, but its exact dimension in humans has not yet been determined.[27]

Epidemiology of GTC-SE[8,29,45]

The overall incidence of GTC-SE (30-min duration) ranges from 6.1 to 41 per 100,000 population per year.[8] In childhood this is 18–27 per 100,000 children per year; febrile convulsive SE is the most common.[46] A high incidence of 86 per 100,000 per year in the elderly has been found. Patients with neurological abnormalities are at higher risk. GTC-SE is relatively rare in idiopathic generalised epilepsies (IGEs) when compared to other, mainly symptomatic epilepsies or epileptic encephalopathies.[8]

Aetiology

The aetiology of convulsive SE is similar to that of convulsive epileptic seizures (GTCS, tonic or clonic). It may be acute symptomatic, febrile, idiopathic, cryptogenic or symptomatic (Table 3.2).

Acute symptomatic convulsive SE is more difficult to control and is associated with higher morbidity and mortality. This, like acute symptomatic seizures, 'occurs in close temporal association with a transient CNS insult and is presumed to be an acute manifestation of the insult'. The most common causes are CNS infections, metabolic and toxic disturbances, alcohol abuse, brain tumour, head injury, hypoxia/anoxia and cerebrovascular events. In patients with

Aetiology of GTC-SE
• Established epilepsy of most types (probably one third of GTC-SE); AED changes or discontinuation is a common cause
• First manifestation of an epileptic disorder
• Febrile convulsive status epilepticus in children (the commoner cause of GTC-SE in children)
• Toxins and poisons (alcohol intoxication or withdrawal is a common cause)
• Drug overdose (can be accidental but most likely to be suicidal)
• CNS infections (encephalitis, meningitis, brain abscess of any cause; tuberculosis and malaria are common in resource-poor countries)
• Brain space-occupying lesions
• Acute head injury
• Acute metabolic (diabetic, renal, hepatic, hypoglycaemia, non-ketotic hyperglycaemia and others)
• Acute electrolyte imbalance (hypocalcaemia, hyponatraemia, hypomagnesaemia and others)
• Hypoxia or anoxia
• Cerebrovascular accidents
• Hereditary or acquired metabolic diseases

Table 3.2

established epilepsy, the abrupt withdrawal of anti-epileptic drugs (AEDs) is a main cause of GTC-SE.

Differential diagnosis

Considering the dramatic and typical features of GTC-SE, it may sound strange that any other condition can be misdiagnosed as GTC-SE. However, convulsive psychogenic SE (also referred to as convulsive pseudo-SE) is common in patients with psychogenic non-epileptic events and it is often misdiagnosed as genuine and life-threatening GTC-SE.[47–50] These patients frequently have multiple episodes of 'status' and receive intensive care unit management. They usually have a history of other unexplained illnesses and deliberate self-poisoning. Episodes of iatrogenic drug-induced respiratory arrest may occur.[47–50]

Remember that serum prolactin levels are normal in GTC-SE (see page 38).

Prognosis[29,51,52]

Mortality of GTC-SE is high but it has declined in the last 30 years from 11% to around 5%. Almost all deaths in childhood have been in the context of neurological insults (acute symptomatic GTC-SE) or progressive neurological disease. GTC-SE is associated with the development of up to 6% cognitive deficits, speech and neurological deficits. However, mortality of refractory GTC-SE remains high at around 20%.[53]

There is some evidence that GTC-SE, especially febrile GTC-SE, might cause hippocampal injury, although its role in the development of mesial temporal sclerosis is unknown.[30] Conversely, pre-existing developmental hippocampal abnormality may predispose individuals to having a febrile convulsive SE.[54]

The management of status epilepticus is detailed in pages 82–91.

Generalised tonic status epilepticus

Generalised tonic SE[55] mainly occur in the context of symptomatic epilepsies, particularly epileptic encephalopathies (see Chapter 10); pathophysiology, risk to the brain, and patient and management requirements may not be particularly different from GTC-SE.

> Characteristically, when the patient is lying down, the neck is flexed, and the arms are flexed at the elbow and slightly elevated. The tonic spasms are brief and can continue at brief intervals for hours. In symptomatic generalised epilepsy the duration of the SE can be much longer.[1]

Whether generalised tonic SE occurs in patients with pure forms of IGEs is debatable. Such cases may be rare, badly treated with inappropriate AEDs[56] or an overlap between idiopathic, cryptogenic and symptomatic generalised epilepsies.

Generalised myoclonic status epilepticus

According to the ILAE Task Force:

> Myoclonic SE consists of irregular, usually bilateral or generalised myoclonic jerking without interference with consciousness. Duration may be up to hours. It is most often seen in patients with insufficiently controlled juvenile myoclonic epilepsy. Dravet syndrome, and in nonprogressive myoclonic epilepsy in infancy, particularly Angelman syndrome. In myoclonic–astatic epilepsy, it pre-

dominates in the extremities of the upper limbs and around the mouth, the areas most represented in the precentral gyrus.[1]

However, myoclonic SE is probably best defined as lengthy, continuous or discontinuous clusters of epileptic myoclonus lasting for more than 30 min with or without impairment of consciousness.

Like the myoclonic epileptic seizures, myoclonic SE can be:

- generalised or focal myoclonic SE
- idiopathic, cryptogenic or symptomatic myoclonic SE.

Generalised myoclonic SE may not have the same pathophysiology and significance as that of other forms of convulsive SE, which is probably the reason why this is not considered a type of convulsive SE (Table 3.1).

'Epilepsia partialis continua (EPC) of Kozhevnikov' is a form of focal myoclonic SE (see page 462).

Idiopathic myoclonic SE

Myoclonic SE in IGEs usually results from violation of precipitating factors and the inappropriate use of AEDs. It is more common in JME (mainly limb jerks) where consciousness is usually unaffected. Myoclonic SE of perioral myoclonia with absences, Jeavons syndrome (the idiopathic form of eyelid myoclonia with absences), epilepsy with myoclonic absences or Doose syndrome (the idiopathic form of epilepsy with myoclonic–astatic seizures) usually manifests with myoclonic jerks intermixed or superimposed on absence seizures. Idiopathic myoclonic SE often terminates with a GTCS.

Symptomatic/cryptogenic myoclonic SE

This type of myoclonic SE is commonly encountered in progressive myoclonus epilepsies, epilepsy with myoclonic–astatic seizures (the symptomatic forms) and Dravet syndrome. Myoclonic status in non-progressive (fixed) encephalopathies is considered to be a syndrome in the ILAE report, and is listed under the name 'myoclonic encephalopathy in non-progressive disorders' (see Chapter 10, page 313).[1,57–60]

Negative myoclonic SE consists of bursts of discontinuous negative myoclonic seizures and drops that may persist for days or months. Negative myoclonus may produce frequent jerks due to the ineffective attempt to oppose gravity between the repeat episodes of loss of tone. However, when the patient lies down, there is no jerk, and the motor phenomenon is purely negative. The EEG shows continuous spike–waves in non-REM sleep.[61,62]

Acute symptomatic myoclonic SE after prolonged anoxia or other severe metabolic insults consists of very brief, sudden movements of restricted parts of the body that may be triggered by external stimuli, such as mechanical ventilation. Myoclonic SE of nearly continuous myoclonus may appear several hours after cardiac arrest and lasts for many days.[63–65]

Absence status epilepticus

Absence SE is defined as a prolonged, more than 30 min, generalised non-convulsive seizure of impairment of the content of consciousness (absence) and EEG slow generalised spike–wave discharges (GSWD) or GPSWD.[18,66,67]

Impairment of consciousness may be mild or severe and associated with other, mainly motor, disturbances, including:

- mild clonic jerks of eyelids, corner of the mouth or other muscles

- atonic components leading to drooping of the head, slumping of the trunk, dropping of the arms and relaxation of the grip
- tonic muscular contraction causing head retropulsion or arching of the trunk
- automatisms ranging from lip licking and swallowing to clothes fumbling or aimless walking
- autonomic components such as pallor and less frequently flushing, sweating, dilatation of pupils and urinary incontinence.

The above symptoms may be continuous or repetitive but the patient does not fully recover in-between before the cessation of the seizure.

The ictal EEG is characteristic with usually regular and symmetrical slow GSWD or GPSWD of 1–4 Hz. The background inter-ictal EEG may be normal or abnormal, and is often associated with brief or long runs of paroxysmal 1–4 Hz GPSWD, polyspike discharges and focal spike or slow-wave abnormalities characterising the underlying epileptic syndrome.

Absence SE is broadly divided into:

- typical absence SE of mainly IGEs (idiopathic absence SE)
- atypical absence SE of symptomatic and cryptogenic generalised epilepsies.

Furthermore, to comply with seizure and syndrome classification, absence SE may be 'situation related'[19] and 'not requiring the diagnosis of epilepsy',[20] and may be caused by the introduction or withdrawal of certain drugs, intoxication, or electrolyte or metabolic disturbances. Acute symptomatic absence SE may also be caused by severe brain anoxia or other brain damage.

It should be emphasised that absence SE, like the absence seizures, is not one but many types of a prolonged absence seizure. Although the common symptom of all types of absence SE is impairment of cognition, this is often associated with other clinical manifestations such as myoclonic jerks, eyelid or perioral myoclonia, which are syndrome related.

Typical absence (idiopathic absence) SE

IGEs manifest with three types of generalised SE (i.e. absence, myoclonic and GTC-SE) corresponding to its three types of generalised epileptic seizures (typical absences, myoclonic jerks and GTCSs, respectively). Absence SE is probably the most common and the most likely to escape diagnosis or be misdiagnosed.[2,67–69]

With the possible exception of childhood absence epilepsy, all IGEs with typical absences may manifest with typical absence SE either as a spontaneous expression of their natural course or provoked by external factors or inappropriate treatment manoeuvres.

Impairment of consciousness, memory and higher cognitive functions

The cardinal symptom shared by all cases of typical absence SE is altered content of consciousness of a usually fully alert patient. Memory and higher cognitive intellectual functions such as abstract thinking, computation and personal awareness are the main areas of disturbance. This varies from very mild to very severe with the intermediate states of severity occurring more often.

Mild impairment is experienced as a state of slow reaction, behaviour and mental functioning:

My mind slows down, able to understand but takes longer to formulate answers.

I become slow but can communicate verbally with others.

Slow down in my behaviour, muddling with words.

Like in a trance, missing pieces of conversation.

Moderate and severe impairment of consciousness manifest with varying degrees of confusion, global disorientation and inappropriate behaviour:

Confused, cannot recognise people other than close relatives, disorientated in time and place, very quiet.

Disturbed, vague, uncooperative, confused.

From video-EEG of IGE with phantom absences, absence status epilepticus and GTCSs

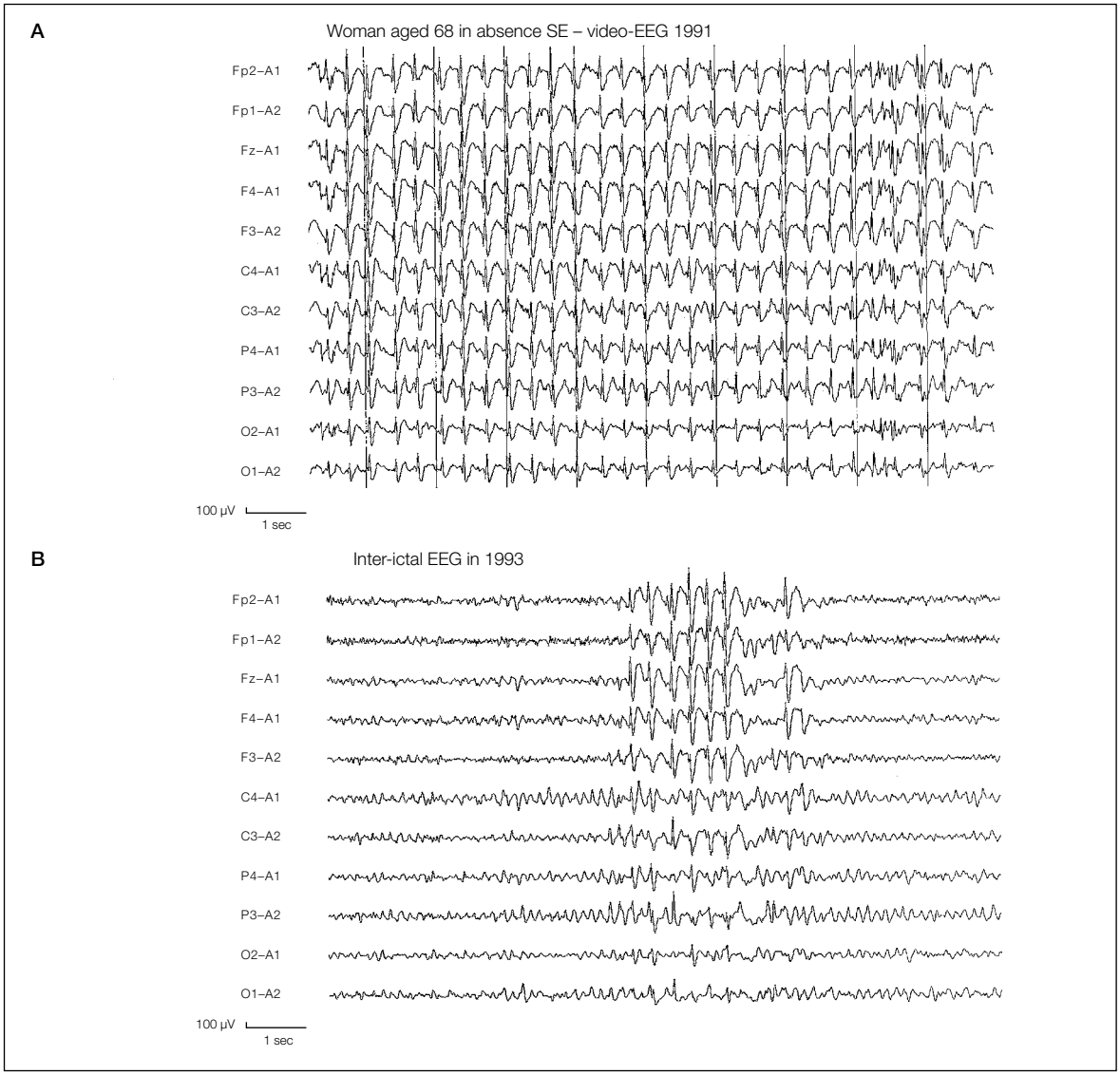

Figure 3.1 From video-EEG of a highly intelligent woman, aged 76 years, with phantom absences, absence SE and GTCSs. She had her first overt seizure at age 30 years. She was moderately confused for 12 hours prior to a GTCS. Since then she had between one and three similar episodes every year. She was misdiagnosed with temporal lobe epilepsy and was on primidone and sulthiame for nearly 40 years. Retrospectively, she admits to brief episodes of mild impairment of cognition. 'The absences lasted a couple of seconds; the other state [absence status] was much longer, for 24 hours or more… They may be linked I suppose'. No further seizures of any type occurred in the next 11 years of follow-up on monotherapy with valproate 1000 mg daily. (**A**) Absence SE. There was continuous slow GSWD mainly at 3 Hz. Note also slower or faster components and some topographic variability of the discharge. The patient was fully alert, attentive and cooperative. Movements and speech were normal. There were no abnormal ictal symptoms other than severe global memory deficit and global diminution of content of consciousness. She was unable to remember her name, how many children she had, date and location. She could not perform simple calculations but could repeat up to five numbers given to her. She could read text correctly and she rightly wrote her address, although she could not remember it on verbal questioning. She did not know where she was but, given the choice between various locations, she correctly recognised that she was in the hospital. This absence SE was successfully terminated with intravenous administration of diazepam. (**B**) Inter-ictal video-EEG showing brief 3 Hz GPSWD lasting 2 or 3 s without apparent clinical manifestations.

Markedly confused, goes into a dreamy state, able to formulate some monolectic answers to simple questions, puts trousers over pyjamas.

Confused, makes coffee twice, fades away mentally and physically, disoriented in time and place.

Usually, the patient is alert, attentive and co-operative. Verbal functioning is relatively well preserved but this is often slow with stereotypic and usually monosyllabic or monolectic answers. Movement and co-ordination are intact; rarely, the patient may become completely unresponsive.

Behavioural abnormalities and experiential phenomena

Although the most common behavioural changes refer to daily activities disturbed by the impairment of consciousness, some patients become depressed, agitated and occasionally hostile and aggressive. More common than usually appreciated are experiential and other complex internal sensations such as:

Sensation of viewing the word through a different medium and a feeling of not being in the same world as everyone else. Uncontrollable rush of thoughts. A feeling of fear of losing control of my mind.

A feeling of closeness.

A funny feeling that I cannot elaborate.

A strange feeling of not being myself.

Edgy, worried and uncomfortable.

My character changes completely, I become extremely snappy, have a severe headache.

Weird.

Simple gestural and ambulatory automatisms, autonomic behaviour and fugue-like states may occur in 20% of the patients who also have severe impairment of consciousness:

Replies yes to any question and fumbles with his clothes.

Myoclonic jerks in idiopathic absence SE

Segmental, usually eyelid or perioral and less often limb, myoclonic jerks frequently occur during typical absence status, and vary in degree and severity. They are most likely to occur in syndromes manifesting with similar myoclonic phenomena during brief absences (see descriptions in the relevant sections of individual IGE syndromes).

GTCSs associated with idiopathic absence SE

Ending with a GTCS is probably the rule irrespective of syndrome. However, this occurs in only a third of episodes of absence SE if left untreated. The remining attacks of absence SE may terminate spontaneously without GTCS. It is exceptional for GTCSs to precede or intersperse with typical absence SE. It is also exceptional for more than one GTCS to occur following an absence SE.

Duration and frequency of idiopathic absence SE

This usually lasts for an average of 3 or 4 hours, rarely the minimum of 30 min. It often exceeds a duration of 6–10 hours and occasionally continues for 2–10 days. Frequency also varies from once in a life-time to an average of 10–20 or catamenial. This depends on treatment strategies and syndromic classification.

Post-ictal state

Amnesia of the event is exceptional. Usually the patient is aware of what happens during the absence SE, some are able to write down their experiences even when in SE, others have a patchy recollection of the events, usually missing the last part prior to GTCSs. Following a GTCS the patient feels tired, has a headache and is confused for a varying duration of time.

Age at onset and sex

It is rare for absence SE in IGEs to start during the first decade of life. Other types of seizure such as absences, myoclonic jerks and GTCSs may predate the first occurrence of absence SE by many years. Mean age at onset of absence SE is 29 years with a range of 9–56.[57] Absence SE may be the first overt type of seizures.

Precipitating factors

Inappropriate or discontinuation of anti-absence medication is the most common precipitant of

idiopathic absence SE. Sleep deprivation, stress and excess of alcohol consumption, either alone or more usually combined, are common precipitating factors. Some patients may have catamenial precipitation. In others this mainly starts upon awakening.

Differential diagnosis

Idiopathic absence SE is commonly unrecognised or misdiagnosed. It is surprising how often physicians are deceived by the general good appearance, alertness and co-operation of the patient, who may also be aware of the impaired mental state during absence SE. Basic testing of memory and higher cognitive functions are essential for diagnosis.

It is important to remember that more than half of the patients are aware of the situation when entering or during absence SE, which is of great practical significance regarding termination of this state and prevention of the impending GTCS by self-administered appropriate medication.

Idiopathic absence SE is easy to diagnose provided that the associated IGE with typical absences (often combined with myoclonic jerks and GTCSs) is correctly identified. The most common misdiagnosis is because absences are not recognised or are misdiagnosed as complex focal seizures (Table 6.1). A previous or a new EEG invariably shows generalised discharges in IGEs. It may be normal or show specific focal spikes in partial epilepsies, mainly temporal lobe epilepsy.

In the generalised symptomatic epilepsies, there is overlap with focal SE due to lesions of certain frontal lobe areas.[1]

The differentiation of typical (idiopathic) absence status from atypical (usually symptomatic or possibly symptomatic) absence status is also easy (see atypical absence SE below).

Atypical absence SE

Atypical absence status is clinically characterised by fluctuating impairment of consciousness, often with other ictal symptoms such as repeated serial tonic or atonic seizures and segmental or generalised jerks. The ictal EEG pattern is of slow, less than 2.5 Hz, GSWD or GPSWD activity. Both the clinical patterns and the EEG abnormalities are more variable than those of typical absence SE.

Atypical absence SE occurs mainly in children with symptomatic or cryptogenic generalised epilepsies who also have a plethora of other types of frequent seizures such as atypical absences, tonic and atonic seizures, myoclonic jerks and GTCSs. Most of them also have moderate or severe learning and physical handicaps. In addition, inter-ictal EEG is often very abnormal with slow background and frequent brief or long runs of slow GSWD/GPSWD, paroxysmal fast activity and paroxysms of polyspikes. It is often difficult to define the boundaries (i.e. the onset and termination) of atypical absence SE because these children frequently have alterations of behaviour and alertness as well as long inter-ictal slow-spike and slow-wave discharges.

Additional discriminating features of atypical absence SE are:

- gradual onset and offset
- level of consciousness and other co-existent types of seizure tend to fluctuate sometimes for weeks with little distinction between ictal and inter-ictal phases
- their initiation or termination with a GTCS is exceptional
- incontinence is common.

Obtundation SE

Obtundation SE is a term used to describe various forms of non-convulsive SE characterised by fluctuating obtundation (a reduced level of alertness or consciousness), with low-amplitude, fragmentary, segmental and erratic myoclonic jerks of the face and limbs and sometimes tonic manifestations.[70] Duration is usually extremely lengthy for several hours or days. GTCSs can initiate, occur or terminate obtundation SE. Ictal EEG shows a mixture of irregular, arrhythmic, diffuse and focal spike–wave discharges. Focal obtundation SE occurs more rarely.[71]

Obtundation SE occurs in severe myoclonic epilepsies such as Dravet syndrome and 'myoclonic encephalopathy in non-progressive disorders'.

Obtundation SE is a symptomatic form of myoclonic SE rather than atypical absence SE.

Situation-related and *de novo* absence SE

Absence SE may be induced by drugs, and electrolyte and metabolic disturbances in mainly middle-aged or elderly patients who do not suffer from an epilepsy disorder.[72,73] The best-documented examples are of drug induction and drug withdrawal (mainly benzodiazepine withdrawal). *De novo* absence SE is often misdiagnosed as a psychotic state or dementia.

Focal status epilepticus

Any type of focal epileptic seizure can sometimes exceed its usual duration and last for over 30 min, thus constituting, by definition, a focal SE. Therefore, focal SE can exist in as many different types as focal epileptic seizures. These may remain simple without impairment of consciousness or complex with impairment of consciousness. They may remain entirely localised or progress to more complex symptomatology and to secondarily generalised epileptic seizures or secondarily generalised SE. The various forms of focal SE are detailed in the relevant chapters of this book. Of the long list of focal SE, the ones that have attracted attention from the ILAE Task Force[1] are:

- epilepsia partialis continua (EPC)
- supplementary motor area (SMA) SE
- aura continua
- dyscognitive focal (psychomotor, complex partial) SE, subdivided into:
  - mesial temporal lobe SE
  - neocortical SE

Epilepsia partialis continua[1]

EPC is a typical example of symptomatic focal myoclonic SE as detailed in Chapter 15 (see page 462). According to the ILEA Task Force[1] report:

> EPC of Kozhevnikov is a combination of focal seizures with continuous twitching in the same area. The clinical and EEG features permit distinction of three conditions that correlate with aetiology:
>
> A. As occurs with Rasmussen syndrome. EPC in this subacute lateralized encephalitis of unknown cause (half the cases show the clinical expression of this encephalitis) combines focal myoclonus and focal seizures affecting various areas of the same hemisphere, with or without clear EEG correlation of the myoclonic jerks, and at times persistence of the jerks in sleep. There is progressive slowing of the background EEG activity on the affected side.
> B. As occurs with focal lesions. Various dysplastic, vascular, or tumor lesions produce EPC lasting a few days, weeks, or months before the patient returns to baseline. EPC is also seen with nonketotic hyperglycemia. The jerks affect the same area as the focal seizures, and have an EEG correlate; they do not persist in sleep.
> C. As a component of inborn errors of metabolism. Various conditions affecting energy metabolism, namely, Alpers disease or myoclonus epilepsy with ragged-red fibers (MERRF), produce uni- and then bilateral rhythmic jerks that persist in sleep, with EEG correlates.[1]

Supplementary motor area SE[1]

According to the ILEA Task Force[1] report:

> Frequently repeated seizures from the SMA usually present as a type of focal SE with preserved consciousness and individual tonic motor seizures occurring every few minutes throughout the night. Another type of SMA SE consists of secondarily generalized seizures that evolve into repetitive

asymmetrical tonic motor seizures with profound impairment of consciousness.[1]

See details in Chapters 14 and 15.

Aura continua[1]

The term 'aura continua' is not found in the recent ILAE glossary of epilepsy terminology[17] and I would agree with others that 'this term is an appropriate clinical description for a subtype of simple partial SE'.[74]

According to the ILEA Task Force report:[1]

> Aura continua is a rare but well-described manifestation of focal epilepsy. The symptoms depend on the localization. The attacks are usually without impairment of consciousness. The symptoms wax and wane, often for hours, and may be associated with a motor component, depending on the spread. Dysaesthesia, painful sensations and visual changes are examples. Limbic aura continua is the most common clinical pattern. Fear, an epigastric rising sensation, or other features may recur every few minutes for many hours or for more than a day without going on to seizures, with impairment of awareness. Electrographic correlation is variable. Diagnosis must be entertained, particularly in patients with well-established epilepsy.[1]

Wiesel has extensively reviewed aura continua.[75] The term 'aura continua' is restricted to subjective feelings without visible motor phenomena. Symptoms excluded are simple focal SE with motor phenomena or any other objective phenomena such as aphasia.

Dyscognitive focal (psychomotor, complex partial) SE[1]

According to the ILEA Task Force[1] (Table 3.1):

> *Mesial temporal SE:* Focal SE predominantly involving mesial limbic structures consists of serial dyscognitive focal ictal events without return of clear consciousness in-between. Onset can be limited to one side or can alternate between hemispheres.[1]

> *Neocortical SE:* Focal SE originating in various neocortical regions can present with a wide variety of unpredictable clinical patterns. SE from some frontal foci can resemble absence status or generalized tonic–clonic status. It can present as repetitive discrete behavioural seizures. To some extent, this type of SE can reflect the neocortical region of origin. For example, occipital SE might present with experiential unexplained blindness, whereas dysphasia or aphasia could represent focal status in language cortex.[1]

Clarifications on nomenclature

In this book I use the term complex focal SE (limbic, mesial temporal or neocortical) in concordance with the seizure classification. Psychomotor SE may be used as a synonym. I would discourage the use of the term dyscognitive, however, which I consider confusing because this type of SE manifests with various mental aberrations at various combinations and degrees of predominance. Other than dyscognitive (impairment of cognition that is the process of knowing, including aspects such as awareness, perception, reasoning and judgement), symptoms include ideational (impairment of thoughts), dysmnesic (impairment of memory), affective (emotional impairment) and behavioural changes.

According to the ILAE glossary,[17] "the term dyscognitive describes events in which: (1) disturbance of cognition is the prominent or most apparent feature, and (2a) two or more of the following components are involved or (2b) contributions of such components remain undetermined. Otherwise, use more specific terms such as 'mnemonic experiential seizure' or 'hallucinatory experiential seizure.'

"Components of cognition include:

- perception (symbolic conception of sensory information)
- attention (appropriate selection of a principal perception or task)
- emotion (appropriate affective significance of a perception)
- memory (ability to store and retrieve percepts or concepts)

- executive function (anticipation, selection, monitoring of consequences, initiation of motor activity including praxis, speech)."[17]

According to the semiological classification of SE by Luders, *et al*,[76] dyscognitive is:

> A new term describing status episodes interfering mainly with the cognitive sphere... For practical purposes, we distinguish three different types of dyscognitive SE according to its predominant clinical feature. Status episodes which cannot be clearly assigned to one of the categories [dialeptic, delirious and aphasic] should be simply termed 'dyscognitive status'.[76]

Furthermore, in this classification of Luders et al., 'dyscognitive' SE may be focal or generalised.[76]

Clinical manifestations

Complex focal SE (limbic or neocortical) is characterised by continuous or rapidly recurring complex focal (psychomotor) seizures that may involve temporal or extratemporal regions, most frequently the limbic regions.[69,75,77,78] Cyclic disturbance of consciousness is characteristic of limbic SE of temporal lobe origin. The diagnosis of complex focal SE of frontal lobe origin remains a challenge.[79] In a third of cases, a frontal lesion is revealed.[80,81] However, according to Wieser:

> With the exception of a few cases with prolonged discharges in the anterior cingulate gyrus associated with confusion and emotional and autonomous signs and symptoms and a few cases with cacosmia from frontal orbital cortices, little evidence exists on the existence of isolated limbic SE in areas other than the temporal lobe.[75]

Symptoms at the beginning depend on the epileptogenic site of origin. Initial symptoms of neocortical onsets include somatosensory, visual and auditory hallucinations. Initial symptoms of limbic onset include usually complex internal sensations, autonomic and other manifestations of limbic seizures (see Chapter 15).

Complex focal SE (usually of temporolimbic origin) may present with features similar to postictal twilight states.[75]

Prevalence

Complex focal SE may be a lot more common than was initially thought.[69]

Aetiology and prognosis

Complex focal SE may be acutely symptomatic (i.e. cerebral trauma and infections, cerebrovascular accidents and ischaemia, metabolic) or occur in patients with focal epilepsies of mainly temporal lobe origin. Acutely precipitated complex focal SE and complex focal SE in the setting of a person with epilepsy should be considered as two separate conditions.[69]

Complex focal SE in someone with focal epilepsy is probably a relatively benign condition that does not cause adverse systemic consequences, although prolonged memory deficits may occur.[82] Patients commonly have repeated episodes, which may respond to oral benzodiazepines.[83]

Conversely, complex focal SE in the setting of an acute medical illness has high mortality and morbidity, which probably relates to the underlying cause.[84]

Differential diagnosis

Complex focal SE is often misdiagnosed as abnormal or strange behaviour, psychological disorder, toxic or metabolic encephalopathy, or global amnesia. If this is recognised as an epileptic SE, the main differential diagnosis is from absence SE (Table 2.7). A previous history of complex focal seizures or an inter-ictal EEG with focal spikes are important diagnostic features of complex focal SE. Conversely, a history of IGEs and absences with 3 Hz GSPWD are typical of absence SE. Ictal EEG offers a definitive diagnosis (Figures 3.1 and 3.2). In the absence of readily available EEG, rapid recovery after appropriate administration of a benzodiazepine favours SE.

See Chapter 4 for imitators of epilepsy.

Hippocampal SE[69,75,77,85]

Synonym: limbic mesial temporal lobe complex focal SE.

The term hippocampal SE (understanding that this also involves parahippocampal regions) is in agreement with the seizure terminology:

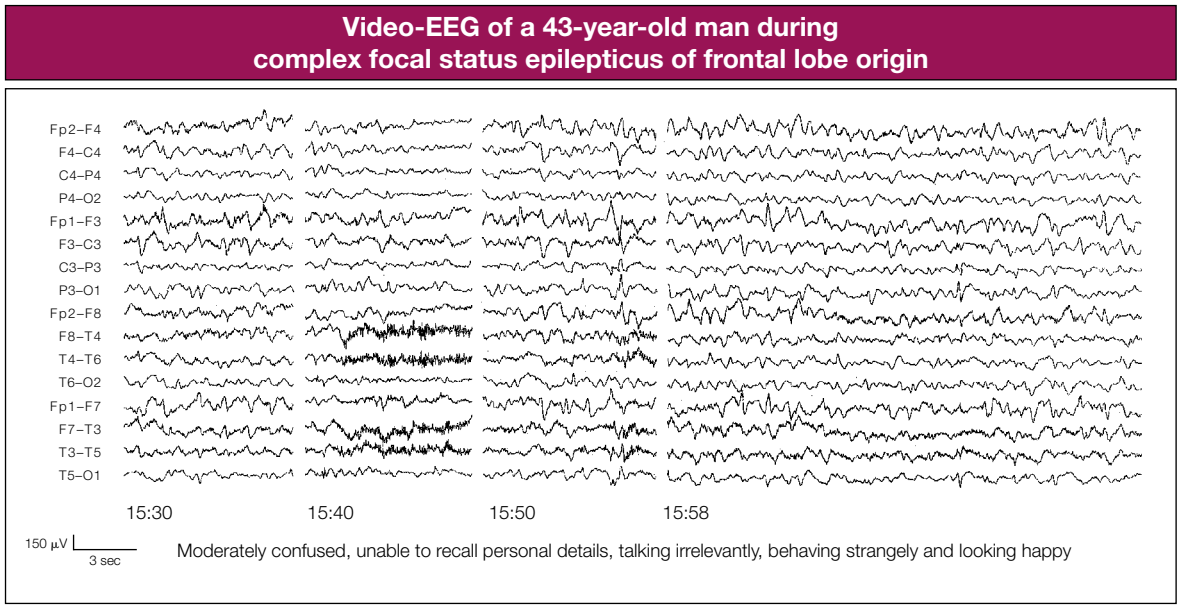

Figure 3.2 He was confused, disorientated in time and place, with bizarre behaviour, laughing and making inappropriate jokes. Note: (1) the frequent, but irregular, appearance of sharp–slow-wave complexes, which are mainly localised in the bifrontal electrodes with left-sided preponderance; (2) the relative preservation of alpha activity; and (3) brief discontinuation of the ictal discharge. The numbers show the actual time of the recording.

Hippocampal and parahippocampal seizures almost always require local spread for clinical manifestation, which may involve insula, amygdala, hypothalamus, and other limbic structures. Autonomic features such as a sensation of epigastric rising is common, as well as emotional experiences such as fear, dysmnesias, focal sensory seizures with olfactory or gustatory symptoms, and vague bilateral sensory phenomena such as tingling.[1]

Clinical manifestations[8,75,77,85]

The typical pattern of hippocampal SE is of fluctuating waxing–waning impairment of consciousness, behavioural, affective and memory aberrations, and complex internal sensations, often with automatisms. Onset is usually with the symptomatology of mesial temporal lobe epilepsy (see Chapter 15) characteristic of the habitual focal seizures of each patient.

There are two clinical forms:

1. discontinuous or type I (clusters of complex focal seizures without recovery of consciousness in-between the attacks)
2. continuous or type II (continuous ongoing complex focal seizures with a twilight state).

These forms most likely represent a continuum.[86]

Consciousness is impaired and often fluctuates (cycles) from mild to severe between a continuous twilight state with partial and amnestic responsiveness and an arrest reaction with motionless stare, complete unresponsiveness and stereotyped automatisms. Patients are usually responsive but responsiveness also fluctuates significantly in the same episode of SE and in-between attacks and patients. Frank stupor or catatonic states are rare. Memory of the event is usually impaired. Complete amnesia is common, which is also the reason that this SE may be misdiagnosed as global amnesia.[87]

Behavioural changes, irritability, fear, panic and anxiety are common and these also fluctuate. Automatisms, as with complex focal seizures, mainly occur when consciousness is severely impaired.

Hallucinations (olfactory and gustatory), as with the habitual seizures of the patient, may be present (aura continua).[74]

Autonomic symptoms of all types are common (see Chapter 15, page 443).[77,88]

Electroencephalography

Inter-ictal EEG is as described for hippocampal epilepsy (see page 451).

Ictal EEG shows continuous or discontinuous focal discharges like those of complex focal hippocampal seizures (Figure 15.4). They are mainly localised in the temporal or frontotemporal electrodes. Unilateral, bilateral or secondarily generalised discharges are frequent; these may be repetitive patterns with irregular or rhythmic spikes without clear-cut seizure discharges or temporal theta and delta activity without clear-cut epileptiform features.[89]

Focal SE of frontal lobe origin

Focal SE of frontal lobe origin is of undetermined prevalence.[79,80] In addition to EPC and SE of the SMA, other types include:

- focal simple motor SE, which manifests with continuous focal motor clonic hemiconvulsions of lips, eyelids, hand or foot
- frontal lobe complex SE, which manifests with prolonged impairment of consciousness and inappropriate behaviours (Figure 3.2).

In frontal lobe complex SE, symptoms fluctuate in intensity and severity over time. Concurrent turning of the head and focal jerking may occur. It commonly ends with GTCS. Ictal EEG shows repetitive fronto-polar, frontocentral and frontotemporal epileptiform discharges with unilateral emphasis. There may be two types of frontal lobe complex SE.[80] The first, more common type manifests with mood disturbances with affective disinhibition or affective indifference, which are associated with subtle impairment of cognitive functions without overt confusion. The EEG shows a unilateral frontal ictal pattern and normal background activity. In the second type, impaired consciousness is associated with bilateral, asymmetric frontal EEG discharges on an abnormal background. The response to intravenous benzodiazepines is poor, whereas intravenous phenytoin successfully controls seizures in most patients.[80]

It is difficult to differentiate frontal from idiopathic absence SE without an EEG (Figures 3.1 and 3.2).

Focal SE of occipital lobe origin

Visual seizures develop rapidly, within seconds, and they are usually brief, lasting from a few seconds to 1–3 min, rarely longer.[90–92] Exceptionally, they can last for 20–150 min, sometimes constituting focal visual SE without other ictal symptoms.[93–96] Occasionally, ictal blindness may last for hours or days (SE amauroticus).[97,98]

Focal SE of parietal lobe origin

The duration of parietal lobe seizures varies from a few seconds to 1 or 2 min. Prolonged isolated sensory auras comparable to EPC, but without any motor manifestations, have been reported[99,100] and this condition may be misdiagnosed as non-epileptic psychogenic seizures.[101]

Autonomic SE

Autonomic SE is the most common after febrile SE in otherwise normal children; it has distinctive clinical manifestations and has been documented with video-EEG recordings.[102,103]

A major problem is that autonomic SE is frequently misdiagnosed as symptoms of non-epileptic disorders such as encephalitis.[102–104] Yet, autonomic SE has not been recognised in any ILAE classification scheme, including the recent report of the Core Group.[1]

Definition[103]

Autonomic SE is an autonomic seizure that lasts for more than 30 min, or a series of such seizures over a 30-min period without full recovery between seizures.

A fuller definition is:

> Autonomic SE is a condition lasting 30 min and characterised by epileptic activity causing altered

autonomic function of any type at seizure onset or in which manifestations consistent with altered autonomic function are prominent (quantitatively dominant or clinically important) even if not present at seizure onset.[103]

Clinical manifestations

Autonomic SE is mainly childhood related, as first described by Panayiotopoulos,[105] and occurs in 40% of children with Panayiotopoulos syndrome (see Figure 12.5). This type of SE, particularly with ictus emeticus, has not been described in adults.[102,105,106]

In a typical presentation of autonomic SE in Panayiotopoulos syndrome, the child, if awake, begins to complain of feeling sick. Initially, he or she is fully aware and responsive. Retching and/or vomiting frequently follow and these emetic symptoms are often accompanied by other autonomic features, such as pallor, tachycardia/bradycardia, mydriasis and thermoregulatory disturbances. At this stage, it is unlikely that on-lookers will suspect an epileptic seizure. After a variable time, awareness and responsiveness become impaired, often with aversion of the eyes and/or head. There then follows a prolonged period characterised by fluctuating consciousness, interspersed with retching and vomiting with continuing pallor, mydriasis, etc. In a third of the cases, autonomic SE ends with hemi or generalised convulsions.

Other details and EEG findings are provided in Chapter 12.

Opercular SE

Opercular SE usually occurs in atypical evolutions of rolandic epilepsy or exceptionally it may be induced by carbamazepine, oxcarbazepine or lamotrigine. This SE may last for hours to months. It consists of continuous unilateral or bilateral contractions of the mouth, tongue or eyelids, positive or negative subtle perioral or other myoclonus, dysarthria, speech arrest, difficulties in swallowing, buccofacial apraxia and hypersalivation. These are often associated with EEG continuous spikes and waves during sleep (page 309).

Management of status epilepticus

Management of GTC-SE and other convulsive SE

An episode of GTC-SE or other form of convulsive SE (CSE) is a medical emergency and should be properly and promptly managed in order to reduce morbidity and mortality.[4,14,24,107–125] The mortality associated with GTC-SE is around 10%, increasing to more than 20% when it becomes refractory.

The longer the GTC-SE lasts, the harder it is to treat and the greater the morbidity and mortality.

The aim of treatment is early termination of GTC-SE in order to prevent neuronal damage caused by systemic and metabolic disturbances and by the direct excitotoxic effect of electrical seizure discharges.

Control of overt and electrical seizures is imperative.

The risk of brain damage increases progressively if continuous GTC-SE persists for more than 30 min and particularly after 1 or 2 hours.

Out of hospital management

Considering that convulsive SE should be terminated as soon as possible, out of hospital treatment[108,126] is an important part of the optimal management of CSE. Appropriate administration of available medications may prevent an impending GTC-SE or terminate a GTC-SE at its crucial initial stages. The therapeutic window for most effective treatment with benzodiazepines may have already passed by the time that hospital treatment starts, which is usually more than 20 min after the onset of GTC-SE. It is during

this window that the patient, family caregivers and ambulance paramedics can play a significant role in the management of CSE. They can safely and accurately administer drugs by buccal, rectal, nasal and other non-invasive routes if appropriately instructed and if proper "rescue medications" are available for emergency use.[126] The home management of febrile seizures by parents is a good example of this, particularly considering that febrile convulsive SE is the commonest amongst such emergencies in childhood.[127]

Patients, including older children and teenagers, frequently know when a GTC-SE is about to start and can prevent it happening by self-administration of available medications. This is often the case with secondarily GTCS, which may occur after clusters of focal seizures that can alert the patient and relatives. The same applies for patients with absence or myoclonic status epilepticus.

Clinical studies have shown that pre-hospital treatment with non-invasive administration of rescue benzodiazepines shortens the duration of SE and reduces the likelihood of recurrent seizures with no increased risk of complications related to therapy.[126] In particularly, respiratory or circulatory complications are absent or minimal in the active treatment groups.[126]

Rectal diazepam and buccal or intranasal midazolam are first line options.[14] Because of the inconvenience and often embarrassment of administering rectal medications, buccal and intranasal routes are currently preferred.

Rectal diazepam (0.5 mg/ kg for children and 10–20 mg for adults) has been used for many years and is still the preferred benzodiazepine. It has the most rapid and consistent absorption of all the benzodiazepines from this route of administration. It has a near-intravenous efficacy, stopping recurrent seizures in around 70% of patients.[125] Suppositories or intramuscular diazepam are not useful because absorption is very slow.

Buccal midazolam (0.4–0.5 mg/kg in children and 10–20 mg in adults) is gaining wide acceptance as "a safe and more effective choice" for terminating prolonged seizures in the home.[108,122] It is more convenient and more socially acceptable and is preferred by parents to rectal diazepam. Midazolam drawn up from an injectable formulation is dissolved with peppermint (otherwise it smells and tastes very unpleasant) and should be swirled around the mouth for 4 or 5 min and then spat out, although it is harmless if swallowed. However, some authors argue that keeping the solution in the buccal pouch may be difficult to achieve in a convulsive emergency and that place¬ment of an object or fingers in the mouth of a patient having a seizure runs counter to standard first aid advice.[126]

Intranasal midazolam (0.2 mg/Kg in children and 5 mg in adults) is already recommended in some consensus guidelines for out of hospital treatment of status epilepticus.[14,128] The drug should be delivered to both nostrils to increase absorption surface area. Intranasal administration of drugs may cause considerable but transient discomfort and often result in leakage out of the nose thus delaying or decreasing absorption.[126]

For any of these medications a repeat dose can be given at least 10 min after the first dose.

See more details in the forthcoming section on AEDs recommended for the treatment of status epilepticus.

Hospital emergency management of GTC-SE

Emergency management of GTC-SE should be in accordance with established and well-publicised protocols (Table 3.3).[107–125] Most protocols are similar, with differences usually concerning the recommended drug dosage and less often the drugs used or the treatment order. Following any of these protocols results in appropriate and rapid management of GTC-SE and hence reduces morbidity and mortality.[24]

Recommended useful treatment protocols for SE in websites

In addition to protocols found in the cited reports and reviews, other useful protocols are those of the New South Wales (http://www.health.nsw.gov.au/policies/pd/2006/PD2006_023.html accessed 7 September 2009) and the Starship Children's Hospital in New Zealand (http://www.starship.org.nz/Clinical%20Guideline%20PDFs/Convulsions%20-%20Status%20Epilepticus.pdf, accessed 7 September 2009).

General emergency management

Initial and immediate general emergency management of a patient with CSE is vital. This includes standard measures applicable to any acute medical situation.

- Assess and support airway. Insert nasal airway, begin nasal oxygen or intubate if needed
- Assess and support cardiorespiratory function, which is often compromised. Check blood pressure, monitor ECG and respiration
- Establish intravenous line containing isotonic saline at a low infusion rate. Administer glucose (50 ml of 50% solution) and/or intravenous thiamine (250–500 mg) if alcohol abuse or impaired nutrition is suspected
- Check temperature frequently. Hyperthermia (which occurs in 28–79% of patients in CSE) is often a manifestation of CSE rather than evidence of an infection and should be appropriately treated.
- Send sample serum for emergency investigations (see below) such as evaluation of electrolytes, blood urea nitrogen, glucose level, complete blood cell count, toxic drug screen, and AED levels. Arterial-blood gas monitoring is especially useful because of the frequent occurrence of profound metabolic acidosis or respiratory acidosis and hypoxia requiring immediate treatment.

Other concurrent life threatening conditions such as haemorrhage should be indentified and treated. An acute symptomatic aetiology such as meningitis or nonketotic hyperglycaemia requires specific treatment.

Diagnostic procedures and investigations to determine the cause of CSE must be carried out without delaying the drug treatment needed to stop seizures.

General measures should be instituted along with antiepileptic drug therapy.

Diagnosis: Establish by fast-track history taking and examination that the patient suffers from genuine GTC-SE and determine the likely aetiology (Table 3.2). GTC-SE is easy to diagnose if the patient has a history of epileptic seizures or status epilepticus and/or if the current event has been preceded by clusters of brief seizures. Significant clues are also provided by precipitating factors and recent changes or discontinuation of AED medication. Patients with de novo GTC-SE are more demanding to diagnose because of the numerous potential aetiological factors. Acute symptomatic seizures are the most common and their various causes should be considered (infections, metabolic disorders, toxicity, alcohol and other drugs) as listed in Table 3.2.

Non-epileptic psychogenic convulsive SE is common and should be considered, particularly in drug-resistant cases.

Emergency investigations:[129] Blood should be taken in order to evaluate blood gases, glucose, renal and liver function, calcium and magnesium, full blood count (including platelets), blood clotting and AED drug levels; 5ml of serum and 50ml of urine samples should be saved for future analysis, including toxicology, especially if the cause of the status epilepticus is uncertain. A chest radiograph to evaluate the possibility of aspiration should be carried out. Other investigations depend on the clinical circumstances and may include brain imaging, lumbar puncture and EEG.

Monitoring of vital signs:[129] Regular neurological observations and measurements of pulse, blood pressure, temperature, ECG, biochemistry, blood gases, clotting, blood count and drug levels should be carried out. Patients require the full range of intensive therapy unit facilities and care should be shared between anaesthetist and neurologist.

Pharmacological treatment of GTC-SE

Administration of drugs to terminate GTC-SE should start as soon as possible and in parallel with the other emergency assessments of the patients as outlined above.

Drug treatment of GTC-SE in the hospital setting can be divided into the following three stages when intravenous access has been established (Table 3.3):

1. In the early stage of GTC-SE (first 30 min, preferably first 10 min), treatment comprises intravenous administration of a fast-acting benzodiazepine. Diazepam is the traditional drug but now lorazepam is the first choice.[24] Midazolam infusion is becoming increasingly popular as an effective and well-tolerated

therapeutic option. The use of paraldehyde has significantly declined and only rectal administration is recommended in the UK.[108]

2. In the stage of established GTC-SE (from 10–30 to 60–90 min), first-line drug options are intravenous phenytoin or fosphenytoin. Intravenous valproate is also included in some protocols. If these are ineffective, subanaesthetic doses of phenobarbital are used. If seizures are not controlled at this stage the patient enters refractory SE.

3. Refractory GTC-SE (>60–90 min) requires general anaesthesia and a continuous infusion of AEDs,

Staging and order of drug administration in GTC-SE*

Stage 1: stage of early SE (0–10/30 min); drugs in order of preference

Lorazepam:	4 mg (adult) or 0.1 mg/kg (child) in IV slow bolus not exceeding 2 mg/min OR
Diazepam:	10–20 mg (adult) or 0.25-0.5 mg/kg (child) in IV bolus not exceeding 5 mg/min OR
Midazolam:	0.1–0.25 mg/kg in IV bolus not exceeding 0.15 mg/kg/min or 4 mg/min OR
Clonazepam:	1–2 mg (adult) or 0.01–0.03 mg/kg (child) in IV bolus not exceeding 1 mg/min

If after 10 minutes of first drug administration seizures continue a second dose can be given

Paraldehyde:	0.4 ml/kg rectally may be used in children in whom benzodiazepines have failed or intravenous access has not been established, or in patients with respiratory distress

If seizures continue after 30 min proceed to stage 2

Stage 2: stage of established SE (10/30–60/90 min)

Fosphenytoin:	IV infusion 15–20 mg PE/kg at a max rate of 150 mg PE/min OR
Phenytoin:	IV bolus 1 g (adult) or 15-20 mg/Kg (child) at a max rate of 50 mg/min (1 mg/Kg/min) OR
Phenobarbital:	IV infusion 10–20 mg/kg (adult) or 15-20 mg/Kg (child) at a max rate of 100 mg/min OR
Valproate:	IV infusion 25 mg/kg at 3–6 mg/kg/min

If seizures continue after 30–90 min proceed to stage 3

Stage 3: stage of refractory SE (>60/90 min)[14]

Propofol:	IV bolus 2 mg/kg, repeated if necessary, and then followed by a continuous infusion of 5–10 mg/kg/hour initially, reducing to a dose sufficient to maintain a burst suppression pattern on the EEG (usually 1–3 mg/kg/hour), OR
Thiopental:	IV bolus 100–250 mg given over 20 s with further 50 mg boluses every 2–3 min until seizures are controlled, followed by a continuous IV infusion at a dose sufficient to maintain a burst suppression pattern on the EEG (usually 3–5 mg/kg/hour), OR
Midazolam:	IV bolus 0.1–0.3 mg/kg at a rate not exceeding 4 mg/min initially, followed by a continuous IV infusion at a dose sufficient to maintain a burst suppression pattern on the EEG (usually 0.05–0.4 mg/kg/hour).

When seizures have been controlled for 12 hours, the drug dosage should be slowly reduced over a further 12 hours. If seizures recur, the drug infusion should be given again for another 12 hours, and then withdrawal attempted again. This cycle may need to be repeated every 24 hours until seizure control is achieved.

Confirmation of seizure termination with EEG may be mandatory because electroclinical dissociation is associated with a poor prognosis.

Table 3.3 *The doses cited in this table have been derived from the study of various protocols recommended for the treatment of SE. Because of considerable variations between protocols and recommendations, doses and rates of drug administration should be verified according to the local settings, age and particular circumstances of the patient. IV, intravenous; PE, phenytoin equivalents.

such as propofol, thiopental or midazolam, with concomitant and continuous EEG monitoring of seizure or EEG background suppression. Medication is usually titrated to the EEG burst-suppression pattern, maintained for 12–48 hours, and then slowly withdrawn while the patient is observed and the EEG is monitored for seizures. If seizures recur, the process is repeated at progressively longer intervals. Despite these measures, the mortality of refractory GTC-SE is more than 20% from underlying illness, cardiovascular collapse, or medical complications.[53] Surgical intervention is the last and desperate resort in medically refractory convulsive status epilepticus and can sometimes be successful when the aetiology is focal. [129]

When intravenous access cannot be established, acute management employs all approaches described in the out-of-hospital treatment. Rectal diazepam or buccal/intranasal midazolam (though intramuscular midazolam may also be appropriate) should be administered, repeating every 10 minutes for a maximal 3 times until intravenous access is achieved.[108]

Other AEDs that are available in parenteral forms and which may be used for the control of SE include valproate and the more recently developed levetiracetam.

For more details, see the forthcoming section on AEDs for status epilepticus.

Absence SE

Absence SE[3,18,67,121,131–135] occurs in 10–20% of cases of IGE and in as many as 50% of cases of some syndromes of IGE, such as those manifesting with phantom absences or perioral myoclonia. Nearly all patients are fully aware of this epileptic status and know that it may inevitably lead to a GTCS, although it is avoidable:

It is the same feeling of 'slowing down', 'uncontrollable rush of thoughts', 'losing control of my mind', 'taking me much longer to formulate my response, which occasionally is inappropriate and bumbled. Then I know that I will have the fit. If I can, I just go in a private place and wait for it'.

This stage is unlikely to be considered as a genuine SE by the physicians in accident and emergency departments. Therefore, advice to the patient regarding therapeutic options for self-administration of drugs is imperative. Benzodiazepines – mainly diazepam, lorazepam or midazolam – are the most effective agents.

This is similar to the management of myoclonic or myoclonic-absence and other forms of the so-called non-convulsive focal SE.[3,67,121,131–135]

Self-administration of medication

This is the same as in the out of hospital management of CSE (page 82). Rectal diazepam, or buccal/intranasal midazolam administered as soon as the first symptoms appear, may stop absence SE and prevent an impending GTCS (see page 86). Buccal or intranasal routes of administration are more convenient and less traumatising than rectal preparations, particularly in adults.

Other less effective options are an oral bolus dose of valproate (usually twice the daily prophylactic dose). Oral clonazepam (1–4 mg) at the onset of generalised non-convulsive SE is a preferred option for patients with mainly myoclonic jerks.

This helps me to go to sleep and when I wake up I am fine.

Hospital management

With intravenous administration of any type of the benzodiazepines discussed above (Table 3.3), absence SE usually stops abruptly. The problem is that this condition is not recognised and the patients are not believed when they seek such treatment, even when they produce a relevant letter from their treating physician that clearly explains their situation and the need for urgent attention.

She started doing the same silly things. I recognised it. The doctor told me that she is ok. No, no I said, she is going to have the fit.

Focal simple and complex SE

The treatment of focal SE follows the same principles and emergency drug administration as for absence SE described above.[3,121,131–135] It has been reported

that rectal diazepam terminated focal SE in 88% of 67patients.[2] Patients with simple focal SE should be advised and provided self-administration rescue medication.

Antiepileptic drugs in the treatment of status epilepticus

Benzodiazepines[108,110,136-139]

Of the benzodiazepines, diazepam, lorazepam, midazolam and clonazepam have potent fast-acting efficacy in terminating seizures and are therefore the first-line drugs used for the initial emergency treatment of status epilepticus (Table 3.3). They are GABAergic drugs promoting neuronal inhibition by binding at the $GABA_A$ receptor (see Pharmacopoeia). There are two clinically important matters to remember:

a. During status epilepticus, the number of active $GABA_A$ receptors progressively decreases with time and they become less effective.
b. Benzodiazepines at higher concentrations also inhibit sustained repetitive neuronal firing, as with carbamazepine and phenytoin

Adverse effects of intravenous benzodiazepines include respiratory and circulatory collapse (in 3–10% of patients), hypotension (in <2%), and impaired consciousness (in 20–60%).[140] Especially in older subjects, infusion speed should be slowed and accompanied by gentle fluid expansion.

Currently, the main benzodiazepines and their route of administration for the treatment of status epilepticus are:

- Lorazepam in intravenous administration
- Diazepam in rectal administration
- Midazolam in buccal, intanasal and less frequently in intramuscular and intravenous administration

Intravenous diazepam has been the first-line option in the acute therapy of SE for many years,[141] though recently lorazepam has been preferred.[111] In both premonitory and established CSE, both drugs are equally effective at terminating seizures with no significant differences in reported ADRs. However, with lorazepam there are fewer seizure recurrences and fewer repeat doses are needed. Midazolam is emerging as a first line AED in out of hospital treatment of status epilepticus.

Diazepam is highly lipid-soluble and rapidly crosses the blood-brain barrier; its antiepileptic effect occurs within 3 min but it does not last more than 30 min. This is because diazepam is quickly re-distributed to other parts of the body due to its marked lipophilia and high degree of plasma protein binding (90–99%). Thus, non-effective concentrations of diazepam occur within about 20 min of intravenous administration.[12,13] Repeated dosing with diazepam results in saturation of lipid stores and high levels of active drug, with an attendant risk of respiratory and circulatory depression. Saturated lipid stores would release the drug for at least as long as 30 hours, which is the half-elimination life of diazepam.

Metabolism and elimination of diazepam in the neonate are markedly slower than in children and adults. In the elderly and in patients with impaired hepatic and renal function, elimination is prolonged by a factor of 2 to 4.

The intravenous diazepam dose is 10–20 mg (adult) or 0.25–0.5 mg/kg (child) at a rate not exceeding 5 mg/min.

The rectal diazepam dose is 10–20 mg (adults) or 0.5 mg/kg (child).

Rectal diazepam is quickly absorbed from the rectal mucosa and reaches the brain within 5–10 min in children (10–15 min in adults); maximum plasma concentration is achieved within 17 min. Absorption is 100% compared with that of intravenous diazepam. Stesolid® in Europe and Diastat® in USA are proprietary formulations for direct rectal administration of diazepam. Stesolid® rectal tubes are enemas containing 5 or 10 mg ready-made liquid diazepam. Diastat® is a prefilled, unit-dose, diazepam rectal gel delivery system containing 5 mg/ml diazepam.

Intramuscular diazepam is of no benefit in the treatment of status epilepticus because absorption

is erratic and peak plasma concentrations are lower even than those following oral administration.

Lorazepam has become the first line intravenous treatment of CSE, although it does not have an FDA approval for this indication. Its efficacy may be as good as that of diazepam but existing evidence indicates that (a) it has longer duration of action, thus reducing the likehood of recurrent seizures and (b) it probably causes fewer adverse reactions, including cardirespiratory depression, than diazepam in the treatment of GTC-SE.[14,108,109,111,116]

Lorazepam is less lipid-soluble than diazepam. Effective brain concentrations after intravenous lorazepam are achieved within the first 5 min and last for at least 12 hours (range 8 to 48 hours).

Intravenous lorazepam dose is 4 mg (adult) or 0.1 mg/kg (child) in intravenous slow bolus not exceeding 2mg/min.

Repeat doses of lorazepam have been associated with tachyphylaxis (rapidly decreasing response following its initial administration) but this is of no practical significance, as the relevant protocols for the treatment of GTC-SE indicate that a second line AED should be administered instead when 2 (or at most 3) doses of lorazepam have failed.

Experience with other than intravenous routes of administration of lorazepam is limited, though there are indications that both rectal and intranasal lorazepam are effective.[107]

Intramuscular lorazepam is of no benefit because absorption is slow.

Formulations of lorazepam may contain benzyl alcohol, which is contraindicated in infants and young children up to 3 years old.

Midazolam, the first water-soluble benzodiazepine, is increasingly being used in the treatment of SE and has several advantages over the other benzodiazepines:[108,142,143]

- It is water soluble while most of the other benzodiazepines and effective drugs, such as phenytoin, need to be dissolved in propylene glycol or benzyl alcohol, which may be harmful, particularly in infants[143]
- It is the only benzodiazepine that can reliably be given intramuscularly, thus making it very useful when other routes of administration cannot be used
- Its buccal and intranasal use has been successful in effectively stopping ongoing seizures; it has become first line option in at-home management of status epilepticus
- Its intravenous application has stopped seizures that have been resistant to other benzodiazepines and to phenytoin.

Midazolam at pH 4 has an open ring, which makes it water soluble, but at physiological pH the ring closes, thus making midazolam highly lipid-soluble and allowing rapid cerebral penetration.

Midazolam has an extremely short duration of action with an elimination half-life of 2 hours (range 1.5–2.5 hours); therefore there is a high recurrence rate of seizures.

Buccal midazolam (10–20 mg in adults; 0.4–0.5 mg/Kg in children) is rapidly absorbed with fast onset of effect within 5–10 min.

Intranasal midazolam (5 mg in adults; 0.2 mg/Kg in children) reaches maximum plasma concentration faster (in around 14 min) than other benzodiazepine formulations for intranasal administration (clonazepam takes 17 min, diazepam and lorazepam over 30 min).[128]

Intramuscular midazolam has a rapid onset of effect, within 10 or 15 min.[126] Conversely, intramuscular lorazepam and diazepam are very slow in reaching maximum plasma concentrations, averaging an hour or more.[126]

Clonazepam:[2,136,139,144] Though effective and of particular importance in the treatment of myoclonic status epilepticus, the use of clonazepam has significantly declined in recent years, mainly because of sedative and other ADRs.[144] A major problem associated with intravenous clonazepam is excessive bronchial secretions that may result in obstructive hypopnoea and aggravate respiratory depression.

The dose of intravenous clonazepam is 1–2 mg (adult) or 0.01–0.03 mg/kg (child) at a rate not exceeding 1 mg /min.

Clonazepam is completely absorbed after oral administration, reaching peak plasma concentrations within 1–4 hours. Its elimination half-life is around 30 hours (range 20–60 hours).

Phenytoin sodium[2,108,137,140,145]

Phenytoin sodium is recommended for the treatment of established status epilepticus if benzodiazepines have failed. Around half of the patients who do not respond to the initial benzodiazepine alone will respond to subsequently given intravenous phenytoin.

The parenteral preparation of phenytoin sodium is a hydroalcoholic mixture of 40% propylene glycol, 10% alcohol, and 50% water with the pH adjusted to 12, necessary to provide 50 mg/ml solution of phenytoin sodium. Propylene glycol can be harmful in neonates, young children and slow metabolisers of the substance.

Phenytoin is highly protein-bound; only its free portion is metabolically active. Effective levels of intravenous phenytoin are reached within 10 to 30 min and its elimination half-life ranges from 10–15 hours.

Phenytoin should be given as a bolus of 1 g (adult) or 15–20 mg/kg (child) at 25–50 mg/min (1 mg/kg/min) under ECG and blood pressure monitoring. Because of the dangers of precipitation, it should not be given through the same line as other medication and should not be given with glucose solutions. It should be followed by an injection of sterile saline through the same needle or intravenous catheter to avoid local venous irritation due to the alkalinity of the solution. Continuous infusion should be avoided. Most adult patients may need more than 1 g of phenytoin; an additional 10 mg/kg may be given to reach plasma levels of approximately 25–30 mg/l. In neonates, the drug should be administered at a rate not exceeding 1–3 mg/kg/min.

Problems with phenytoin include (a) difficulty in maintaining therapeutic plasma levels because of multiple drug interactions and its saturable pharmacokinetics of hepatic metabolism and protein binding and (b) ADRs in intravenous phenytoin administration. These include:

- cardiac arrhythmias, QT prolongation, hypotension and less often respiratory depression that may be reduced by slower infusion rates; hence blood pressure and ECG monitoring is needed.
- severe tissue reactions that may occur with and without extravasation of phenytoin into adjacent tissue (patient discomfort, vein irritation/tissue damage). The 'purple glove' syndrome manifests with pain, oedema and discolouration in the distribution of a glove at the intravenous injection site and occurs in up to 6% of patients. Elderly patients are particularly at risk. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required invasive interventions such as fasciotomies, skin grafting and amputation.[146]

Intramuscular phenytoin is of no use in CSE because its absorption is even slower than after oral administration.

Important clinical note

Patients on oral phenytoin treatment when this is temporarily not feasible

A 50–60% fall in plasma levels may occur when patients are changed from oral to intramuscular administration of phenytoin. The drop is caused by slower absorption via the intramuscular route, as compared to oral administration, due to the poor water solubility of phenytoin. Therefore, a sufficient dose must be administered intramuscularly to maintain the plasma level within the therapeutic range. Where oral dosage is resumed following intramuscular usage, the oral dose should be properly adjusted to compensate for the slow, continuing intramuscular absorption in order to avoid toxic symptoms.

Intravenous administration may be the preferred route for producing rapid therapeutic plasma levels in these patients.

Fosphenytoin

Fosphenytoin is an aqueous parenteral phosphate ester prodrug of phenytoin developed in order to avoid the local complications associated with parenteral phenytoin.[108,110,147] Fosphenytoin is extensively plasma protein bound (95%–99%), and this binding is saturable – the percent bound decreases as total fosphenytoin concentrations increase. Fosphenytoin is rapidly and completely converted, mainly by phosphatises, to phenytoin, which is its active metabolite. The conversion half-life of fosphenytoin to phenytoin is approximately

15 min. Conversion time is unaffected by plasma concentrations but can be affected by low albumin states. Fosphenytoin displaces phenytoin from protein binding sites.

Fosphenytoin is measured and labelled in phenytoin equivalents to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. For every mmol of fosphenytoin administered, one mmol of phenytoin is produced. A vial containing 75 mg/ml fosphenytoin sodium is equivalent to 50 mg/ml phenytoin sodium after administration.

The dose of intravenous fosphenytoin in CSE is 15–20 mg/kg of phenytoin equivalent administered at a maximal rate of 150 mg/min of phenytoin equivalent. Accounting for conversion time, peak concentrations are reached within 10 min of completion. Despite this rapid administration, it is unclear whether fosphenytoin controls seizures faster than phenytoin.

Regarding ADRs, fosphenytoin is fulfilling its promise of avoiding the local tissue reactions associated with phenytoin use, but otherwise probably has the same ADRs as phenytoin, including cardiovascular ADRs. Fosphenytoin is contra-indicated in patients with sinus bradycardia, sino-atrial block, second and third degree A-V block, and Adams-Stokes syndrome.

The role of intramuscular fosphenytoin is unclear, but peak concentrations occur at approximately 30 min post dose and plasma concentrations are lower (but more sustainable) than those following intravenous administration. In general, intramuscular fosphenytoin generates systemic phenytoin concentrations that are similar to those following administration of oral phenytoin sodium, thus allowing essentially interchangeable use.

Phenobarbital sodium

Phenobarbital sodium[2,108,110,137,148] has equivalent efficacy to phenytoin. It is handicapped by its depressant effect on respiration and consciousness and a high risk of hypotension (34%).[148] For these reasons, phenobarbital is recommended as a third-line AED in CSE only when benzodiazepines and phenytoin fail. Respiratory and blood-pressure support should be immediately available.

The parenteral preparation of phenobarbital sodium usually consists of 200 mg active substance in a mixture of 90% propylene glycol and 10% water.

The dose of intravenous phenobarbital in CSE is 10–20 mg/kg (adult) or 15–20 mg/kg (child) at a maximal rate of 100 mg/min and a total dose for adults no more than 1g. Peak concentrations are reached within 20–40 min of completion and elimination half-life is around 100 hours. A maintenance dose of 1–5 mg/kg is given at 24 and for 48 hours after the loading dose.

Phenobarbital sodium is still a first line AED for neonatal seizures (see page 246) and in resource-poor countries.[149]

Intramuscular and oral phenobarbital have similar rates of absorption and distribution; peak plasma levels are reached within 4 hours with 80–100% bioavailability. They are suitable only for patients on oral phenobarbital who have failed to take their medication.

Paraldehyde

Paraldehyde, a cyclic trimer of acetaldehyde molecules, is an old CNS depressant used as anti-epileptic, hypnotic and sedative drug. Its use for the treatment of status epilepticus started in 1924, when it significantly reduced CSE-associated mortality.

Paraldehyde is particularly useful in the absence of resuscitation facilities or for patients in whom respiration is compromised because, unlike benzo-diazepines and phenobarbital, it does not cause respiratory depression. Currently, in the UK only rectal paraldehyde is recommended for status epilepticus if benzodiazepines fail. Its effectiveness has been confirmed in a recent prospective audit report in the management of acute, including prolonged, tonic-clonic convulsions.[150] Rectal paraldehyde terminated the convulsion in 33 (62.3%) of the 53 episodes. There was no recorded respiratory depression in any episode.[150]

A probable consensus is that paraldehyde should be given as an alternative to diazepam in children in whom it is already known to be effective, or when intravenous access has not been established and rectal benzodiazepines have failed. The only acceptable route is rectal, as above.[142] Intramuscular or intravenous administration often causes local tissue damage and sterile abscesses as well as other complications.[108,142] Intravenous administration can also cause pulmonary edema, circulatory collapse and other complications. Orally, it can be irritating to the throat and stomach.

For rectal use, a pre-mixed solution comprising 1:1 paraldehyde liquid with olive oil is often used. The dose prescribed is 0.8 ml/kg (0.4 ml/kg paraldehyde with 0.4 ml/kg of olive oil).

Paraldehyde is not available in the USA.

Valproate, levetiracetam and lacosamide

There is an increasing body of evidence[14,108,151–153] that some AEDs available in parenteral formulations suitable for intravenous administration are good treatment options for status epilepticus. In particular, valproate and levetiracetam are considered to be first class agents, although they do not have approved licensed indications for this purpose; valproate is already included in some national guidelines as an agent to treat status epilepticus.

Their use is mainly based on case series that describe impressive efficacy with usually minimal ADRs. Publication bias is expected because favourable results are more likely to be reported. However, commercially sponsored RCTs are unlikely to be carried out because of the lack of incentives and the high morbidity and mortality associated with CSE in general.

Both valproate and levetiracetam can be given by relatively rapid infusion rates, have a broad therapeutic spectrum, can be used in all age groups, show low protein binding and linear kinetics, are non-sedative and have a relatively safe profile with regard to respiratory and circulatory adverse effects.

Valproate has been available in parenteral formulations since 1993. In unblind randomised control studies and numerous case reports it has shown equal or better efficacy than phenytoin or diazepam with fewer ADRs. In particular, respiratory and circulatory depression were very uncommon even at high infusion rates. However, valproate does have other ADRs, as detailed in the Pharmacopoeia.

Valproate is usually given at intravenous infusion of 25–30 mg/kg over 2–15 min or at 3–6mg/kg/min. According to manufacturers, administration in adults is by intravenous injection (over 3–5 min) of 400–800 mg (up to 10 mg/kg), followed by intravenous infusion up to a maximum of 2.5 g daily; in children under 12 years 20–30 mg/kg daily is usually administered, which may be increased provided plasma concentrations are monitored (with doses above 40 mg/kg daily, clinical chemistry and haematological parameters should also be monitored).

Treatment efficacy with valproate is time-dependent – that is, the earlier it is given, the more likely it is to terminate the seizures.[154]

Levetiracetam has been available in parenteral formulations since 1993. Its use in status epilepticus of various types and severities and in different patient age groups (including neonates) has been reported in over 150 cases, as recently reviewed and assessed.[153,155–159] The evidence so far indicates that levetiracetam has a significant role to play in the treatment of status epilepticus because of its efficacy, relatively safe profile, lack of clinically significant drug interactions and lack of sedative effects. However, the results are sometimes conflicting with regard to the type of status epilepticus most likely to respond to levetiracetam.

Levetiracetam 1000–2000 mg (adults) or 15 to 70 mg/kg (median 30 mg/kg) diluted with at least 100 ml of infusion fluid is given over 15 min. It may also be administered in slow bolus.

Lacosamide is the newest AED available in parenteral formulation and there are already a few case reports demonstrating its effectiveness in the treatment of status epilepticus.[160,161] Any conclusions regarding its use would be entirely premature at this time.

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Imitators of epileptic seizures

'Non-epileptic seizures' or 'non-epileptic paroxysmal disorders' are the currently preferred descriptive names for the common and numerous, diverse paroxysmal clinical events that mimic or look like but are not epileptic seizures.[1–3]

The ILAE[4,5] defines the imitators of epileptic seizures as:

> Clinical manifestations presumed to be unrelated to an abnormal and excessive discharge of a set of neurons of the brain including (a) disturbances in brain function (vertigo or dizziness, syncope, sleep and movement disorders, transient global amnesia, migraine, enuresis); and (b) pseudoseizures (non-epileptic sudden behavioural episodes presumed to be of psychogenic origin; these may coexist with true epileptic seizures).

I use the term non-epileptic paroxysmal events (NEPEs) or imitators of epileptic seizures to also include normal paroxysmal behaviours that are neither seizures nor disorders. NEPEs occur at any age, but their highest incidence is seen in childhood, particularly during the first years of life.

NEPEs misdiagnosed as epileptic seizures affect as many as 20–30% of patients diagnosed with, and often treated for many years for, epilepsy or admitted to tertiary care epilepsy units.[6–8] The problem is complicated by the fact that approximately 30% of patients with genuine epileptic seizures also suffer from non-epileptic, mainly psychogenic, seizures.

NEPEs are divided into two groups:

- physiological or organic NEPEs
- psychogenic NEPEs.

Author's note to junior physicians

In the process of making a diagnosis be prepared to challenge yourself with complicated cases and enrich your knowledge through the discussion of cases with other colleagues and reading about possible seizure imitators other than the epileptic disorders. The classic book by Adams and Victor, *Principles of Neurology*, now in its eight edition, is the best place to start with your reading.[9]

There are also excellent and reliable website sources of information such as PubMed, WEMOVE and GeneTests. The Bookshelf of the National Center for Biotechnology Information provides free of charge a growing collection of biomedical books that can be easily searched and used (http://www.ncbi.nlm.nih.gov/sites/entrez?db=books). Amongst these books, *Imitators of Epilepsy*[3] is an excellent and relevant read. The *Merck Manuals*, a series of healthcare books for medical professionals and consumers, are now freely available in enhanced online versions (www.merck.com/mmpe/index.html); these have been appropriately updated and contain photographs, and audio and video materials.

There is always something new to learn and find. It is not shameful not to know the answer, nor is it embarrassing to ask other colleagues.

No-one, even the most expert, knows everything.

Making a personal database and recording unclassified or strange cases that elude diagnosis is a very useful and rewarding learning exercise. Some of these cases may cluster either into a well-described syndrome unknown to you or constitute a new unrecognised syndrome that you may be the first to describe.

The physiological or organic NEPEs are a broad spectrum of episodic manifestations ranging from normal phenomena, such as hypnagogic jerks, hallucinations or illusions, to a galaxy of abnormal paroxysmal symptoms of a variety of brain and systemic disorders. The differential diagnosis is much more demanding in neonates, babies, toddlers and young children in whom there are many different causes and seizure imitators of normal and abnormal behaviours and symptoms.

The assessment of a patient referred for epilepsy should follow the same approach as any other disorder (see page 3).

The clinical diagnosis is often easy and secured only if individual elements of clinical events are meaningfully synthesised with regard to quantity, quality, location, onset, chronological sequence, development, speed of progress and duration.

An inadequate history is the most common reason for misdiagnosis.

Video and video-EEG illustrations of epileptic seizures and NEPEs can be found in the CD companion of references[10–12].

Useful clinical note

Diagnosis may be elusive even after the most assiduous application of clinical methods, even for astute experts.

When a definite diagnosis is not possible:

- explain this to the patient/carers
- state it in the patient's notes
- whenever reasonable and safe, allow time and seek additional information by clinical history, progress and tests
- discuss or refer the patient to another colleague for a second opinion
- avoid initiating treatment but if the paroxysmal events are potentially dangerous and epileptic seizures are the most likely diagnosis, anti-epileptic drugs (AEDs) may be started (but always be prepared to modify diagnosis and treatment).

Main types of epileptic seizures and their imitators

Generalised tonic–clonic seizures

Generalised tonic–clonic seizures (GTCSs), because of their dramatic features, are the main reason for referral for medical consultation. This first demands careful exclusion of syncope, psychogenic non-epileptic seizures and other NEPEs. Once an unequivocal diagnosis of genuine epileptic GTCS has been established, the main differential diagnosis is between primarily GTCS (PGTCS) and secondarily GTCS (SGTCS) (Table 2.4).

Considering their dramatic and stereotypical features, GTCSs should not be difficult to diagnose. So, why are NEPEs so frequently misdiagnosed as GTCSs and less often *vice versa*? There are four main reasons for this:

1. The patient is amnesic of the ictal events, although other symptoms preceding a GTCS are often of diagnostic value.
2. The events have not been adequately witnessed, although the physical and mental consequences of a GTCS are often of diagnostic value.
3. The events, even when adequately witnessed and identified, are abbreviated in diagnostic terms (tonic–clonic seizures or grand mal or syncope or pseudoseizure) rather than describing in detail what had happened.
4. Previous minor paroxysmal events (which may be focal or generalised seizures) are not detected.

The medical training in GTCSs and epilepsies in general is largely inadequate (see lessons to be learned below).

That psychogenic convulsive status epilepticus can be mistaken by physicians as genuine GTCS status epilepticus – a misdiagnosis that may have avoidable and grave consequences – is of concern for all those involved.

Lessons to be learned

Tutorials on differential diagnosis of GTCSs

For educational purposes I often present to junior colleagues a video-recorded convulsive NEPE with a hypothetical scenario in which they witness this patient's symptoms in the accident and emergency department. The video shows a middle-aged man who, while sitting in the company of others, slowly takes his glasses off, places them on the table and immediately, smoothly slips to the floor where he stretches out, apparently unconscious and with eyes closed, hands crossed on the front of his chest and legs cycling rather than convulsing.

The attendants are allowed to see the video many times, in slow motion if they wish, before giving their diagnosis and what they are likely to put down in his medical notes. Almost all the attendants consider this a genuine GTCS, although some made the remark that this was a SGTCS in order to explain why the patient removed his glasses before the convulsions. More than 80% would put the diagnostic term GTCS down in the patient notes, without describing the sequence of the events, although some would make a remark that there was no tongue biting or urinary incontinence. None of the attendants considered the diagnostic significance of the patient having his eyes closed during the whole event, which alone would exclude the possibility of a GTCS.[13] All attendants knew that a GTCS manifests with tonic–clonic convulsions and their sequences, but more than half had not seen a genuine GTCS, even though this should be a routine video teaching material in every medical school. The tutorial ends with the presentation and analysis of a video-recorded genuine GTCS.

Of the numerous imitators of epileptic seizures, the syncope and convulsive NEPEs are detailed in this chapter because they are the most likely of the imitators to be misdiagnosed as GTCSs. Suspicion of nocturnal GTCSs (if not witnessed by a room- or bed-partner) is usually raised by symptoms and signs that result from the direct or indirect impact of GTCSs on patients (injury, muscle pains, bedwetting, confusion), which are usually apparent when the patient wakes up.

Symptoms preceding SGTCSs have as many imitators as focal epileptic seizures.

Prodromes (non-epileptic) preceding the onset of a GTCS

Prodrome is a non-epileptic, subjective or objective clinical alteration preceding the onset of an epileptic seizure by several hours. This can take the form of a headache, changes in mood or behaviour, sleep disturbances, light-headedness, anxiety and difficulty in concentrating before the attack. Prodrome should not be confused with aura, which is a brief seizure itself. Prodromes are most probably symptoms of systemic or metabolic disturbances that are the causative or precipitating factors of the following seizure (i.e. hypoglycaemia, premenstrual period). Prodromes are attributed to a pre-ictal increase of excitability of an epileptogenic focus or of the entire brain,[14] but there is no proof for this.

For almost all the patients whom I have seen with a diagnosis of prodrome, it was either an epileptic seizure itself (prolonged or clusters of brief, focal or generalised) or a symptom of a metabolic or electrolyte disturbance that caused the GTCS.

The following quote was taken from a medical report of a patient with phantom absences, GTCSs and absence status epilepticus:

This man has GTCSs from 16 years of age. Interestingly, each of his GTCSs is preceded by a prodrome of half an hour to 12 hours of mental slowing down during which he makes some effort to formulate his response, which occassionally is inappropriate and bumbled.

Ictal events preceding the onset of a GTCS

These differ between PGTCSs and SGTCSs; for example, clusters of myoclonic jerks precede and herald PGTCSs in juvenile myoclonic epilepsy (JME), whereas SGTCSs develop from focal seizures (see Chapter 2).

Epileptic myoclonic jerks

There are many types of epileptic myoclonic jerks that may manifest as:

- the only manifestation of an epileptic seizure
- one component of an epileptic attack occurring in continuity with another type of seizure, such as myoclonic–atonic seizures, myoclonic absence seizures or myoclonic tonic–clonic seizures.

Furthermore, in some epileptic syndromes, myoclonic jerks may be:

- the predominant, but rarely the only type of epileptic seizure
- infrequent or inconspicuous
- concurrent with genuine non-epileptic myoclonus or myoclonic-like jerks.

Frequently, epileptic myoclonic jerks are not reported by the patient and not detected by the physicians. A typical example of this is JME (see Chapter 13).

The yield of detecting myoclonic jerks increases significantly by questions such as 'do you spill your morning tea easily?', 'do you become unduly clumsy in the morning?' and 'do you have sudden rigors?', and mainly by physical demonstrations of what the myoclonic jerks look like (videos may be much more useful for this).

If hypnagogic jerks are reported then it is certain that the concept of myoclonic jerks has been understood.

Epileptic myoclonus should be distinguished from normal myoclonic jerks, such as hypnagogic myoclonus (page 118), non-epileptic (subcortical) myoclonus and non-epileptic, non-myoclonic phenomena. Non-epileptic (subcortical) myoclonus includes:

- essential myoclonus
- opsoclonus–myoclonus syndrome (Kinsbourne syndrome), dancing eyes syndrome or myoclonic encephalopathy of infants; myoclonus is nearly continuous, erratic and movement-induced (action myoclonus)
- benign neonatal sleep myoclonus (see page 112)
- normal startle responses or hyperekplexia (see page 113)
- psychogenic myoclonus, which is usually segmental or generalised, and usually worsens with exposure to stress or anxiety
- toxic or drug-induced myoclonus.

Non-epileptic, non-myoclonic phenomena include:

- tremor (see page 110)
- tics (see page 110)
- involuntary movements (page 114).

Diagnostic tips

Myoclonic NEPEs frequently occur during any stage of sleep.

Myoclonic jerks consistently or exclusively occurring in the transitional state from wakefulness to sleep are unlikely to be epileptic.

Conversely, myoclonic jerks predominantly occurring upon awakening are probably of epileptic origin.

Absence seizures

Absence seizures with severe impairment of consciousness should not be difficult to diagnose. However, these (including absence status epilepticus) are often misdiagnosed as NEPEs, and include episodes of daydreaming, preoccupation, mannerisms, drug-induced abnormal mental states, organic confusional states, prodromes of GTCS or transient global amnesia. NEPEs of vacant spells frequently occur in children with learning difficulties such as Rett or Lennox–Gastaut syndrome.

If there is uncertainty as to the nature of the attacks, an EEG is mandatory. A normal EEG with appropriately performed hyperventilation makes absence seizures (but not complex focal seizures) improbable.

An EEG is the most appropriate test to differentiate absence epileptic seizures from NEPEs.

Tonic seizures

Tonic seizures of epileptic encephalopathies are sometimes inconspicuous and occur predominantly or only during sleep. Imitators of tonic seizures are NEPEs that cause sustained increase in muscle contraction such as:

- tonic spasms of multiple sclerosis, which rarely may be a presenting symptom
- dystonic symptoms of paroxysmal movement disorders (see page 109)
- tonic reflex seizures of early infancy (page 111)
- gastro-oesophageal reflux attacks (see page 112)
- occupational spasms such as writer's spasm.

Epileptic spasms

The epileptic spasms should be easy to diagnose because of the unique characteristic features of each attack and because of their serial and unprovoked clustering. However, parents and physicians often miss this.[15] Erroneous diagnoses include exaggerated startle responses or 'colic and abdominal pain', non-epileptic episodic disorders and gastro-oesophageal reflux.[15] Benign myoclonus of early infancy (Fejerman syndrome or benign non-epileptic infantile spasms)[16–18] is not an epileptic condition, but may cause diagnostic problems because of a similar age at onset and similar spasms (see page 112).

Epileptic drop attacks

Epileptic drop attacks (synonyms: sudden falls, astatic seizures) are due to loss of erect posture that results from an atonic, myoclonic or tonic mechanism.[19,20] Falls may be due to atonic, myoclonic, myoclonic–atonic or tonic seizures. They are common in epileptic encephalopathies (see Chapter 10). Convulsions and loss of consciousness may not occur or may not be apparent. Falls may also occur in focal epilepsies.[21,22]

Of the imitators of epileptic astatic seizures (i.e. syncopes, movement disorders, brain-stem, otological causes like in Meniere diseases, spinal or lower limb abnormalities, cataplexy, periodic paralysis, drug-induced) the most likely to cause diagnostic problems are drop attacks associated with:

- colloid cysts of the third ventricle
- neurological conditions of lower limb muscle weakness with sudden give-way weakness leading to falls without impairment of awareness
- vertebrobasilar insufficiency (see page 130)
- carotid sinus hypersensitivity (see page 104).

Drop attacks in the elderly are associated with high levels of morbidity; diagnoses are achievable in the majority of cases and these are unlikely to be of epileptic origin.[23]

Idiopathic drop attacks without a detectable cause manifest with sudden fall without loss of consciousness and with instantaneous recovery, although injury may occur. They are more common in middle-aged women.

Focal epileptic seizures

There is a myriad of normal and abnormal NEPEs that imitate focal epileptic seizures. These vary according to the type of focal epileptic seizure (Tables 2.1 and 2.3). Typical examples of NEPEs imitating focal epileptic seizures are:

- the migraine auras (page 126), déjà vu and other experiential phenomena of normal people
- hallucinations of psychiatric patients, drug-related olfactory and other hallucinations
- transient paraesthesias of peripheral neuropathies, paroxysmal movement disorders and parasomnias.

Conversely, focal epileptic seizures may be misdiagnosed as NEPEs:

- visual occipital seizures are commonly considered to be visual aura of migraines
- hypermotor seizures are a typical example of mistaking epileptic seizures for NEPEs; so-called 'paroxysmal nocturnal dystonia' or 'hypnogenic paroxysmal dystonia' is frontal lobe epilepsy
- autonomic seizures of childhood are another disturbing example of erroneous diagnoses as encephalitis, migraine, syncope, cyclic vomiting syndrome (CVS) or gastroenteritis.[24]

The differential diagnosis of focal seizures is detailed in the relevant chapters of this book.

Syncopal attacks imitating epileptic seizures

Syncopes are among the most common non-epileptic attacks misdiagnosed as epileptic seizures, including GTCSs.[1,25–39]

A syncope is defined as a loss of consciousness and postural tone caused by cerebral hypoperfusion with spontaneous recovery.[38] There is an abrupt cutting off of the energy substrates to the cerebral cortex, usually through a sudden decrease in cerebral perfusion by oxygenated blood.[31] If cerebral perfusion/oxygenation is cut off for a period of 8–10 s, then a clinical picture comprising loss of consciousness and postural tone, pallor and sweating, brief (lasting seconds) extensor stiffening or spasms, and a few irregular myoclonic jerks of the limbs may occur. The whole episode is brief, usually lasting less than 10 s. There is a great variety in the amplitude of the myoclonic jerks, the degree of stiffening and the recovery time after syncope.[31]

Cerebral syncope is defined as a syncope that results from derangement of cerebral autoregulation leading to cerebral vasoconstriction with resultant cerebral hypoxia in the absence of systemic hypotension.

Convulsive syncope is a term used for any type of syncope manifesting with convulsive movements.

Prodromal warning symptoms (presyncope) are commonly present but sometimes these are only recalled when syncope is reproduced, as in the head-up tilt test. They develop over 1–5 min and include light headedness, nausea, a feeling of warmth, sweating, palpitation, greying or blacking of vision, muffled hearing and feeling distant. At this stage a syncope may be averted by lying down in a horizontal position with the head down and legs up. Lack of prodromal symptoms, such as in a tussive syncope, are explained by the rapidly developing cerebral hypoperfusion.

The setting and stimulus are the most important identifiable factors/precipitants in allowing the presumptive diagnosis of syncope. Simple faints or vasovagal syncope most often occur upon getting up quickly or after prolonged standing, particularly if associated with peripheral vasodilatation (e.g. hot, unventilated, crowded places, or after drug or alcohol use) or increased vagal tone (e.g. bloody, terrifying, or obnoxious scenes, and painful stimuli).

Cerebral hypoperfusion most commonly results from conditions that decrease venous return (e.g. reflex-mediated vasomotor instability) or disorders that decrease cardiac output, such as primary cardiac disorders.

In general, syncopes are categorised into:

- neurally mediated syncopes (neurocardiogenic or reflex-mediated syncope) that are usually benign
- cardiogenic syncopes from either cardiac rhythm or structural cardiac disorders, which are potentially life threatening.

Autonomic disturbances may also lead to cerebral hypoperfusion and fainting as with orthostatic syncope.

In differentiating syncopes from GTCSs, textbooks usually emphasise the characteristics of typical syncopes that are listed in Table 4.1.

Based on a proper synthesis of the quality and chronological order of the clustering of these symptoms, the differential diagnosis of syncopes from GTCSs is rarely a problem. However, there are important points to consider and these are listed in Table 4.2.

Neurally mediated syncope

Examples of neurally mediated or non-cardiogenic syncopes include:

- vasovagal syncope (simple faint) – variants of which may include reflex anoxic seizures (reflex asystolic syncope) and cyanotic breath-holding attacks (of prolonged expiratory apnoea) in infants and children
- situation-related syncope caused by increased intrathoracic pressure, as a result of, for example, cough (tussive syncope), Valsalva manoeuvres, or straining to void (micturition syncope) or defecate
- carotid sinus syncope.

Commonly emphasised clinical manifestations of syncope

- Precipitating factors or triggers such as upright position, bathroom, crowded and humid places, lack of food, unpleasant circumstances, venipuncture
- Prodromal symptoms of cerebral ischaemia, such as dizziness, greying of vision and tinnitus
- Gradual onset over seconds to 1 min
- Pallor and sweating
- Lack or rare occurrence of convulsions (other than myoclonic jerks), urinary incontinence or tongue biting
- Brief duration (1–30 s)
- Rapid recovery with no post-ictal confusion

Table 4.1

Clinical features of syncopes not emphasised in their differentiation from epileptic seizures

- Convulsions occur in 70–90% of syncopes; symptoms include myoclonus, tonic flexion or extension, more complex movements and automatisms such as lip licking, chewing or fumbling
- Visual hallucinations (a perception of grey haze, coloured patches, glaring lights or more complex scenes involving landscapes, familiar situations or people) and, less often, auditory hallucinations (rushing and roaring sounds, traffic and machine noises, and talking and screaming human voices, but never intelligible speech) are frequent (60%) in both convulsive and non-convulsive syncope[40]
- Syncope usually happens in an upright position but may also occur in the supine position (e.g. venipuncture)
- Sudden onset, urinary incontinence and trauma are not uncommon
- Abdominal pain that may be confused with epigastric aura may occur at onset. Auras comprising epigastric, vertiginous, visual or somatosensory experiences occur both in neurally mediated and cardiogenic syncope[41]
- Pallor and sweating are not invariable symptoms at onset and may be symptoms of autonomic epileptic seizures with or without secondarily GTCSs
- Complete recovery may not be rapid and post-ictal confusion may occur, although neither of them reaches even close to the severity of that after a GTCS
- Eyes, as in GTCSs, are always open during syncope and the most consistent oculomotor sign is an upward turning of the eyes early in its course, which may be followed by lateral eye deviation[42,43]

Table 4.2

Vasovagal syncope

Vasovagal syncope is the most common and familiar form of neurally mediated syncope, and results from a combination of excessive vagal tone, abnormal catecholamine response to stress, venous pooling during an upright stance and impaired cardiac filling. Episodes may begin in infancy, sometimes with reflex anoxic seizures, and thereafter are seen at all ages, although it predominates in otherwise normal children and adolescents. The frequency of vasovagal syncopes varies considerably from one to two during a lifetime to as common as more than once a day.

Reflex anoxic seizures

Reflex anoxic seizures (synonyms: pallid breath-holding attacks, pallid infantile syncope) are reflex asystolic syncopes in young children. An unexpected bump to the head, an occasional fright or seeing blood triggers a neurally mediated vagal discharge leading

to severe bradycardia, asystole, syncope and anoxic seizure. The child falls unconscious, white as a sheet and looks dead.

Useful clinical note

Breath-holding attacks in children

In children, there are two main types of so-called 'breath-holding attacks':

- cyanotic or blue breath-holding attacks (prolonged expiratory apnoea usually without syncope)
- pallid or white breath-holding attacks (reflex anoxic seizures, which are reflex asystolic syncopes).

The term 'breath-holding' has been discouraged by Stephenson and Zuberi because it erroneously implies a voluntary action to obtain gains or a behavioural disorder; psychological disorders in those afflicted do not differ from those in control children.[37] In contrast to voluntary breath holding that occurs during inspiration, cyanotic breath-holding attacks occur during expiration.

The cyanotic or blue breath-holding attacks, which are more common than the pallid forms, are purely respiratory consisting of prolonged expiratory apnoea without any change in cardiac rate or rhythm. Attacks of prolonged expiratory apnoea have similar triggers to reflex anoxic seizures, but they usually occur when the child has reasons to suddenly become angry or frustrated or fearful. The child stops breathing and becomes cyanotic until spontaneous recovery with a deep breath.

Mixed breath-holding of expiratory apnoea and a degree of bradycardia or cardiac asystole occur.[37]

Clarification on terminology

- Reflex anoxic seizures are syncopes (and not epileptic seizures).
- Anoxic epileptic seizures are epileptic seizures caused by syncopes.
- Cyanotic or blue breath-holding attacks are not syncopes.

Orthostatic syncope

Orthostatic syncope (autonomic failure) results from failure of normal mechanisms to compensate for the temporary decrease in venous return after standing.

Syncope occurs within seconds or minutes of becoming upright, especially when rising and after meals. Unlike with reflex vasovagal syncope, the skin stays warm, the pulse rate is unchanged despite the fall in blood pressure, and sweating is absent. Assuming a horizontal position results in complete recovery. Causes include autonomic dysfunction, cardiovascular disorders and drugs. Orthostatic syncope secondary to autonomic failure is rare in childhood. Dopamine β-decarboxylase deficiency is a possibility in such a clinical situation.

Syncopes induced by Valsalva manoeuvre

During a Valsalva manoeuvre (powerful effort to exhale against a closed glottis) increased intrathoracic pressure limits the venous return to the heart and increases vagal tone, resulting in decreased cardiac outflow and syncope.

Rarely, patients may have self-induced syncope by Valsalva manoeuvre. This particularly occurs in children with learning disabilities and Rett syndrome. The anoxic attacks may be severe.

Micturition syncope

Micturition syncope is a reflex-mediated situational syncope usually occurring in men while standing for nighttime micturition.

Several mechanisms act in concert:

- postural – standing on leaving a warm bed causing hypotension
- straining – Valsalva manoeuvre increasing an already high nocturnal vagal tone, causing bradycardia
- emptying bladder – abrupt decrease in stimulus to bladder stretch receptors causing reflex vasodilatation and hypotension.

Carotid sinus syncope

Carotid sinus hypersensitivity is a common cause of unexplained falls in elderly people of over 50 years of age.[44,45] The incidence steeply increases with age. Activation of one or both carotid sinuses causes peripheral vasodilation, hypotension and syncope

in people with carotid sinus hypersensitivity. Clinical attacks of syncope or falls without definite loss of consciousness are attributed to carotid sinus pressure by head turning or tight collars. Some patients may suffer from orthostatic hypotension but usually there is no evidence of sympathetic or parasympathetic failure.

Diagnostic carotid sinus massage may be positive in asymptomatic elderly patients[45] and carries a risk of prolonged asystole, transient or permanent neurological deficit, stroke and sudden death.

Cardiogenic syncopes

Cardiogenic syncopes result from either rhythm (e.g. tachyarrhythmias or bradyarrhythmias) or structural (e.g. aortic or mitral stenosis, intracardiac tumours, cardiomyopathy, ischaemic heart disease) cardiac disorders. Cardiogenic syncopes are potentially life threatening and may be treatable. Morbidity and mortality is up to 50% within the first 3 years following the initial attack, and it is cause-dependent.

Palpitations, chest pain, shortness of breath, extreme fatigue or other features of cardiovascular insufficiency occur with other presyncopal symptoms of simple faints. Cardiac syncopes occur from any posture (e.g. arrhythmogenic syncope is common in bed), and during periods of high exertion or emotion. Anoxic seizures precipitated by exercise require the urgent exclusion of cardiac causes, although most turn out to be neurally mediated syncopes.

In tachyarrhythmias, a heart rate of more than 150–180 beats/min prevents adequate ventricular filling. In bradyarrhythmias, a heart rate of less than 30–35 beats/min prevents adequate cardiac output.

Attacks due to transient complete heart block are abrupt and short with rapid loss of consciousness. Lack of cardiac output may be due to short episodes of ventricular tachycardia or fibrillation. Prolongation of the QT interval may lead to such events. Attacks may be preceded by palpitations, extreme fatigue or presyncopal features. Mitral valve prolapse and aortic stenosis may present with episodic loss of awareness due to fluctuating cardiac output or associated arrhythmias. Aortic stenosis and hypertrophic cardiomyopathy is especially prone to episodes of sudden collapse with loss of awareness during exercise. Sometimes ventricular tachyarrhythmias occur with normal QT intervals.

The long QT syndrome

Of various cardiogenic syncopes, the long QT syndrome is of particular significance because it may be associated with convulsive syncopes that cause unexplained sudden death in a young person and closely imitate GTCSs. It is often of autosomal dominant inheritance with mutations in genes encoding potassium or sodium channels, depending on lineage. The mechanism of the syncope is a ventricular tachyarrhythmia, normally torsades de pointes triggered by fear or fright, particularly during exercise (especially when that exercise is emotionally charged) and during sleep.

The ECG is diagnostic. Genetic testing is available.

A 33-year-old apparently normal man had, over a period of 6 months, three unwitnessed rather severe falls due to loss of consciousness that resulted in head trauma. All of them occurred while cycling or jogging in days that he recalls were particularly intense. EEG was normal but a synchronous ECG showed long QT syndrome, verified with appropriate cardiological evaluation.

Brugada syndrome, characterised by ST-segment abnormalities, is another genetic ion channelopathy (SCN5A mutation) that may imitate epileptic attacks and other causes of sudden death. Genetic testing is available.

Useful note

A proper ECG should be obtained in any patients suspected or newly diagnosed with epilepsy.

Misdiagnosis of cardiac diseases as epilepsy is common and often difficult to recognise on clinical information alone. Therefore a proper ECG is mandatory for this crucial differentiation.

Also consider that the adverse cardiac effects of some AEDs may have fatal consequences for patients with conditions such as long QT or Brugada syndrome and other disorders of cardiac conductivity.

Syncopes induced by drugs and electrolyte abnormalities

Drugs and electrolyte abnormalities are common causes of syncope secondarily to cardiac rhythm changes or autonomic disturbances. Some examples include beta-blockers, quinidine, calcium channel blockers, digoxin, hypomagnesaemia and hypokalaemia.

Syncopal attacks provoking epileptic seizures: Anoxic epileptic seizures

Occasionally, but likely more often than is reported, true epileptic seizures are triggered by non-epileptic syncopes in children and adults.[39,46] This combination of syncope and epileptic seizure has been called an *anoxic epileptic seizure* (do not confuse with reflex anoxic seizure, which is a syncope). Of anoxic epileptic seizures documented with home video recordings, examples include a neurally mediated syncope inducing a long, clonic epileptic seizure with some features of myoclonic absence, and a compulsive Valsalva manoeuvre in an older autistic child provoking a vibratory tonic epileptic seizure.[46]

Epileptic seizures imitating syncope

Epileptic seizures may manifest with syncopal-like attacks (see ictal syncope in Panayiotopoulos syndrome, page 349).

Psychogenic NEPEs imitating epileptic seizures

Psychogenic NEPEs (PNEPEs) or psychogenic non-epileptic seizures are among the most common recurrent paroxysmal seizure-imitating events that result from a variety of psychological disturbances.[2,6,47–49] Their synonym 'pseudoseizures' is discouraged because it is considered prejudicial. PNEPEs are not 'pseudo' in that they are extremely real episodes and 'pseudo' implies a disparaging element for the event. Similar to epileptic seizures, PNEPEs can be very troublesome to a person's life and have their own stigma.

Patients with PNEPEs often experience severe depression, anxiety, emotional stress, rage, fear and panic, in addition to other mental disturbances. Conversion disorder is the most common cause of PNEPEs.[50] Other causes, with natural histories and treatments different from those of conversion disorder, include anxiety, dissociative, depersonalisation, somatisation, panic and psychotic disorders.[2,6,47–49] Factitious PNEPEs, including Munchausen syndrome, are sometimes difficult to diagnose and prove.

According to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[51] psychological causes of physical symptoms are categorised as:

- somatoform disorders
- factitious disorders
- malingering.

Somatoform disorders are the unconscious production of physical symptoms due to psychological factors, which means that the symptoms are not under voluntary control. Patients with somatoform disorders are not faking illness; they sincerely believe that they have a serious physical problem. Specific somatoform disorders include:

- somatisation disorder
- conversion disorder
- pain disorder
- hypochondriasis
- body dysmorphic disorder.

Somatisation disorder is a relatively rare disorder that is associated with high medical resource utilisation. *In factitious disorders and malingering* there is a conscious production of physical symptoms, in which individuals present with an illness that is deliberately produced or falsified. However, in factitious disorders patients intentionally act physically or mentally ill due to psychological factors of pathological needs without obvious benefits. Conversely, in malingering, patients fake an illness for a clear motive and benefit such as financial gain.

Somatoform PNEPEs are much more common than malingering and factitious disorders.

PNEPEs, including staring spells,[52,53] are often extremely difficult to differentiate from epileptic seizures[2,6,47–49,54] and, conversely, certain types of epileptic seizures, such as those of mesial frontal lobe origin, masquerade as psychogenic-like attacks (page 459).

Table 4.3 provides some key diagnostic clues for recognising convulsive PNEPEs.

Convulsive psychogenic status epilepticus

Convulsive psychogenic status epilepticus (commonly referred to as convulsive pseudostatus epilepticus) is common in patients with PNEPEs and it is often misdiagnosed as genuine and life-threatening convulsive status epilepticus.[57–60] These patients frequently have multiple episodes of 'status' and receive intensive

Diagnostic clues for convulsive psychogenic non-epileptic events (the more common of the PNEPEs)

- Often precipitated by stressful circumstances (stress is also a precipitating factor in epilepsies)
- Can be induced in response to suggestion (useful in diagnostic provocative activating techniques; also called 'inductions')[55]
- Occur in wakefulness and in the presence of witnesses (not unusual in epilepsies)
- Lack stereotypical characteristics
- 'Convulsions' consist of asynchronous, asymmetrical, waxing and waning, accelerating and decelerating, convulsive-like movements, often with pelvic thrusts, flailing and tremors. These may be interrupted or resistant to restraint, and imitate seizures from the supplementary somatosensory area and are not GTCSs
- Eyes are commonly closed (probably the most important symptom to enable differentiation from GTCSs and syncopes, where the eyes are invariably open)
- Attempts to open the eyes passively often result in tightening of the eyelids (this may also occur infrequently in post-ictal confusion after a GTCS)
- 'Give-way weakness' on examination is common[55]
- Consciousness may be retained throughout or shows marked fluctuations
- There is no actual post-ictal confusion. The patient may become emotional and cry after the end of the non-epileptic seizure (this symptom is not unusual in patients with epileptic seizures)
- Post-ictal behaviour of responding to questions in a whispered voice or responding to commands with partial motor responses is common and may be helpful in the diagnosis of PNEPEs[56]
- Intractable to anti-epileptic medication (also occurring in epilepsies)
- *Belle indifference:* Paradoxical lack of concern about the seizures, which contrasts to the emotional distress and behaviours exhibited during the attacks

Table 4.3

care unit management. They usually have a history of other unexplained illness and deliberate self-poisoning. Episodes of anticonvulsant-induced respiratory arrest may occur.[57–60]

Diagnostic traps

At least one of the usual signs associated with a GTCS (tongue biting, falling or incontinence) is reported by about a third of the patients with non-epileptic seizures.[61]

An ictal EEG is not always abnormal during epileptic seizures.

Psychogenic non-epileptic syncope (synonyms: psychogenic pseudosyncope, hysterical fainting) is a term used to include NEPEs with clinical manifestations of psychogenic origin that mimic syncope.[62] Patients suffer frequently recurrent syncopal-like episodes of 'limp, motionless fainting' with eyes closed, unresponsiveness and a normal EEG, including normal alpha rhythm. This is often associated with complaints of vertigo and with greater reported disability. The condition may be underdiagnosed and often remains misdiagnosed for many years. Patients may go through lengthy and sometimes invasive diagnostic procedures. The psychogenic non-epileptic syncope can be easily elicited by induction.[62]

Useful clinical notes

Look at the eyes and make the diagnosis

When eyes are closed during a paroxysmal event of convulsions with loss of consciousness, the probability (almost a certainty) is that this is a PNEPE. Eyes remain open or become open, if not previously open, during GTCSs and syncopes.

Try to passively open the eyes and make the diagnosis

The eyes may be closed in post-ictal states of epileptic seizures or other causes of organic impairment of consciousness. In these cases the eyes can usually be passively opened without resistance as opposed to PNEPEs where attempts to passively open the eyes are met with resistance or tightening of the eyelids.

Suffocation in Munchausen syndrome by proxy[37,63–66]

Intentional suffocation of an infant is an uncommon but severe event. In this situation, an adult, usually the mother, suffering from Munchausen syndrome by proxy repeatedly suffocates the infant by either pressing a hand or some other material over the infant's mouth or presses the infant's face against the adult's chest, with a resultant syncope and anoxic seizure. The evolution is much longer than the usual anoxic seizures, but a definitive diagnosis requires unequivocal *covert* video-recording evidence.

Panic attacks[67–69]

Panic attacks are of abrupt onset, manifesting with an intense sense of extreme fear often with concomitant symptoms of trembling, shortness of breath, heart palpitations, chest pain, sweating, dizziness, hyperventilation, paraesthesias, nausea or vomiting, or sensations of choking. Panic attacks are actually a fight-or-flight response occurring out of context or as a response to minimal provocative factors. Patients suffer from panic, other anxiety disorders or phobias. Psychogenic non-epileptic panic attacks should mainly be differentiated from simple focal seizures of mesial temporal lobe epilepsy (see Figure 15.4).

Hyperventilation syndrome[70–73]

Hyperventilation syndrome is defined as:

> A syndrome, characterized by a variety of somatic symptoms induced by physiologically inappropriate hyperventilation and usually reproduced by voluntary hyperventilation.[70]

Hyperventilation is defined as breathing in excess of the metabolic needs of the body, eliminating more carbon dioxide than is produced and, consequently, resulting in respiratory alkalosis and an elevated blood pH.

Hyperventilation may have organic or physiological causes, but the syndrome of hyperventilation is

usually associated with emotional triggers and thoracic breathing tendency.

Hyperventilation syndrome is a frequent disorder probably affecting 6% of the population, mainly aged 15–55 years old. Women are seven times more frequently affected than men. It occurs in acute (1% of cases) and chronic forms.

The acute forms of hyperventilation syndrome manifest with agitation, hyperpnoea, tachypnoea and dyspnoea, chest pain, dizziness, palpitations, carpopedal spasm, paraesthesia, generalised weakness, a sense of suffocation and syncope. An emotionally stressful precipitating event can often be identified. Symptoms may be unilateral. The chest pain is often relieved rather than provoked by exercise. ECG abnormalities may occur and include prolonged QT interval, ST depression or elevation, and T-wave inversion.

The chronic hyperventilation syndrome presents with a galaxy of multi-system symptoms without any clinically apparent hyperventilatory respiratory pattern. Hypocapnoea and respiratory alkalosis develop rapidly upon the onset of hyperventilation and can be maintained by nearly imperceptible hyperventilation, such as by taking an occasional deep breath or frequent sighs interspersed with normal respirations, usually with thoracic muscle use.

The therapeutic approach includes psychological counselling, breathing exercises, physiotherapy and relaxation. Techniques of rebreathing into a paper bag are discouraged by some experts because significant hypoxia and death have been reported in patients with organic causes of hyperventilation. Simple reassurance and an explanation of how hyperventilation produces the symptoms is usually sufficient to terminate the episode. Physically compressing the upper thorax and having the patient exhale maximally decreases hyperinflation of the lungs. Instructing the patient to breathe abdominally, using the diaphragm more than the chest wall, often leads to improvement in subjective dyspnoea and eventually corrects many of the associated symptoms.

Management of PNEPEs

PNEPEs need urgent and skilful treatment, which is often successful, particularly if they are recognised and managed during the early stages.[2,6,49,74,75] The role of the physician is not just simply to announce to the patient: 'You do not suffer from epileptic seizures'. At this stage, the patient requires a thorough and tactful explanation of what this new diagnosis of PNEPE means and the appropriate management procedures. These patients have been allowed to believe for many years that they suffered from 'epilepsy' that was intractable to medication. Their reaction and that of their family to a new diagnosis of 'psychogenic seizures' (also taking into consideration the negative social implications and attitudes to this term) should be thoroughly considered. Patients' understanding and reactions to a diagnosis of these non-epileptic attacks are important factors that should contribute to the development of more tailored treatment approaches.[76]

> Sensitivity to the patient, the use of a multidisciplinary team and the recognition that PNEPEs are as devastating as medically refractory epilepsy are critical to a successful treatment outcome.[6]

Non-epileptic paroxysmal movement disorders imitating epileptic seizures

Non-epileptic paroxysmal movement disorders of whatever cause are common imitators of epileptic seizures and *vice versa*.

'WE MOVE' (Worldwide Education and Awareness for Movement Disorders; www.wemove.org/) is a highly recommended website source for excellent reviews, glossaries, and slide and video presentations for medical educational purposes. It also hosts the MDVU site (Movement Disorders Virtual University; www.mdvu.org).

Paroxysmal movement disorders are neurological disorders characterised by abrupt, transient episodes of abnormal involuntary movement, such as chorea, athetosis, dystonia and/or ballismus (paroxysmal dyskinesias) or impaired coordination of voluntary actions and other associated findings (paroxysmal ataxias). Depending upon the specific disorder, episodes may be precipitated or worsened by different factors. For example:

- in those with paroxysmal kinesigenic dyskinesia, episodes may be triggered by sudden voluntary movements
- in non-kinesigenic dyskinesia, episodes occur spontaneously and may be worsened by caffeine or alcohol consumption, stress, fatigue or other factors
- in patients with paroxysmal kinesigenic ataxias, episodes may be triggered by sudden voluntary movements or postural changes.

These disorders may be familial, appear to occur randomly for unknown reasons, or occur secondary to other underlying conditions or disorders.

Tics, compulsions, stereotypies and mannerisms

Tics are intermittent, repeated, stereotyped movements or sounds that may occur in an infrequent or almost continuous manner. Tics may be 'simple', such as a cough, grunt, facial twitch or shoulder shrug, or 'complex', such as a word, phrase or a stereotyped sequence of movements. Tics are often made worse by stress, upset or demand for mental concentration. Tics last more than 200 ms with a frequency that may be altered voluntarily.

Tics are not voluntary movements, although they may be incorporated into an apparently voluntary gesture to avoid embarrassment.

Tic disorders frequently occur in association with compulsions and attention-deficit disorder.

Compulsions are complex behaviours that respond to a psychological need, such as hand washing due to a fear of germs. The actions 'feel' voluntary, but the patient may describe a sense of fear or impending doom if the action is not performed. Compulsions are frequently associated with obsessions, tics or Tourette's syndrome.

Stereotypies are repetitive, stereotyped, purposeless movements that may be made by normal children when they are bored, excited or engrossed in an activity. Stereotypies are often associated with attention-deficit disorder, developmental delay or autism. They may consist of hand flapping, clapping, slapping, fluttering, rocking or facial movements. These children are not necessarily aware that they are making the movements. In some cases, these movements can be voluntarily suppressed.

Mannerisms are normal voluntary phenomena; i.e. the particular movement accompaniments that people develop while performing certain movements or gestures. They may appear abnormal, particularly if the mannerism involves unusual or unnecessary postures. The subjects can modify them by command.

Tremor

In tremor the contraction is bidirectional, affects agonist and antagonist muscles alternatively, and is more rhythmic than myoclonus; however, the phenomenological border between tremor and myoclonus is sometimes unclear (e.g. recently some authorities have categorised palatal myoclonus as tremor rather than myoclonus,[77] and further, in some neurodegenerative disorders, the initial stages of action in myoclonus may in fact be small amplitude tremor).[77]

Non-epileptic movement disorders in neonates and infants imitating seizures

Non-epileptic movement disorders in neonates and infants may be misdiagnosed as epileptic seizures. The description of the following conditions are based on a recent review by Vigevano[78] with video presentations of these events.

Jitteriness[78]

Jitteriness manifests with involuntary rhythmic movements of rapid alternating contraction of agonist and antagonist muscles at 4 or 5 Hz with equal

intensity. It may be symmetrical or asymmetrical, involves mainly limbs and commonly occurs in the first days or months of age. Jitteriness may be spontaneous, or is stimulus-triggered and mainly occurs when the child cries. It can be terminated by passive flexion of the affected limb. Jitteriness tends to remit within the fourth and fifth months of life.

Jitteriness occurs in normal children but is more frequent in those with perinatal ischaemic encephalopathy or preterm babies with dyselectrolytaemia or hypoglycaemia. Children whose mothers have taken sedatives during pregnancy are vulnerable. Hypertonia, hyperexcitability and persistence of primitive reflexes can be observed.

Tonic reflex seizures of early infancy[79]

This is an episodic benign movement disorder of healthy, mainly male babies aged between 2 and 3 months. Attacks manifest with tonic contraction with extension of four limbs, apnoea and cyanosis, without loss of consciousness. They last for 3–10 s. They are triggered by movement or tactile stimulation and occur only when the child is awake and held in a vertical position by an adult. Ictal and inter-ictal EEG are normal. Spontaneous remission occurs within 2 months of onset.

Alternating hemiplegia[78]

This is a very rare and severe disease of unkown aetiology. It starts in the first few months of age. Episodes of hemiplegia have a duration ranging from a few minutes to several hours. They are often preceded by other paroxysmal manifestations, such as short periods of muscle hypertonia or monocular nystagmus. Hemiplegia alternates from one to the other side but may also affect both sides simultaneously. The attack begins with a deviation of the head towards the hemiplegic side of the body and progresses to hemiplegia, causing difficulty with swallowing and breathing. Attacks last for hours or sometimes several days, and recur with a frequency of more than one attack per month. The baby shows full recovery after sleep. Children develop severe motor and mental deficits. Epileptic seizures may appear in late infancy. Brain imaging is normal. EEG shows unilateral slow waves. Anti-migraine and AEDs prove to be ineffective.

Benign paroxysmal torticollis[78]

This consists of lateral head deviation sometimes associated with trunk torsion and paroxysmal crying. It may alternate from side to side. It ranges from several seconds to hours in duration. Attacks are often accompanied by vomiting, pallor, and ataxia, settling spontaneously within hours or days. Onset is generally in early infancy, and attacks may be frequent but remit before the age of 2 years. Some patients may later develop paroxysmal vertigo, migraine and transient episodic ataxia.

Rhythmic behavioural movements[78]

Normal children, especially when feeling pleasure and joy, may manifest rhythmic movements of the head and neck. These start, with a variable frequency, around the age of 1 year and remit by the age of 2 or 3 years (see also rhythmic movements in sleep, page 120).

Self-gratification disorder[80]

Gratification disorder, otherwise called infantile masturbation, is an important consideration in the differential diagnosis of epilepsy and other paroxysmal events in early childhood. Median age at onset is 10 months (range: 3 months to 5 years) with several episodes per week. There may be direct genital stimulation but other manoeuvres, particularly involving flexion and adduction of the thighs, may achieve the same effect. Types of behaviour manifested include dystonic posturing, grunting, rocking, eidetic imagery and sweating. Cyanosis, lip smacking, staring, shaking, pallor, giggling and appearing frightened/in discomfort are also reported. Infantile masturbation takes place in a variety of situations and is particularly common in car seats. The children can usually be distracted during the episodes, often appearing annoyed, and may quickly resume the activity. The diagnosis can usually be secured by taking a detailed history. Video recordings, usually easily obtained, are very helpful.

Gastro-oesophageal reflux in infants

Gastro-oesophageal reflux disease is the passage of gastric contents into the oesophagus. This is a normal physiological process including regurgitation

(passage of gastric contents up to the mouth). It peaks between 1 and 4 months of age, and usually resolves by 6–12 months of age.

Gastro-oesophageal reflux disease is a pathological process in infants manifested by poor weight gain, signs of oesophagitis, persistent respiratory symptoms and neurobehavioural changes. These are unlikely to imitate epileptic seizures. However, in infants some gastro-oesophageal reflux attacks may sometimes impose diagnostic problems.[39] Babies cannot complain of heartburn, but they may cry and have disturbed sleep. There may be significant vomiting with poor weight gain and risk of aspiration. Approximately 85% of infants vomit during the first week of life and another 10% have symptoms by 6 weeks of age. Symptoms abate without treatment in 60% of infants by 2 years of age, as these infants begin to assume an upright position and eat solid foods. Reflux may cause wheeze and cough. In premature babies it can cause apnoea and bradycardia.

Sandifer syndrome manifests with brief (about 1–3 min) NEPEs of dystonic posturing associated with gastro-oesophageal reflux; hiatal hernia is common. The attacks consist of sudden torticollis, with arching of the back and rigid opisthotonic posturing, mainly involving the neck, back and upper extremities. During the attack, the infant may become very quiet or, less commonly, become very distressed and uncomfortable. Agitation is most commonly observed as the dystonic posturing abates. Sandifer syndrome occurs from infancy to early childhood with a peak at age 18–36 months. Children with severe mental impairment or spasticity may experience Sandifer syndrome in late childhood to adolescence. Sandifer syndrome is most commonly mistaken for seizures. However, NEPEs of Sandifer syndrome occur within 1 hour of feeding, often following an imposed change of posture and the babies frequently have a history of vomiting, failure to thrive and repeated chest infections. The EEG is normal. A barium oesophagogram, oesophagoscopy or a pH probe may demonstrate the reflux.

Benign neonatal sleep myoclonus

Benign neonatal sleep myoclonus is a common non-epileptic condition misdiagnosed as epileptic myoclonic seizures or sometimes as infantile spasms. The myoclonus occurs during non-rapid eye movement (NREM) sleep in otherwise normal neonates.[81–83] It mainly affects the distal parts of the upper extremities. The lower limbs and axial muscles are less often involved. The myoclonic jerks – synchronous or asynchronous, unilateral or bilateral, mild or violent – are fast and usually last for 10–20 s. Occasionally they may occur in repetitive clusters of 2 or 3 s for 30 min or longer imitating myoclonic status epilepticus or a series of epileptic fits. The myoclonic jerks may get worse by gentle restraint. They abruptly stop when the child is awakened. Sleep is not disturbed.

There are no other clinical manifestations like those accompanying neonatal seizures, such as apnoea, autonomic disturbances, automatisms, eye deviation, oral–buccal–lingual movements or crying.

Neurological mental state and development are normal.

Aetiology: This is unknown and the condition does not appear to be familial. The myoclonus is likely to be generated in the brain stem.

Diagnostic procedures: The diagnosis is based on clinical features. All relevant laboratory studies, including sleep EEG during the myoclonus, are normal.

Differential diagnosis: Benign neonatal sleep myoclonus should be easy to differentiate from relevant epileptic disorders in this age group by its occurrence in normal neonates and only during sleep. When in doubt, a normal sleep EEG during the myoclonus is confirmatory of this non-epileptic condition.

Prognosis: The prognosis is excellent with the myoclonus commonly remitting by the age of 2–7 months.

Management: There is no need for any treatment, although minute doses of clonazepam before bed are often beneficial. Other AEDs are contraindicated.

Benign non-epileptic myoclonus of early infancy (Fejerman syndrome)

This syndrome, which has recently been thoroughly re-assessed,[16] is a paroxysmal non-epileptic movement disorder of otherwise healthy infants who have normal EEG and development. The name "Fejerman

syndrome" has been proposed[17] to replace various unsatisfactory descriptive terms such as "benign non-epileptic infantile spasms" or "shuddering attacks".[18,84,85]

Demographic data: Peak age at onset is from 1–12 (peak at 6) months. Boys slightly predominate (59%).

Clinical manifestations: The attacks are sudden and brief (1–2 s) and consist of spasms or tonic contractions (38%), shuddering (35%), myoclonus (23%), atonia or negative myoclonus, combined (9%). They affect the head and neck, upper limbs and trunk muscles. They are usually symmetrical and in flexion. Less frequently, there may be flexion, abduction or adduction of the elbows and knees and extension or elevation of the arms. They do not involve localised muscle groups and there are no focal or lateralising features. The attacks are often repeated at frequent and brief intervals several times a day but not necessarily every day; 40% occur in clusters. The intensity varies from mild attacks, which are most usual, to severe attacks mimicking infantile spasms, which occur less frequently. Attacks mainly occur while the babies are awake but in 15% of babies they occur both while awake and during sleep. Excitement, fear, anger, frustration or the need to move the bowels or to void are precipitating factors.

Aetiology: Fejerman syndrome is of unknown aetiology. Non-epileptic paroxysmal movements may result from an exaggeration of physiological myoclonus.[18]

Diagnostic procedures: The diagnosis is based on clinical features. All relevant laboratory studies including sleep- and awake-stage EEGs during the spasms, are normal.

Differential diagnosis: The main differential diagnosis is from epileptic spasms that may share similar clinical features. A normal ictal and inter-ictal EEG in benign non-epileptic infantile spasms is of decisive significance.

Prognosis: Fejerman syndrome has a good prognosis, with spontaneous remission usually occuring by age 2 or 3 years. There is no increase in the incidence of epilepsy or developmental delay.

Management: There is no convincing evidence of any beneficial treatment. AEDs are unnecessary and potentially harmful.[18]

Hyperekplexia

Hyperekplexia (synonym: familial startle disease) is the first human disease shown to result from mutations within a neurotransmitter gene.[86,87]

Demographic data: Onset ranges from intra-uterine life or birth, to later at any time from the neonatal period to adulthood. Both sexes are equally affected. It is a rare disorder. Only approximately 150 cases have been reported.

Clinical manifestations: Clinically, hyperekplexia is characterised by:

- pathological and excessive startle responses to unexpected auditory or tactile stimuli (e.g. sudden noise, movement or touch)
- severe generalised stiffness (i.e. hypertonia in flexion, which disappears in sleep).

The startle response is characterised by a sudden generalised muscular rigidity and resistance to habituation. In babies, the muscle stiffening often causes respiratory impairment and apnoea that may be fatal. In older patients, the startle response causes frequent falls, like a log, without loss of consciousness.

If an unborn baby is affected the mother may first notice abnormal intra-uterine movements. In neonates, apnoea and sluggish feeding efforts occur as a consequence of episodic extreme stiffening during the first 24 hour of life. After the first 24 hours, surviving infants exhibit the hyperekplexic startle response to nose tapping, which is a useful diagnostic test (see page 114).

Clinical phenotypic expression varies from mild to very severe forms.

The minor forms manifest with excessive but often mild startle responses, but without hypertonia. In infancy these are facilitated by febrile illness, whereas in adults these are facilitated by emotional stress.

In the major forms affected neonates have hypertonia and marked startle responses that result in falls. There is no impairment of consciousness, but the patient remains temporarily stiff after the attack.

Sleep episodic shaking of the limbs (nocturnal or sleep myoclonus) resembling generalised clonus or repetitive myoclonus is often prominent, lasting for

minutes with no impairment of consciousness. The jerks are spontaneous arousal reactions.

Neurologically, there is generalised muscle hypertonia–stiffness, hence the term *stiff baby syndrome* (which is probably the same disease as hyperekplexia).[88] Gait may be unstable, insecure and puppet-like. Brain-stem and tendon reflexes are exaggerated.

Umbilical and inguinal hernias, presumably due to increased intra-abdominal pressure, are common.

Aetiology: Hyperekplexia is usually inherited as an autosomal dominant and less often recessive trait. It is due to mutations within the *GLRA1* gene on chromosome 5q31-33, which encodes the alpha 1 subunit of the glycine receptor.[89–91] The minor form of hyperekplexia is usually sporadic and seldom due to a genetic defect in the *GLRA1* gene.[87]

Diagnostic procedures: The nose tap test is the most useful test. Tapping the tip of the nose of an unaffected baby will elicit either a blink response or no response, but in hyperekplexia there is a distinct startle response, which is repeated each time the nose is tapped.

The EEG of startle responses in hyperekplexia is normal.[92] A slowing of background activity with eventual flattening may occur, but this corresponds to the phase of apnoea, bradycardia and cyanosis.[92]

Differential diagnosis: Hyperekplexia in the neonatal period may be misdiagnosed as one of the following disorders: congenital stiffman syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, cerebral palsy or drug (phenothiazine) toxicity. Accurate recognition of hyperekplexia in a newborn is important in order to initiate early and appropriate treatment, which may be life saving.

Prognosis: This is generally good in treated patients. Untreated infants experience recurring apnoea until 1 year of age. The exaggerated startle response persists to adulthood. Hypertonia gradually improves during the course of the first and second year of life and tone is usually almost normal by the age of 3 years. Hypertonia may recur in adult life.

Management: There is a dramatic response to clonazepam (0.1–0.2 mg/kg/day).[93] A simple manoeuvre to terminate the startle response is forcibly flexing the baby by pressing the head towards the knees. This may be life saving when prolonged stiffness impedes respiration. Affected families are advised to seek genetic counselling.

Other non-epileptic paroxysmal movement disorders

Familial paroxysmal dystonic choreoathetosis

Familial paroxysmal dystonic choreoathetosis (synonyms: paroxysmal non-kinesigenic dyskinesia, paroxysmal non-kinesigenic dystonia [Mount-Reback syndrome]) is a non-epileptic hyperkinetic movement disorder linked to chromosome 2q35. It is characterised by attacks of involuntary chorea, dystonia and ballism with onset in childhood.[94–96] Attacks typically last from half an hour to several hours (with no signs of abnormality between attacks) and may occur several times each week. There is no impairment of consciousness and the EEG is normal during the episodes. Attacks are precipitated by a variety of factors, including caffeine, alcohol and emotion. Contrary to frontal lobe seizures, attacks in familial paroxysmal dystonic choreoathetosis can be relieved by short periods of sleep in most subjects.

Non-epileptic paroxysmal kinesigenic choreoathetosis[97–100]

Non-epileptic paroxysmal kinesigenic choreoathetosis is characterised by recurrent, brief attacks of involuntary movements induced by sudden voluntary movements. The involuntary movements combine tonic, dystonic and choreoathetoid features on one or both sides. They are often associated with dysarthria, upwards gaze and sensory aura. Consciousness is entirely intact. Their duration is usually 10–30 s and no more than 3 min. The EEG during the attacks is normal. There may be tens of attacks per day in more than half of patients. Onset is in the mid-teens with a range of 5–16 years. Most patients respond well to AEDs, such as carbamazepine, phenytoin or phenobarbital.[101] In nearly all patients, spontaneous remissions occur between 20 and 30 years of age.

Paroxysmal kinesigenic choreoathetosis is distinct from reflex epilepsy. However, patients may have a history of benign infantile seizures between the ages of 3 and 8 months.[102,103] There are no differences in the clinical presentation of cases with and without infantile seizures.[102] In addition, there may be a family history of epileptic seizures in 8% of cases.

Non-epileptic paroxysmal choreoathetosis may also be induced by exercise.

A 9-year-old child was referred for a second EEG because of a 'history of left-sided focal motor seizures, which recently increased. Previous EEG showed non-specific paroxysmal abnormalities'. Intelligent history taking and application of 'seizure' provocation by the EEG technologist allowed a definite diagnosis of exercise-induced paroxysmal choreoathetosis. After establishing by history taking that the events were induced by exercise, the child was asked to exercise and this induced three typical attacks which were video-EEG recorded. These were brief (under 2 min) episodes of asymmetrical dystonia, choreoathetosis and ballistic movements.

Paroxysmal kinesigenic choreoathetosis, paroxysmal exercise-induced choreoathetosis/dystonia and benign infantile seizures map to the same region on chromosome 16, suggesting that they may be allelic disorders.

Episodic ataxia type 1

Of the various types of episodic ataxias,[104,105] only type 1 may cause problems for differential diagnosis. In episodic ataxia type 1, patients suffer from brief attacks of ataxia and dysarthria, lasting seconds to minutes, often associated with continuous inter-attack myokymia. Attacks are diurnal and may occur several times per day. The EEG is frequently abnormal and patients may also have seizures. Episodic ataxia type 1 is a rare, autosomal dominant, potassium channelopathy caused by different point mutations in the the voltage-gated potassium channel gene *KCNA1* on chromosome 12p13.[106,107]

A 19-year-old intelligent woman was erroneously diagnosed as having epileptic seizures. She had brief, for less than 1 min, episodes of ataxia and dysarthria since approximately the age of 10 years. She has three types of attacks:

- The most common type is in her legs. She feels this coming and then her legs 'cannot obey her any more'.
- The second type is restricted in the upper extremities. Again, she feels this coming soon before marked cerebellar type of symptoms in the hands.
- The third type are clear cut attacks of dysarthria. She can initially be understood, but later within seconds her speech is incomprehensible.

In some occasions, there is a successive progression of the symptoms from the legs to the arms and to the speech. The latter episodes are longer, for up to a maximum of 5 min. On no occasion was there impairment of consciousness or inability to recognise her surroundings or to understand people talking to her. Over the years, these episodes appeared to become more frequent (two per week), more apparent and longer in duration. In addition, she started having episodes of marked positional tremor and attacks of periorbital and perioral myokymia.

Series of EEG were abnormal with bursts of sharp–slow-waves bilaterally in the mid-temporal regions. Brain MRI was normal. Molecular analysis revealed the first truncation to be reported in the KCNA1 gene (C1249T).[107]

Non-epileptic severe amnesic and confusional attacks imitating epileptic seizures

Non-epileptic severe amnesic attacks and lengthy confusional episodes may be misdiagnosed as epileptic seizures or non-convulsive status epilepticus (focal or generalised).

Transient epileptic amnesia refers to transient global amnesia of ictal or post-ictal epileptic origin. This is usually briefer and more frequent than transient global amnesia and patients frequently have com-

plaints of 'memory gaps' in their medical history; these 'gaps' are usually caused by complex focal seizures. Pure amnestic epileptic seizures sometimes occur in patients with temporal lobe epilepsy but they never represent the only type of seizure in these patients.[108]

Pure amnestic seizures are defined as seizures during which the only clinical manifestation is the patients' inability to retain in their memory what occurs during the seizure coupled with the preservation of other cognitive functions and the ability to interact normally with their physical and social environment. It is postulated that they result from selective and usually bilateral ictal inactivation of mesial temporal structures without isocortical involvement. In most instances pure amnestic seizures can be distinguished from episodes of transient global amnesia on clinical grounds.[108]

Transient global amnesia[109–111]

Transient global amnesia is a clinical syndrome characterised by a sudden, short-term profound deficit of anterograde and often retrograde memory without any other focal neurological signs or symptoms. Patients may repeatedly ask questions concerning transpiring events and appear agitated and confused. Personal identity, attention, visual-spatial skills and social skills are retained. Symptoms typically last less than 24 hours (median 4 hours). As the attack resolves, the amnesia improves, but the patient has complete or severe permanent amnesia of intra-attack events.

Transient global amnesia usually affects middle-aged or elderly men. In men, they occur more frequently after a physical precipitating event. In women, episodes are mainly associated with an emotional precipitating event, a history of anxiety and a pathological personality. In younger patients, a history of headaches may constitute an important risk factor. The cause is unclear; a history of migraine is common in younger patients. No link is found with vascular risk factors.

Transient global amnesia should be differentiated from epileptic seizures, drug intoxication and psychogenic fugue.

Transient global amnesia of any cause is attributed to transient dysfunction in limbic–hippocampal circuits (or in the basal forebrain cholinergic inputs to that circuitry). It can be considered a model for a focal transient perturbation of memory circuits in the temporomesial region.

Psychogenic (dissociative) fugues

Psychogenic (dissociative) fugues consist of an inability to recall some or all of one's past combined with either loss of identity or the formation of a new identity. They result from trauma or stress. They often manifest with sudden, unexpected, purposeful travel away from home. Diagnosis is based on medical history after ruling out other causes of amnesia. The incidence of dissociative fugue increases in connection with wars, accidents and natural disasters. Fugues are often mistaken for malingering, because fugues may remove the person from accountability for his actions, absolve him of certain responsibilities or reduce his exposure to hazardous situations. However, fugues are spontaneous, unplanned and not faked. Most fugues are brief and self-limited. Impairment after the fugue ends is usually mild and short-lived.

Prolonged confusional states

Prolonged confusional states of acute encephalopathy have many causes such as diabetic ketoacidosis, hypoglycaemia, respiratory, renal or hepatic failure, hyperpyrexia, sepsis and drug poisoning. They may be the predominant features of encephalitis, meningitis, head injury and cerebrovascular accidents. Some disorders such as porphyria and urea cycle enzyme defects may present with acute, periodic, short-lived exacerbations of their symptomatology. Drug abuse is a common cause of confusional episodes.

Non-epileptic staring spells, childhood preoccupation and daydreaming[52,55,112–114]

Staring spells are a frequent epileptic or non-epileptic manifestation.[52]

Non-epileptic staring spells are at the borderline of the PNEPEs and are more accurately described as (normal) episodes of behavioural inattention that are misinterpreted by an over-vigilant adult.[55] Children frequently experience these benign non-epileptic staring spells, and this 'over-vigilance' is particularly likely to occur when the child also has or has had seizures.

Non-epileptic staring spells, especially in younger children, can take the form of prolonged staring without other features or as inattentiveness with the eyes closed.[52]

The main features that suggest non-epileptic events include:[113]

- the events do not interrupt play
- they are first noticed by a professional such as a schoolteacher, speech therapist, occupational therapist or physician (rather than by a parent)
- the staring spell is 'interruptable' by external stimuli.

Factors associated with an epileptic aetiology include twitches of the arms or legs, loss of urine and upwards eye movement.[113]

Diagnostic clues for staring

During a spell of unresponsiveness, documenting an increase in heart rate of more than 30% over baseline has a positive predictive value of 97% in favour of an epileptic event rather than a PNEPE.[53]

Preoccupation implies that the person is concentrating on something tangible and identifiable, such as a television program or an arithmetical calculation.

Daydreaming implies the person is concentrating on something in his or her mind and usually occurs when the child is obviously bored. In both, the child stares ahead, seemingly blankly, and is more or less unresponsive. Colour changes, myoclonic phenomena and changes in muscle tone do not happen. However, automatisms may occur. Usually the child drifts in and out of the attack, although some may 'snap out' of it. In nearly all cases, the episodes can be interrupted.

Inattention or daydreaming was the final diagnosis in 10% of children and adolescents with PNEPEs assessed in an epilepsy monitoring unit.[115]

Daydreams and childhood preoccupations are especially difficult to differentiate from atypical absences in children with learning difficulties; the tendency for the child to drift in and out of the attack may be very similar. The circumstances of when the attacks occur may help.

NEPEs occurring during sleep and sleep disorders[116–122]

Sleep and the epilepsies have reciprocal relationships.[123–129] Sleep accentuates certain types of epileptic seizures, some of which exclusively occur during sleep (nocturnal epilepsy),[130] as well as certain types of epileptiform EEG abnormalities (e.g. benign focal spikes of children). Conversely, epileptic seizures adversely affect sleep quality and architecture.

Some patients with nocturnal seizures become aware of an epileptic seizure because of its adverse effects through injury or post-ictal manifestations. Symptoms such as tongue biting, newly onset bedwetting, unexplained body bruises, confusion or joint dislocations, alone but particularly in combination, discovered upon awakening are highly suggestive of

GTCSs. These symptoms may be the reason for why patients first seek medical attention.

Paroxysmal sleep disorders are abnormal episodic phenomena occurring during sleep. The widespread utilisation of videopolysomnography has contributed to the identification of a variety of previously unrecognised sleep disorders and to the better characterisation of already known clinical entities. Diagnosis is made on the basis of medical history and confirmed with videopolysomnography. Treatment is successful in the majority of cases.

Paroxysmal sleep disorders can cause injuries, psychological distress and other deficits from frequent sleep interruption. They may be misdiagnosed and inappropriately treated as epileptic seizures or psychiatric disorders because of sometimes bizarre and hazardous manifestations. Diagnosis is further complicated by the fact that medical and psychiatric disorders and various medications can precipitate or aggravate parasomnias.[131] Misdiagnosis is more likely in children and the elderly.

Classification of sleep disorders

According to DSM-IV, sleep disorders may be either *primary* (unrelated to any other disorder – medical or psychological) or *secondary* (the result of physical illness, psychological disorders, or drug or alcohol use).[51]

The primary sleep disorders are categorised as:

- dyssomnias, which pertain to the amount, quality or timing of sleep
- parasomnias, which pertain to abnormal behavioural or physiological events that occur during sleep.

Dyssomnias include primary insomnia (i.e. sleep-onset insomnia, sleep-maintenance insomnia and terminal insomnia), primary hypersomnia, narcolepsy, breathing-related sleep disorder (sleep apnoea) and circadian rhythm sleep disorder (delayed sleep phase type, jet lag type, shift work type and unspecified type).

Parasomnias are undesirable physical phenomena accompanying sleep that involve skeletal muscle activity or autonomic nervous system changes, or both.[132] Parasomnias include nightmare, sleep terror, sleep walking disorder and many others not listed in the DSM-IV that are detailed in this section.

Parasomnias are grouped into four different categories according to the sleep-state during which they usually occur:

1. arising from deep sleep (stage III/IV sleep)
2. associated with REM sleep
3. sleep–wake transition
4. other parasomnias non-state sleep-dependent.

Sleep-related non-epileptic movement disorders[118]

Hypnagogic myoclonic jerks (sleep starts)

> When dropping off to sleep at night one may occasionally experience a sudden, momentarily rather alarming jerk of the whole or a part of the body, sometimes accompanied by a vivid sensory experience... The jerks seem to occur, with widely varying frequencies, in nearly every normal person.
>
> Ian Oswald (1959)[133]

Sleep starts (synonyms: hypnic jerks, hypnagogic jerks, and predormital myoclonus) are normal phenomena occurring only at the onset of sleep. They usually manifest with jerks of the body, but legs are more likely to be affected than arms. A sharp cry may also occur and there may be concomitant flashes of sensory manifestations; visual hallucinations or dreams, and a feeling of falling.

The frequency and intensity of sleep starts vary. They may be single jerks but more often occur in clusters. They sometimes are very frequent, intense and repetitive, and may cause bruises of the feet by being kicked against the bed, or lead to a bed partner being hurt. This may prevent the individuals from falling asleep, although sometimes it is only the bed partner who experiences these effects. In most people, they only occur from time to time.

Sleep starts affect all ages and both men and women. Adults are more likely to complain about frequent or intense jerks.

Sleep starts are often exacerbated by fatigue, emotional stress, sleep deprivation and high intake of caffeine or other stimulants.

Useful clinical note

The significance of hypnagogic jerks in history-taking for epileptic seizures and particularly JME

Patients and witnesses do not usually report myoclonic jerks. The yield of detected myoclonic jerks increases significantly with a physical demonstration of myoclonic jerks (videos may also be very useful). If hypnagogic jerks are reported then it is certain that the concept of myoclonic jerks has been understood.

Nocturnal myoclonus[134]

Nocturnal myoclonus and nocturnal myoclonic activity is slightly higher in men than in women and correlates with increasing age. Myoclonic activity occurs most frequently during stage II of sleep. The resulting sleep disturbance is usually minimal. Only about 10% of the events relate to EEG arousals.[134]

Fragmentary hypnic myoclonus[135–137]

Excessive fragmentary hypnic myoclonus of sleep consists of high amounts of brief twitch-like movements occurring asynchronously and asymmetrically throughout the body, limbs and face. It occurs in all stages of sleep but with a somewhat lower frequency in slow-wave sleep and a significantly lower rate in the first hour after onset compared to later hours. Almost all patients are male. It also occurs in association with other sleep disorders such as periodic limb movements, narcolepsy, intermittent hypersomnia and rarely insomnia.

Propriospinal myoclonus[138–140]

This consists of recurrent axial jerks or unpleasant sensorimotor symptoms that occur in drowsiness and often prevent sleep. The jerks are slower and more focal than the sleep starts. Propriospinal myoclonus is rarely caused by spinal cord disease.

Benign neonatal sleep myoclonus

Benign neonatal sleep myoclonus is described on page 112.

Facio-mandibular myoclonus[118,141]

Facio-mandibular myoclonus during sleep may cause nocturnal tongue biting and bleeding, which may lead to suspicions of nocturnal GTCS. Electromyography (EMG) activity starts in the masseters and spreads to orbicularis oris and oculi muscles. It mimics sleep bruxism and may be familial.

Restless legs syndrome and periodic limb movement disorder[142–145]

Restless legs syndrome and the periodic limb movement disorder are distinguishable but overlapping diseases. Both feature periodic nocturnal involuntary limb movements that can cause sleep disruption, but each has distinct clinical features that are relevant to the diagnosis and management of the patient.

Periodic limb movements of sleep manifest with brief 0.5–5 s repetitive flexions of the extremities and occur at regular intervals of 10–60 s or in clusters over many minutes which progressively decline throughout the night. They often lead to brief arousals or repeated full awakenings. They can occur as an isolated phenomenon, but are frequently part of the restless legs syndrome or other sleep disorders, although they also occur in normal individuals. They are age related; they occur in less than 1% of young adults and nearly half of the elderly population.

Restless legs syndrome is a sensorimotor disorder that occurs in 1–5% of the population.[146,147] Manifestations mainly consist of unpleasant sensations experienced predominantly in the legs and rarely in the arms. The symptoms occur only at rest and become more pronounced in the evening or at night. In addition, the patients suffer from a strong urge to move the limbs, typically manifested by walking around, which leads to complete but only temporary relief of the symptoms. Most of the patients have periodic limb movements during sleep and relaxed wakefulness. Pharmacological treatments are mainly with dopamine agonists and benzodiazepines.

Rhythmic movements in sleep

Rhythmic movements in sleep, also known as jactatio capitis nocturna, may be the same disorder as 'rhythmic behavioural movements' (see page 111). Rhythmic movements such as head banging or body rocking occur just before sleep onset and persist into light sleep. Rhythmic movements are repeated about every 2 s in long clusters and may be associated with chanting or other vocalisations. This is more common in children, especially infants, but may persist into adulthood.

Children and patients with learning disabilities often exhibit body rocking when awake or asleep. Patients with daytime dyskinesias may occasionally exhibit similar movements during overnight sleep, usually in the setting of brief arousals.

Sleepwalking and night terrors[119,148,149]

Sleepwalking (somnambulism) and night terrors (pavor nocturnus) are part of the same nosologic continuum caused by a sudden partial arousal from stage III and IV of NREM sleep (*NREM arousal parasomnias*). They usually occur during the first episode of slow-wave sleep, within the first 2 hours of sleep onset and the timing is often stereotyped. They are characterised by agitation and unresponsiveness to external stimuli. They are usually brief, lasting for 1 or 2 min but may also go on for much longer. Patients are unable to fully awaken, are difficult to comfort and have no memory of the event the next day. The episodes seem to occur in cycles. They may happen every night for several weeks and then disappear for months.

In *pavor nocturnus* the patient manifests intense fright with screaming and moaning together with marked tachycardia, rapid respiration and sweating.

In *somnabulism,* the patient walks around, often performing complex automatic activities. Injuries and occasionally death may occur. Brief, abortive episodes are the most common, involving sitting up in bed with fidgeting and shuffling, as seen with the complex focal seizures.

EEG during these events shows a mixture of slow and alpha activity.[150]

Benign forms of NREM arousal parasomnias have high prevalence of around 10–15% of the population; they occur frequently in childhood and attenuate in adolescence. They can persist into or begin in adulthood with more severe and persisting forms.

Sleepwalking and night terrors may be genetically determined in children while adults show high levels of psychopathology. Additional sleep disorders include sleep-disordered breathing and restless legs syndrome.[149]

Attacks may be eliminated by passively awakening the patient just prior to the habitual time of the events. Trying to awaken the patient during the attacks is pointless.

Night terrors are not nightmares

Night terrors are stage III or IV NREM disturbances and there are no dreams.

Nightmares occur during, and are the result of, a dream in REM sleep. The sleeper retains a vivid memory of the dream.

Sleep talking is another parasomnia that may be confused with complex focal seizures. Episodes are usually brief, infrequent and may be spontaneous or induced by conversation.

Paroxysmal nocturnal dystonia (hypnogenic paroxysmal dystonia)

This is frontal lobe epilepsy of the supplementary motor area (see Chapters 14 and 15) and not a sleep disorder.

Sleep-related non-epileptic behavioural and other disorders

Sleep drunkenness[151,152]

'Sleep drunkenness' refers to a failure of attaining full alertness after awakening, usually from deep sleep. The patient appears disorientated, ataxic, dysarthric and may manifest with complex automatic, sometimes aggressive and homicidal, behaviours, as with narcolepsy. This mainly occurs in patients with hypersomnia or after severe sleep deprivation.

It may be misdiagnosed as post-ictal confusion or focal complex seizure.

Bruxism[153–156]

Bruxism (teeth grinding and clenching) occurs at any sleep stage but mainly in stage II of NREM sleep. It may also occur during the daytime. It is common in children, especially those with learning disabilities, and psychiatric patients. Dental occlusive appliances are usually an effective treatment. Episodes of bruxism are usually more prolonged and more frequent than focal seizures, and there are no associated features of other motor phenomena, vocalisation or confusional arousal.

Catathrenia (nocturnal expiratory groaning)

This is a rare form of parasomnia of exclusively expiratory groaning during sleep that occurs in clusters of approximately 30 s each. It happens in young people during the second part of the night in REM and stage II of NREM sleep.[157]

Nocturnal enuresis

Nocturnal enuresis is a very common problem in children and has varying aetiologies.[158] A genetic component is likely. For the idiopathic (primary) nocturnal enuresis there may be two subtypes: those with a functional bladder disorder and those with a maturational delay in nocturnal arginine-vasopressin secretion. Whether in some children nocturnal enuresis is a sleep disorder has been debated.

REM sleep behaviour disorder[159–162]

REM sleep behaviour disorder (RBD) manifests with attacks of vigorous and often dangerous motor activity in response to vivid dreaming in association with intermittent loss of REM sleep skeletal muscle atonia. The patients act out their dreams.

RBD is more prevalent in elderly (mean age 60 years) males (87%) but is also reported in children with autism.[163] Its prevalence in the general population is estimated to be around 0.5%.[161] RBD may be idiopathic (60%) or strongly associated with alpha-synucleinopathies,[161] often heralding the clinical onset of neurodegenerative disease, especially Parkinson's disease, multiple system atrophy and dementia with Lewy bodies. A third of patients injure themselves and two-thirds assault their bed partners. Dream content mostly involves aggressiveness,[160] usually as a defence mechanism against attack.[159]

EEG may show coincidental inter-ictal epileptiform activity of sporadic, frontotemporal sharp waves in a quarter of patients.[164] This may also occur in REM sleep, although rarely. Such EEG abnormalities may reinforce an erroneous diagnosis of nocturnal focal seizures.

Neuroimaging is unlikely to reveal underlying disorders not suspected clinically. Small doses of clonazepam 0.5–1 mg (or melatonin as an alternative) at bedtime are highly effective.[162]

Hypermotor epileptic seizures may be mistaken for RBD. However, the lack of dream recall, the stereotyped movements and occasional SGTCS of hypermotor seizures are useful as distinguishing features.

Sleep-related eating disorder[165]

Some patients have abnormal compulsory nocturnal eating episodes that may be associated with sleepwalking, somniloquy, restless legs syndrome and periodic limb movements during sleep. Eating always occurs after complete awakenings from NREM sleep and exceptionally from REM sleep. During the eating episodes patients are fully alert and EEG shows alpha activity. Most patients manifest with recurring chewing and swallowing movements (resembling the rhythmic masticatory-muscle activity in patients with bruxism) during sleep, which in half of the events is associated with EEG arousals.[165]

Sudden infant death syndrome (Cot death)[166]

Sudden and unexpected death of an infant during sleep and without post-mortem abnormal findings is a rare and tragic event. It occurs mainly between 10 and 12 weeks of age. An epileptic seizure may sometimes be the actual cause.

Narcolepsy[119,167–175]

Narcolepsy is a sleep disorder with frequent episodes of REM-sleep that occur inappropriately

before NREM sleep. In wakefulness, REM periods or fragments of REM occur throughout the day.

Demographic data

Narcolepsy usually begins in childhood[173] with a higher incidence in adolescence (16–30 years). Prevalence is 0.05% in Caucasians and three times higher in Japanese.

Clinical manifestations

Narcolepsy manifests with the tetrad of:

1. *Hypersomnia (excessive and irresistible daytime sleepiness),* which includes the following: daytime sleep attacks, which may occur with or without warning; persistent drowsiness, which may continue for prolonged periods of time; and 'microsleeps', or fleeting moments of sleep. Sleep attacks may happen while standing, eating, driving or during a conversation. Episodes of automatic behaviour (performing a task without conscious awareness of doing it) and amnesia are common, as in all other cases of hypersomnia. Their duration ranges from seconds to 15–30 min and they usually end with a sudden burst of irrelevant words.
2. *Cataplexy,* which consists of a sudden loss of voluntary muscle control, triggered by strong emotions such as laughter, surprise, fear or anger. The attacks mainly affect facial and leg muscles (e.g. sagging, nodding, buckling knees, muddled speech), they may be experienced as mild weakness only and can last for seconds or 15–30 min. Total body collapse may occur with full preservation of consciousness. Cataplexy is sometimes instantaneous with no time to prepare for safety, and thus serious injury can occur.
3. *Sleep paralysis,* which is a brief (seconds to usually 10 min), temporary inability to move that occurs on falling asleep (hypnagogic) and less often on awakening.

Cataplexy and sleep paralysis are related to the muscle atonia of REM.

4. *Hallucinations,* which appear as vivid, realistic, often frightening 'dreams of REM' occur upon falling asleep (hypnagogic) and less often upon awakening. Visual hallucinations are more common than auditory, vestibular or somatosensory hallucinations. They may occur together or precede sleep paralysis.

The patients are fully aware of cataplexy, sleep paralysis and hallucinations.

All patients with narcolepsy have hypersomnia but only around 70% also develop cataplexy; sleep paralysis and hypnagogic hallucination occur in a third.

The clinical picture of narcolepsy is further complicated by intense fatigue, memory problems and visual problems, frequent sleep arousals and other sleep disorders, as well as the psychological and social consequences of having narcolepsy.

Aetiology[175]

Narcolepsy is familial in 10% of cases. Mutations in the region of chromosome 6 controlling the HLA antigen immune complex are found in 90–100% of patients, but these also occur in as many as 50% of people without narcolepsy. Narcolepsy has been attributed to a deficiency of the peptide neurotransmitter hypocretin produced in the hypothalamus. A dog model of narcolepsy exhibits a mutation on chromosome 12 that disrupts the processing of hypocretin. No such mutations were found in human narcolepsy but hypocretin levels are profoundly depressed in cerebrospinal fluid (CSF) and a specific reduction in hypocretin-containing neurones has been described. One hypothesis concerning the pathophysiology of narcolepsy proposes that the HLA subtype resulting from the mutation on chromosome 6 increases the susceptibility of hypocretin-containing brain neurones to immune attack. Because hypocretin may normally participate in the maintenance of wakefulness, the loss of neurones that release this peptide might allow inappropriate occurrence of REM sleep in contrast to its normal cyclic appearance after NREM sleep.

Diagnostic procedures

Overnight polysomnography is often diagnostic and may also reveal other underlying sleep disorders. The multiple sleep latency test (MSLT) measures sleep onset and how quickly REM sleep occurs. A blood genetic test has been developed that measures certain antigens often found in people who have a

predisposition to narcolepsy. Positive results suggest but do not prove narcolepsy.

Differential diagnosis

Narcolepsy should be differentiated from other causes of hypersomnia. Cataplexy is almost unique to narcolepsy but the presence of cataplexy is not required for a diagnosis of narcolepsy.

Cataplectic attacks may be misdiagnosed as atonic seizures, other types of epileptic falls or syncope. Episodes of automatic behaviour may be confused with complex focal seizures.

Isolated episodes of sleep paralysis, cataplectic attacks and hallucinations can occur frequently in normal people.

Prognosis

Narcolepsy is a life-long disorder with no signs of remission or improvement.

Management[167,174]

Modafinil is the first-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep in association with behavioural measures. Sodium oxybate is the first-line treatment of cataplexy and appears to also have a beneficial effect on excessive daytime sleepiness and disturbed nocturnal sleep.

Sleep apnoea

Patients with sleep apnoea usually present with daytime hypersomnia, and apnoeic episodes may cause episodic grunting, flailing about or other restless activity that appears to mimic nocturnal epilepsy. Occasionally the resultant hypoxia leads itself to symptomatic epileptic seizures.

Apnoeic attacks in neonates, whether while awake or asleep, are difficult to differentiate from epileptic seizures.

Sleep disorders in the elderly

Sleep undergoes significant changes with ageing and these are so profound that it is difficult to separate normal from disease.[176] Sleep disorders are estimated to affect nearly 50% of older individuals. These are mostly sleep-disordered breathing, periodic limb movements in sleep and restless legs syndrome, morning headaches, circadian rhythm disorders, excessive daytime sleepiness, RBD, obstructive sleep apnoea and insomnia.[177]

Subjective non-epileptic paroxysmal symptoms imitating simple focal seizures

Visual, auditory, somatosensory, olfactory, gustatory and autonomic paroxysmal symptoms imitating simple focal seizures[178]

There is a galaxy of subjective paroxysmal symptoms that may imitate, and in some cases are identical to, those occurring in simple focal epileptic seizures. These are subjective sensations, simple or complex visual hallucinations or illusions that may be:

- normal experiences of healthy people
- caused by a variety of abnormalities located in the peripheral sensory organs or in the CNS
- of multiple aetiologies (drugs or various brain, psychiatric and systemic disorders).

Thus, the differential diagnosis of these paroxysmal symptoms is extensive, spanning numerous normal phenomena, intoxication, and neurological, systemic

and psychiatric disorders. Diagnosis is possible and usually straightforward if the symptoms are analysed and synthesised in a meaningful manner with regard to their various parameters and characteristics (quality, quantity, time and duration of appearance), development, stereotype, recurrence, precipitating factors, other concurrent symptoms, diseases, drug use, age and so forth. Long-term recurrent isolated subjective sensations without any other symptoms are unlikely to be epileptic seizures, because at some time they would have progressed to more apparent ictal seizure manifestations. Visual symptoms of paroxysmal occurrence are probably among the most common imitators of epileptic seizures.[179–183] The example of visual aura of migraine versus visual occipital seizures has been emphasised on page 125.

Cyclic vomiting, paroxysmal vertigo and motion sickness

Cyclic vomiting syndrome (CVS), paroxysmal vertigo and motion sickness are unlikely to be misdiagnosed as epilepsy. However, some children who are assumed to have CVS or motion sickness may actually be suffering from autonomic seizures or autonomic status epilepticus of Panayiotopoulos syndrome in which emetic symptoms are usually prominent and sometimes occur while, and are probably facilitated by, travelling.[24,184]

Cyclic vomiting syndrome[184–187]

CVS has the following characteristics:

- it is specific to childhood (3–9 years)
- vomiting usually starts in sleep and may last for many hours
- emetic symptoms are the first to appear but these are often associated with other autonomic manifestations.

CVS is an idiopathic non-epileptic disorder of unknown aetiology characterised by periodic clusters of episodic vomiting, often 6–12 times per hour. The pattern is stereotypical within individuals and typified by a rapid onset during the night or early morning, rapid denouement and associated symptoms of pallor, lethargy, anorexia, nausea, retching, vomiting, drooling, diarrhoea, abdominal pain and classical headache, photophobia and phonophobia, but rarely visual disturbances. EEG may show only focal slowing at the time of episodes. On rare occasions focal spikes and waves also appear; these may be a coincidental finding because of the high prevalence of functional spikes in children or they may indicate misdiagnosis.

CVS affects young children aged 3–9 years and resolves during adolescence. A third of patients later develop migraine headaches.

Prevalence may be about 2% of school-aged children, although clinically many may be missed or their symptoms are mild. The vomiting appears to be triggered by a variety of physical and psychological stresses.

The diagnosis of CVS requires exclusionary laboratory testing because it can mimic many surgical, neurological, endocrine, metabolic or renal disorders.

CVS bears considerable similarities to abdominal migraine and to migraine headaches 'though their precise relation and overlap cannot be definitely settled until validated laboratory markers become available'.[185]

The pathogenesis of CVS is unknown but there are now several tenable mechanisms such as migraine, metabolic, neuroendocrine and gastrointestinal.[185] There may also be specific subgroups that have different mechanisms.[185]

CVS is considered to originate in the brain and various mechanisms, probably inter-related, are speculated:

- corticotrophin-releasing factor, which may be the primary mediator of vomiting in CVS[186]
- mitochondrial DNA mutations and disordered respiratory chain function[186]
- defects in the regulation of cellular mechanisms such as cAMP or ion channels in cells at critical locations in the emetic pathway (e.g. nucleus tractus solitarius, area postrema)
- defects in intrinsic pathways (e.g. opioid neurones) that may modulate the brain-stem emetic mechanisms.[187]

Treatment options are improving at present and serotonergic agents have shown the most promise.

Benign positional paroxysmal vertigo

Benign positional paroxysmal vertigo is the most frequent cause of vertigo in adults and manifests with brief episodes of spinning vertigo precipitated by movement such as bending over, turning in bed, looking up or driving. Nausea can be a prominent feature or absent. Attacks may be very frequent and the disorder, although benign, may be disabling. It is a disease of the semicircular canal and occurs when freely floating otoconia enter one or more of the semicircular canals and move under the influence of gravity. It is rarely observed in individuals younger than 35 years without a history of antecedent head trauma. The Epley manoeuvre for repositioning the displaced otoconia is a simple technique that often has therapeutic efficacy.

Benign paroxysmal vertigo of childhood

Benign paroxysmal vertigo of childhood is the most common cause of vertigo in children without any detectable ear disease or hearing loss. It manifests with typical vestibular attack including nystagmus, nausea, vomiting and diaphoresis. The age at onset is usually 1–5 years old. It has been related to migraine and some experts consider it as a precursor of migraine.

Motion sickness

Motion sickness is a common response to real and perceived movement in the environment.[188–192] It occurs while travelling via any form of transport. Children aged between 4 and 10 years are particularly vulnerable. Girls are more susceptible than boys.

Symptoms begin with epigastric discomfort, which is usually accompanied by increased salivation, eructation and a feeling of bodily warmth. With sustained exposure to the triggering stimulus, symptoms progress to nausea, pallor, sweating and, eventually, retching or vomiting. A variant of motion sickness may exist that lacks gastrointestinal complaints and is instead characterised by drowsiness, headache, apathy, depression and generalised discomfort.

Migraine, migralepsy, basilar migraine with EEG occipital paroxysms and diagnostic errors

Migraine with aura may be misdiagnosed as epilepsy but, far more frequently, epileptic seizures are misdiagnosed as migraine.[193–195] As a result, visual occipital lobe seizures (misdiagnosed as visual aura of migraine and SGTCSs) are erroneously attributed to the migraine effect on the brain (hence the inappropriate term 'migralepsy').[196]

Migraine and epilepsy are the most common neurological disorders. Prevalence of migraine is probably around 6% for men and three times more frequent in women. Epilepsy is around 0.5% and equally affects men and women. If a relationship existed between them, this would be obvious in our everyday neurological practice. It would not be revealed only through obscure and complicated cases with bizarre symptomatology. It would be simple and common. It is not. The problem is that occipital seizures are not appropriately differentiated from migraine and therefore, they are often erroneously diagnosed as migraine.

Seizures may be triggered by a migrainous event or caused by a migraine–stroke but this is rare. There should be no doubt that cerebral infarcts due to severe migraine can be responsible for symptomatic seizures. Also, there should be no reason why epileptic seizures, so vulnerable to extrinsic and intrinsic precipitating factors, could not also be susceptible to cortical changes introduced by migraine. Thus a migrainous attack may also be able to trigger epileptic seizures in susceptible individuals. However, both these cases are rare. In my opinion, the most common reason for their

association is through the coincidence of two of the most common neurological disorders and an erroneous interpretation of epileptic seizures as migraine or, less often, *vice versa*. The emerging and more realistic concept of occipital seizures triggering migrainous headache needs consideration and exploration. More importantly, patients with daily visual seizures that may progress to convulsions merit a precise diagnosis and appropriate treatment probably with carbamazepine. Most of these patients with visual seizures are misdiagnosed as migraine with aura, basilar migraine, acephalgic migraine or migralepsy simply because physicians are not properly informed of differential diagnostic criteria. As a result, diagnosis, appropriate investigations and treatment may be delayed for years. There are numerous published reports of such a misdiagnosis. Such high errors of diagnosis are unjustifiable because visual epileptic seizures are distinctly different from visual auras of migraine (Figure 4.1).[194,195]

Based on the results of my studies, my thesis is that visual aura of migraine is entirely different from the visual seizures when all their components are considered together (Table 4.4). Visual seizures and visual aura of migraine may imitate each other but their true identity cannot easily escape clinical scrutiny.

Although brief duration is significant, there are many more clinical manifestations to differentiate visual seizures from visual aura of migraine (Table 4.4).

Visual aura of migraine

> I was startled by a singular shadowy appearance at the outside corner of the field of vision of the left eye. It gradually advanced into the field of view and then appeared to be a pattern in straight-lined angular forms, very much in general aspects like the drawing of a fortification, with salient and re-entering angles, bastions, and ravelins with some suspicion of faint lines of colour between the dark lines.
>
> Sir JFW Herschel (1866)[197]

The visual aura of migraine with aura and acephalgic migraine are adequately studied and illustrated in all relevant textbooks and publications. In one of the most detailed nosographic analyses[198] migraine visual aura:

> Started as a flickering, uncoloured, zigzag line in the centre of the visual field and affected the central vision. It gradually progressed over >4 min usually lasting <30 min towards the periphery of one hemifield and often left a scotoma. The total duration of visual auras was 60 min. Only four patients had exclusively acute onset visual aura.[198]

Furthermore, migraine visual aura has the following characteristics:

- it rarely has a daily frequency
- non-visual ictal occipital symptoms such as eye and head deviation, and eyelid repetitive closures do not occur
- it is debatable and probably exceptional to progress to non-visual epileptic seizures.

Less typical features of migraine visual aura such as spots, circles and beads with or without colours may be experienced during the migraine visual aura but usually they are not dominant. More importantly, clustering of other symptoms, as above, betray their migraine nature.

Basilar migraine

Basilar migraine of Bickerstaff[199,200] is characterised by transient and fully reversible symptoms, indicating focal dysfunction of the brain stem, the occipital lobes or both, followed by headache.[201] Common neurological symptoms include visual manifestations, dizziness, vertigo and tinnitus, ataxia, bilateral weakness and dysaesthesia, diplopia, dysarthria and decreased hearing.

Visual symptoms mainly consist of dimming of vision, blindness, tunnel vision, hemianopia and scotomata. Elementary visual hallucinations are usually bilateral, described as 'teichopsia', 'flashes or blobs of light', 'coloured figures' or 'dysmorphopsia'. Aura symptoms develop gradually over 4 min and last for less than 30 min to up to 1 hour.

Schematic illustration of elementary visual hallucinations of visual occipital lobe epileptic seizures (left) and visual aura of migraine (right)

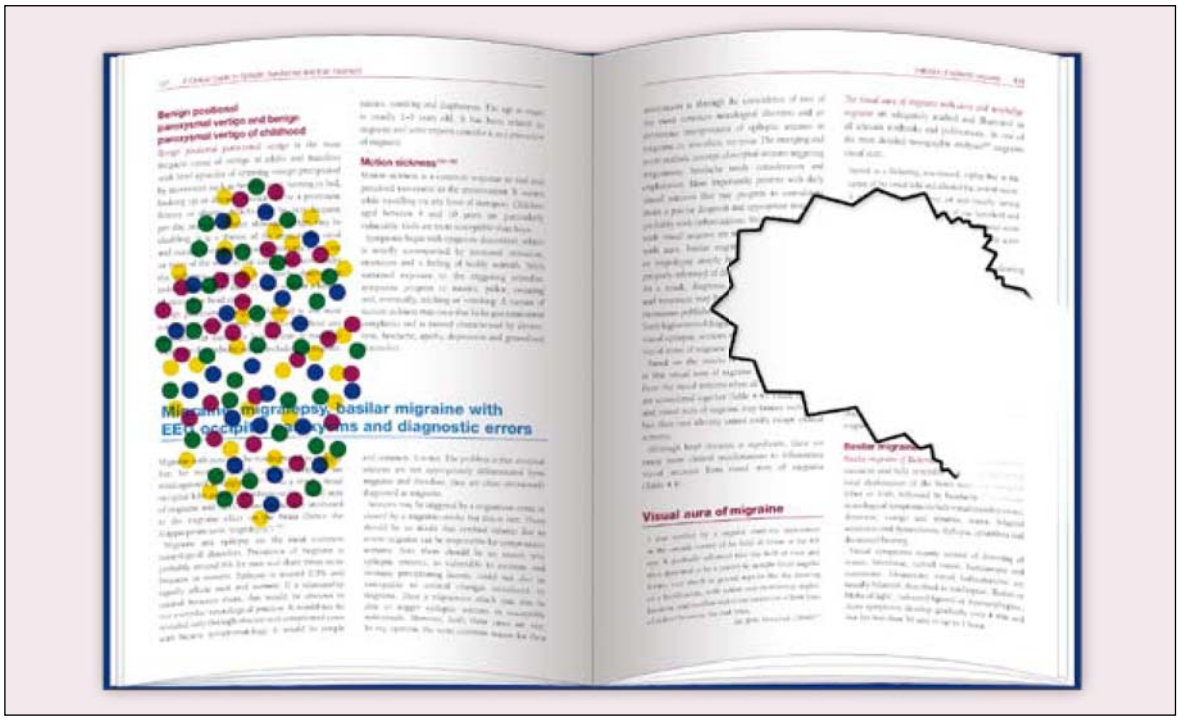

Figure 4.1 *Adapted with permission from Panayiotopoulos (2006).*[196]

Impairment or loss of consciousness without convulsions may occur in a quarter of patients between the aura and the headache phase.

> The loss of consciousness is described as curiously slow in onset – never abrupt, and never causing the patient to fall or to be injured. A dreamlike state sometimes precedes impairment of consciousness. The degree of impairment of consciousness was never profound but the patients were never unrousable; on vigorous stimulation they could be aroused to co-operate but they returned to unconsciousness when the stimulation ceased.[200]

Attacks of basilar migraine are usually infrequent and over the years they may cease or become replaced by common migraine with or without aura.[201]

Migralepsy

Migralepsy – migra(ine) and (epi)lepsy – is a term used to denote 'a seizure that may be a composite of symptoms encountered in epilepsy and migraine'.[202,203] *Intercalated seizures* denote epileptic seizures that occur between the migrainous aura and the headache phase of migraine.[204]

I would discourage the use of the term migralepsy. According to a recent review, most reported cases of so-called migralepsy are likely to be genuine occipital seizures imitating migraine aura.[194,195] Of the most influential cases that I have detailed,[194,195] two of the three 'migralepsy' patients,[202] one 'basilar migraine and epilepsy case'[205] and one 'juvenile migraine with epilepsy' boy,[206] all had symptoms of visual seizures – as defined in this book – that were interpreted as migraine aura. The 'juvenile migraine' patient of Barlow[206] with symptomatic occipital epilepsy may be indicative:

> This boy at age 13 years 'While ski-ing… saw blue to the right associated with blurred vision that lasted for a few seconds' after which he vomited, became confused

Differential diagnosis of occipital seizures from migraine with aura or basilar migraine

	Occipital epilepsy	Migraine with aura	Basilar migraine
Visual hallucinations			
Duration for seconds to 1 min	Exclusive	None	None
Duration for 1–3 min	Frequent	Rare	Rare
Duration for 4–30 min	Rare	As a rule	As a rule
Daily in frequency	As a rule	Rare	None
Mainly coloured circular patterns	As a rule	Rare	Exceptional
Mainly achromatic or black and white linear patterns	Exceptional	As a rule	Rare
Moving to the opposite side of the visual field	Exclusive	None	None
Expanding from the centre to the periphery of a visual hemifield	Rare	As a rule	Frequent
Evolving to blindness	Rare	Rare	As a rule
Evolving to tonic deviation of eyes	Exclusive	None	None
Evolving to impairment of consciousness without convulsions	Frequent	Rare	Frequent
Evolving to impairment of consciousness with convulsions	Frequent	Exceptional	Rare
Associated with post-ictal/post-critical headache	Frequent	As a rule	Frequent
Blindness and hemianopia			
Without other preceding or following symptoms	Frequent	None	Frequent
Brain-stem symptoms	None	None	Exclusive
Post-ictal/post-critical vomiting	Rare	Frequent	Frequent
Post-ictal/post-critical severe headache	Frequent	As a rule	Frequent

Table 4.4 *Modified with permission from Panayiotopoulos (1999).*[195]

for 30 min, followed by a severe throbbing headache. Subsequently he had occasional 'episodes of similar visual disturbance' diagnosed as juvenile migraine successfully treated with phenytoin. An arteriovenous malformation was found in the left occipital lobe. 'Visual scotomata accompanied by flashing lights that only occasionally were followed by headache' continued post-operatively.

None of the 1550 patients I have studied had any evidence of seizures developing from migraine aura, although this was often the initial erroneous diagnosis on referral.[195] Conversely, post-ictal headache and other migraine-like symptoms frequently occurred after occipital seizures. However, an incontrovertible diagnosis may be difficult in some equivocal cases:

A 38-year-old man, who while working with the computer, saw flashing light in between his eyes. They were moving for a few centimetres upwards and to the right repetitively. Gradually, the intensity of the light and the area increased in the next 30 min obscuring his

vision. This ended with a GTCS as he was entering the examination room of his general practitioner where he went walking for help. He had never experienced similar symptoms, seizures or migraine in the past. MRI was normal. EEG showed minor non-specific abnormalities.

Visual seizures

> They commenced with the appearance of several small spheres, white in the centre with an intermediate zone of blue and outside this a ring of red, immediately to the left of the point at which the patient gazed; from here they moved either at a uniform rate or in jerks to the left and downwards... In all attacks the eyes deviated towards the left and the head turned in the same direction as soon as the visual spectra appeared.
>
> G. Holmes (1927)[207]

The elementary hallucinations of visual epileptic seizures are detailed in the relevant section of occipital lobe epilepsy (see Chapter 15, page 474, and Table 4.4).[194,195] Briefly, elementary visual hallucinations of visual seizures are mainly coloured and circular, develop fast (within seconds) and are of brief duration (Figure 4.1). They often appear in the periphery of a temporal visual hemifield, becoming larger and multiplying in the course of the seizure, frequently moving horizontally towards the other side. They are fundamentally different to the visual aura of migraine with which they are often mistaken.[194,195,208]

Differentiating visual seizures from migraine

The misdiagnosis of visual seizures as migraine appears to be high, although their differentiation should not be difficult.[193–196] Occipital seizures manifesting with elementary visual hallucinations, blindness and headache, alone or in combination, may imitate migraine, which is the reason why they are often mistaken for migraine with aura, acephalgic or basilar migraine (Table 4.4 and Figure 4.1)[194,195] Even lesional occipital epilepsy is often misdiagnosed as migraine and, on many occasions, visual seizures are considered as a visual aura of migraine, thus limiting their prognostic significance with regard to the continuation of treatment.[195] The following are quotes from medical referrals of patients with visual seizures:

This patient has visual migraine-like disturbances, such as teichopsias.

Scintillating scotoma or sparkling scotoma of migraine.

Migrainous aura before the fit.

Diagnostic tips

Factors contributing to error in the diagnosis of visual seizures

The major contributory factor to error is that the description of visual hallucinations is often abbreviated in terms such as fortification spectrum, teichopsia, scintillating scotoma, phosphenes and their variations.[208] Their meaning does not always represent the actual descriptions, which should be meticulously requested. Erroneously, they are frequently unquestionably equated with migraine.

Diagnostic tips

As a rule, brief (<1 min), elementary visual hallucinations that develop rapidly within seconds, with coloured and circular patterns and daily frequency are probably pathognomonic of visual seizures, despite the severe headache and vomiting that may follow. EEGs may be normal, show non-specific abnormalities, or reveal slow focal or occipital spikes. A high-resolution MRI is mandatory because it may detect a structural lesion requiring early attention and management.

There are two main reasons that visual seizures are misdiagnosed as migraine.[193–195] First, visual seizures are not examined in a comprehensive manner; instead they are abbreviated to terms such as 'scintillating scotoma' or 'teichopsia', which often do not represent the actual description of the patients. Second, their differential diagnostic criteria have only recently been adequately studied and addressed.[194,195,208] The diagnosis of visual seizures may comfortably rely on

clinical criteria only; other investigative procedures are essential, but even ictal EEG may not identify a third or more of cases.

Misconceptions

There is a misconception that there is a syndrome of 'basilar migraine with EEG occipital paroxysms', which is perpetuated in every relevant publication and textbook to date. Retrospective analysis of cases described as 'basilar migraine with occipital paroxysms'[209–212] showed that these patients genuinely suffer from idiopathic occipital epilepsy.[193,195,212]

Note of caution

A recent population-based, case–control study concluded that children with migraine with aura have a substantial increased risk of developing subsequent epilepsy (odds ratio, 8.1; 95% CI, 2.7–24.3).[213] Migraine without aura did not increase the risk for epilepsy. The diagnosis was made on clinical grounds. However, considering the differential diagnostic problems and the frequency by which epilepsy is misdiagnosed as migraine, I would like to raise this note of caution for such a conclusion and its important consequences.

Cerebrovascular NEPEs imitating epileptic seizures

Cerebrovascular disease is a common cause of epileptic seizures, particularly in the elderly. However, with the exception of vertebrobasilar falls and transient ischaemic attacks, cerebrovascular accidents are unlikely to be misdiagnosed as epileptic seizures.

Transient ischaemic attacks are brief episodes of neurological dysfunction caused by focal brain or retinal ischaemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of acute infarction. Symptoms are usually negative phenomena of blindness, paresis or other deficits. The difficulty, therefore, in their differentiation from focal seizures arises when positive phenomena such as paraesthesiae occur. Furthermore, transient ischaemic attacks are not usually stereotyped or repeated with the frequency of epileptic seizures, and there are usually associated features to suggest vascular disease.

Falls in vertebrobasilar insufficency are of sudden onset often with other concurrent features of brain-stem ischaemia such as diplopia, vertigo and bilateral motor-sensory symptoms. They commonly affect elderly people, with evidence of vascular disease and cervical spondylosis. They are usually precipitated by head turning or neck extension resulting in the distortion of vertebral arteries.

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five

Epileptic syndromes and their classification

This chapter provides the classification of epileptic syndromes as reported by the relevant ILAE Commission. Individual syndromes, comments on their classification and personal views are detailed in Chapters 8–17 of this book.

The most important milestone in modern epileptology has been the recognition of epileptic syndromes and diseases, most of which are well defined and easy to diagnose (see Chapter 1). The concept of epilepsies as specific syndromes is old (see, for example, pyknolepsy, described by Addie in 1924, which even today is used synonymously with childhood absence epilepsy)[1] and the first attempt to formalise them in an international classification was published in 1970.[2]

The currently valid 1989 ILAE syndromic classification of epilepsies[3] is almost the same as the original proposal of 1985.[4] It originates from a meeting in the Centre Saint-Paul, Marseilles, France, in July 1983 and was the basis of the book *Epileptic Syndromes in Infancy, Childhood and Adolescence*, also known as *Guide Bleu*, which is now in an updated fourth edition.[5]

The 1989 ILAE classification has been widely accepted, is universally employed and will remain formally recognised 'until, a clearly better classification [is] devised, although some modifications are anticipated'.[6]

ILAE definitions of epilepsies and epileptic syndromes and clarifications of terminology

Definitions and terminology relating to epilepsies and epileptic syndromes[3] have been the subject of a continuing process of discussion and debate through the various ILAE proposals, leading to a number of changes, clarifications and replacements[3,4,6–8]. There is also considerable concern that certain terminology is "imprecise, misused or misunderstood".[8] Revised terminology is a significant part of the newest report of the ILAE Commission.[8] Therefore, it is important to present key definitions and terminology "as is" in the ILAE publications. Comments are also made in order to assist the Commission and readers by providing an insight into how these are perceived by a clinical epileptologist. See also Chapter 1 pages xxx.

Epileptic syndrome

An epileptic syndrome is "an epileptic disorder characterised by a cluster of signs and symptoms customarily occurring together; these include such items as the type of seizure, aetiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and sometimes prognosis. However, in contradistinction to a disease, a syndrome does not necessarily have a common aetiology and prognosis."[3]

An epilepsy syndrome is "a complex of signs and symptoms that define a unique epilepsy condition. This must involve more than just the seizure type; thus, for instance, frontal lobe seizures per se do not constitute a syndrome [changed concept]."[7]

An "epilepsy syndrome, more precisely an electro-clinical syndrome" is "a complex of clinical features, signs and symptoms that together define a distinctive, recognizable clinical disorder. These often become the focus of treatment trials as well as of genetic, neuropsychological, and neuroimaging investigations. Use of the term 'syndrome,' and more precisely 'electro-clinical syndrome,' will be restricted to a group of clinical entities that are reliably identified by a cluster of electro-clinical and developmental characteristics. These are largely but not exclusively genetic in origin, and tend to have a strong relationship to developmental aspects of the brain. These are distinctive disorders identifiable on the basis of a typical age onset, specific EEG characteristics, seizure types, and often other features which, when taken together, permit a specific diagnosis. The diagnosis in turn often has implications for treatment, management, and prognosis. The term for these entities is 'Electro-clinical Syndromes.' While ultimately common usage will likely shorten the term again to 'syndrome' alone, this is still specifically defined to mean entities that can be considered electro-clinical syndromes. It would be inappropriate to refer to, for example, epilepsy with a frontal lobe focus and not otherwise specified as a 'syndrome.'"[8]

Comment: It is apparent that the definition of an epileptic syndrome does not differ significantly between the ILAE proposals. Further, "syndrome" (syndrome, to run together) is well defined and widely used in medicine, probably from the times of Galen.[9] The definition of syndrome in current medical dictionaries is also relevant: "a distinct group of symptoms and signs which, associated together, form a characteristic clinical picture or entity", while "a disease has common aetiology and prognosis despite individual modifications".[10]

Epilepsy disease

Epilepsy disease: "A pathological condition with a single, specific, welldefined aetiology. Thus, progressive myoclonus epilepsy is a syndrome, but Unverricht–Lundborg is a disease [new concept]".[7]

Comment: "Disease" is clearly differentiated from "syndrome" in any medical dictionary and in the ILAE classifications (see above definitions). It is therefore surprising to read in the newer ILAE report

"Disease versus syndrome: Although there is reason to distinguish the concepts of disease and syndrome, these terms are not consistently used in medicine. Ultimately, it was decided not to insist on the disease-syndrome distinction in referring to the epilepsies at this time, although either or both terms may be used depending on the context and custom."[8]

Of note also is that "Progressive myoclonus epilepsy" is not a syndrome but a group of heterogeneous genetic diseases such as Lafora and Unverricht-Lundborg disease (detailed in chapter 17). Also, relevant to the discussion on classification by age (see page 15), the various progressive myoclonic episodes may start at any age from infancy to adulthood.

Idiopathic epilepsy syndrome

Idiopathic epilepsies are "defined by age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic etiology. There is no underlying cause other than a possible hereditary predisposition. Idiopathic epilepsies and syndromes are described as disorders 'not preceded or occasioned by another,' according to the Oxford English Dictionary."[3]

Idiopathic epilepsy syndrome: "A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurological signs or symptoms. These are presumed to be genetic and are usually age dependent [unchanged term]".[7]

Comment: The word 'idiopathic' comes from the Greek words idios (meaning self, own and personal) and pathic (meaning suffer), as explained in the important note on page 23.[11] Idiopathic is not synonymous with benign. There are some idiopathic epilepsies that have a bad prognosis or lifelong duration and, conversely, there are symptomatic epilepsies with a few seizures that may not even require treatment. Also, idiopathic is not synonymous with pharmaco-responsive; even within the same syndrome (idiopathic or otherwise) some patients are pharmaco-responsive while others are pharmaco-resistant.

Idiopathic is not and should not be equated with prognostic outcome and response to treatment, though this is usually better than in symptomatic and cryptogenic epilepsies.

Despite all these clarifications and the unequivocal meaning of what an idiopathic epileptic syndrome is, the new ILAE Commmision[8] proposes to abandon this term with the following justification: "The term idiopathic, however, is also used to convey the idea of a highly pharmaco-responsive form of epilepsy. Many, although not all, of the traditional 'idiopathic' epilepsies also spontaneously remit during a predictable age range (a separate quality or dimension) and were generally thought to be unaccompanied by other consequences or disabilities, although this is clearly not the case as a variety of subtle cognitive and behavioral disorders are seen in association with these forms of epilepsies.[8] Cause is no longer equated with prognosis, and the implication that "idiopathic" implies "benign" is intentionally discarded."[8]

Symptomatic epilepsy syndrome

Symptomatic epilepsies and syndromes "are considered the consequence of a known or suspected disorder of the central nervous system".[3]

Symptomatic epilepsy syndrome: "A syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain (unchanged term)".[7]

Comment: It is true that "symptomatic" may not be the best term to characterise these epilepsies; other synonyms such as "lesional" and "structural" have been proposed. "Epilepsy is symptomatic of something".[8] See also use of the word in "symptomatic treatment", "symptomatic relief" and so on. However, this term has now been well established and with further clarification of its meaning it may continue to serve its purpose. If it is "substituted for the concept of a poor prognosis for seizure control",this is incorrect; this should also be clarified and will be easily understood. [8]

Cryptogenic or probably symptomatic epilepsy syndrome

Cryptogenic epilepsies "are presumed to be symptomatic, but the aetiology is not known. The term cryptogenic refers to a disorder whose cause is hidden or occult. The cryptogenic epilepsies are also age related but often do not have well-defined electro- clinical characteristics".[3]

Probably symptomatic epilepsy syndrome: "This is synonymous with, but preferred to, the term 'cryptogenic', used for defining syndromes that are believed to be symptomatic but no aetiology has been identified [new term]".[7]

Comment: The number of cryptogenic epilepsies is decreasing in favour of the symptomatic ones with the use of high-resolution MRI, which identifies previously undetected structural brain abnormalities. However, as Peter Wolf has pointed out, "some cryptogenic conditions may also turn out to be idiopathic, and this could be true even for the one well-known case where, at the syndrome level, the aetiology remains unclarified but a specific, 'idiopathic' pathogenesis may still be revealed, i.e. mesiotemporal lobe epilepsy with hippocampal sclerosis". Cryptogenic is the preferred term in this book.

Despite all these clarifications and the unequivocal meaning of what cryptogenic epilepsies are (at least in the original classification of 1989)[3], the new ILAE Commission proposes to abandon this term with the following justification: "cryptogenic" was defined in 1989 as meaning 'presumed symptomatic' apparently in the sense of 'lesional'. It is, however, from among these 'cryptogenic' epilepsies that syndromes such as autosomal dominant nocturnal frontal lobe epilepsy and autosomal dominant partial epilepsy with auditory features have been discovered."[8]

The latter is absolutely consistent with the view that cryptogenic is a general term that includes "syndromes of causes that are hidden or occult".

"Idiopathic" and "cryptogenic" refer to epilepsies that their cause is not definitely known. The only difference from the newly proposed group of "epilepsies of unknown aetiology"[8] is that idiopathic are more likely to be of genetic and cryptogenic of symptomatic cause. When certain aetiology is found, these syndromes are not any more idiopathic, cryptogenic or unknown; they are re-classified appropriately as symptomatic, genetic or other syndromic categorisations.

Benign epilepsy syndrome

Benign epilepsy syndrome: "A syndrome characterised by epileptic seizures that are easily treated or require no treatment and remit without sequelae [clarified concept]."[7]

Benign: "The names of many syndromes contain the word 'benign.' Two key features of 'benign' epilepsy syndromes are that they a) involve seizures which are self-limited in that spontaneous remission, regardless of treatment, occurs at an expected age and is the anticipated outcome in the vast majority of cases, b) the consequences, if any, of the seizures are generally not disabling over the course of the active seizure disorder. This does not preclude an increased risk of subtle to moderate cognitive and behavioral disorders prior to, during, or extending beyond the active phase of the seizures."[8]

Comment: The prefix "benign" in a number of epileptic syndromes is to contrast them from the stigmatising word "epilepsy" and to differentiate them from the most severe forms of epilepsies such as "epileptic encephalopathies" and "catastrophic epilepsies". Benign in medicine indicates conditions that are not recurrent, progressive or malignant, have little or no detrimental consequences, are associated with a favourable prognosis for recovery and are generally not life-threatening. See also benign tumours.

With all these in mind, it may be difficult to understand the reasoning that the term benign epileptic syndrome should be abandoned: "With our increasing awareness, however, of the cognitive and behavioural comorbidities, psychiatric disorders, migraine, and even sudden death that may accompany any form of epilepsy, the term "benign" itself seems inappropriate as it may lead to false hopes and unrealistic expectations."[8] This is the most worrying statement; it is unjustified and particularly discouraging to those of us who have campaigned for years that, on evidence, a significant number of patients, in particular children, have a form of epilepsy (or just one or a few epileptic seizures) that is entirely benign with few or no detrimental consequences, as documented with long term prospective studies over the last 50 years (see relevant syndromes with the prefix "benign" detailed in this book). The main consequences for the vast majority of these patients and their families are psychosocial, resulting from erroneously unifying them in a single diagnostic entity, "epilepsy". Many patients with "benign" epilepsies do as well and sometimes better than those with febrile seizures, which is an example of "benignity" despite the fact that some patients with febrile seizures may not do well (see complex febrile seizures). Another alternative is to classify them as "Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se" with benign neonatal seizures and febrile seizures.

Proposed terms such as "pharmaco-responsive" may be more problematic than "benign" because (a) at least one third of these children do not need pharmacological treatment and (b) patients with the same syndrome may be "pharmaco-responsive" or "pharmaco-resistant".

"Self-limited" may be better but this also applies to a significant number of other unrelated epilepsies and this term has also been used to define epileptic seizures (see "self-limited epileptic seizures" in reference 6).

That benign and idiopathic are not synonymous have been unequivocally clarified above (see idiopathic epilepsy syndrome).

Genetic epilepsy

"The concept of genetic epilepsy is that the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. The knowledge regarding the genetic contributions may derive from specific molecular genetic studies that have been well replicated and even become the basis of diagnostic tests (e.g. SCN1A and Dravet syndrome) or the central role of a genetic component may rely on evidence from appropriately designed family studies. Designation of the fundamental nature of the disorder as being genetic does not exclude the possibility that environmental factors (outside the individual) may contribute to the expression of disease. At the present time, there is virtually no knowledge to support specific environmental influences as causes of or contributors to these forms of epilepsy.... It is possible that the genetic defect may have other effects in addition to the seizures but, as best we can tell, these other effects are not interposed between the genetic effect and the seizures".[8]

Comment: Genetic epilepsies are the best example of how the classification of epilepsies could be expanded in order to take advantage of the tremendous advances made in recent years. Nobody could do this better that the current ILAE Commission, which includes the protagonists of this progress.[12,13] The familial autosomal dominant focal epilepsies constitute chapter 14 in this book based on their recognition by the ILAE Task Force.[6,7] The same may apply to other genetic epilepsies as they are definitely discovered to be such, as in the case of Dravet syndrome. For other epilepsies thought to have a genetic element, such as childhood absence epilepsy, juvenile myoclonic epilepsy and rolandic epilepsy, we may have to wait until more concrete evidence emerges. Until then, they can be nested in their corresponding grouping of IGEs and benign childhood focal epilepsies.

The ILAE 1989 classification of epileptic syndromes[3]

The currently valid 1989 syndromic classification of the ILAE (Table 5.1) uses two fundamentally different divisions to shape four major classes of epileptic syndromes.[3]

The first division separates epilepsies with generalised seizures (*generalised epilepsies*) from epilepsies with partial seizures (*localisation related*, *partial* or *focal epilepsies*).

The second division is aetiological and separates epilepsies of known aetiology (*symptomatic* or *'secondary' epilepsies*) from those that are *idiopathic* (or *'primary'*) and those that are *cryptogenic*.

The four major classes of syndromes are:[3]

1. localisation-related (focal, local and partial) epilepsies and syndromes
2. generalised epilepsies and syndromes
3. epilepsies and syndromes that are undetermined as to whether they are focal or generalised
4. special syndromes.

Important note

Clarification on primary/primarily and secondary/secondarily seizures or syndromes

There is significant confusion about the words 'primary' and 'secondary' as adjuncts to seizures or syndromes (see also Chapter 2, page 23).

In syndromes, primary is synonymous with idiopathic and secondary is synonymous with symptomatic epileptic syndromes.

In seizures, primary denotes seizures that are generalised from onset (primarily generalised seizures), whereas secondary denotes generalised seizures that are generated from a cortical focus (secondarily or focal-onset generalised seizures).

In this book the terms 'primary/primarily' and 'secondary/secondarily' are used only in relation to seizures. In syndromes, only the terms 'idiopathic', 'symptomatic' and 'cryptogenic' are used.

Localisation-related (focal) epilepsies and syndromes

Localisation-related (focal) epilepsies and syndromes are epileptic disorders in which seizure semiology or findings at investigation disclose localised seizure origins. This includes not only patients with small, circumscribed, constant epileptogenic lesions (anatomical or functional), i.e. true focal epilepsies, but also patients with less well-defined lesions, whose seizures may originate from variable loci. In most symptomatic localisation-related epilepsies, the epileptogenic lesions can be traced to one part of a cerebral hemisphere, but in idiopathic age-related epilepsies with focal seizures corresponding regions of both hemispheres may be functionally involved.[3] The breakdown of the classification is as follows:

1. localisation-related (focal, local and partial) epilepsies and syndromes:
   - 1.1. idiopathic
   - 1.2. symptomatic
     - temporal lobe epilepsies
     - frontal lobe epilepsies
     - parietal lobe epilepsies
     - occipital lobe epilepsies
   - 1.3. cryptogenic.

Idiopathic localisation-related epilepsies are childhood epilepsies with focal seizures and focal EEG abnormalities. They are age related, with no demonstrable anatomical lesions and are subject to spontaneous remission. Clinically, patients have neither a neurological nor intellectual deficit, nor a history of antecedent illness, although frequently they have a family history of benign epilepsy. The seizures are usually brief and rare, but may be frequent early in the course of the disorder. The seizure patterns may vary from case to case, but usually remain constant in the same child. The EEG is characterised by normal background activity and localised high-voltage repetitive spikes, which are sometimes independently multi-focal. Brief bursts of generalised spikes and waves can occur. Focal abnormalities are increased by sleep and have no change in morphology.[3]

Symptomatic localisation-related epilepsies: Apart from the rare conditions of the Kozhevnikov–Rasmussen syndrome and focal reflex epilepsies, the symptomatic category comprises syndromes of great individual variability, based mainly on seizure types and other clinical features, as well as anatomical localisation and aetiology – as far as these are known. The seizure types refer to the ILAE classification. Inferences about anatomical localisation must be drawn carefully. The scalp EEG (both interictal and ictal) may be misleading and even local morphological findings detected by neuroimaging techniques are not necessarily concordant with an epileptogenic lesion.

Seizure symptomatology and, sometimes, additional clinical features often provide important clues. The first sign or symptom of a seizure is often the most important indicator of the site of origin of seizure discharge, whereas the subsequent sequence of ictal events can reflect its further propagation through the brain. This sequence can, however, still be of high localising importance. One must bear in mind that a seizure may start in a clinically silent region, so that the first clinical event occurs only after spread to a site more or less distant from the locus of initial discharge.

The tentative descriptions of syndromes related to anatomical localisations are based on data that include findings in studies with depth electrodes.[3]

Generalised epilepsies and syndromes

Generalised epilepsies and syndromes are epileptic disorders with generalised seizures, i.e. seizures in which the first clinical changes indicate initial involvement of both hemispheres. The ictal encephalographic patterns are initially bilateral.[3] The breakdown of the classification is as follows:

2. generalised epilepsies and syndromes:
   - 2.1. idiopathic
   - 2.2. cryptogenic
   - 2.3. symptomatic:
     - 2.3.1. non-specific aetiology
     - 2.3.2. specific syndrome.

Idiopathic generalised epilepsies (IGEs) are forms of generalised epilepsies in which all seizures are initially generalised with an EEG expression that is a generalised, bilateral, synchronous, symmetrical discharge (as described in the seizure classification of the corresponding type). The patient usually has a normal inter-ictal state, with no neurological or neuroradiological signs. In general, inter-ictal EEGs show normal background activity and generalised discharges, such as spikes, polyspikes, spikes and waves, and polyspikes and waves of about 3 Hz. The discharges are increased by slow sleep. The various syndromes of IGEs differ mainly in age of onset.[3]

Symptomatic generalised epilepsies, occurring most often in infancy and childhood, are characterised by generalised seizures with clinical and EEG features that differ from those of the IGEs. There may be only one type, but more often there are several types, including myoclonic jerks, tonic seizures, atonic seizures and atypical absences. EEG expression is bilateral but less rhythmic than in the IGEs and is more or less asymmetrical. Inter-ictal EEG abnormalities differ from IGEs, appearing as suppression bursts, hypsarrhythmia, slow spikes and waves or generalised fast rhythms. Focal abnormalities may be associated with any of the above. There are clinical, neuropsychological and neuroradiological signs of a usually diffuse, specific or non-specific encephalopathy.[3]

Symptomatic generalised epilepsies of specific aetiologies are 'only diseases in which epileptic seizures are the presenting or a prominent feature'.[3] These diseases often have epileptic features that resemble 'symptomatic generalised epilepsies without specific aetiology', appearing at similar ages, and include diseases such as Aicardi syndrome, lissencephaly–pachygyria, Sturge–Weber syndrome, hypothalamic hamartomas, disorders of inborn error of metabolism, Lafora disease and others.

Author's note: Many of these 'symptomatic generalised epilepsies' are focal rather than generalised (see relevant chapters).

Epilepsies and syndromes undetermined as to whether they are focal or generalised

The ILAE suggests two reasons as to why it may not be possible to determine whether seizures are focal or generalised:

1. The patient has both focal and generalised seizures together or in succession (e.g. focal seizures plus absences) and has both focal and generalised EEG seizure discharges (e.g. temporal lobe spike focus plus independent bilateral spike and wave discharges).[3]
2. There are no positive signs of either focal or generalised seizure onset. The most common reasons for this are that the seizures occur during sleep, the patient recalls no aura and ancillary investigations including EEG are not revealing.[3]

Therefore, epilepsies and syndromes undetermined as to whether they are focal or generalised may be:

- 3.1. With both generalised and focal seizures
- 3.2. With no unequivocal generalised or focal features.

Syndromic classification of the ILAE 1989[3]

1. Localisation-related (focal, local, partial) epilepsies and syndromes

1.1 Idiopathic (with age-related onset)

At present, the following syndromes are established, but more may be identified in the future:

- Benign childhood epilepsy with centrotemporal spike
- Childhood epilepsy with occipital paroxysms
- Primary reading epilepsy

1.2 Symptomatic

- Chronic progressive epilepsia partialis continua of childhood (Kozhevnikov syndrome)
- Syndromes characterised by seizures with specific modes of precipitation
- Temporal lobe epilepsies
- Frontal lobe epilepsies
- Parietal lobe epilepsies
- Occipital lobe epilepsies

1.3 Cryptogenic

Cryptogenic epilepsies are presumed to be symptomatic and the aetiology is unknown. This category thus differs from the previous one by the lack of aetiological evidence

2. Generalised epilepsies and syndromes

2.1 Idiopathic (with age-related onset – listed in order of age)

- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with grand mal (GTCS) seizures on awakening
- Other generalised idiopathic epilepsies not defined above
- Epilepsies with seizures precipitated by specific modes of activation

2.2 Cryptogenic or symptomatic (in order of age)

- West syndrome (infantile spasms, Blitz–Nick–Salaam Krampfe)
- Lennox–Gastaut syndrome
- Epilepsy with myoclonic–astatic seizures
- Epilepsy with myoclonic absences

2.3 Symptomatic

2.3.1 Non-specific aetiology

- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy with suppression burst
- Other symptomatic generalised epilepsies not defined above

2.3.2 Specific syndromes

- Epileptic seizures may complicate many disease states. Under this heading are included diseases in which seizures are a presenting or predominant feature

Table 5.1 *Continued on facing page.*

Syndromic classification of the ILAE *(continued)*

3. Epilepsies and syndromes undetermined whether focal or generalised

3.1 With both generalised and focal seizures
- Neonatal seizures
- Severe myoclonic epilepsy in infancy
- Epilepsy with continuous spike–waves during slow-wave sleep
- Acquired epileptic aphasia (Landau–Kleffner syndrome)
- Other undetermined epilepsies not defined above

3.2 Without unequivocal generalised or focal features. All cases with GTCSs in which clinical and EEG findings do not permit classifications as clearly generalised or localisation related, e.g. many cases of sleep-grand mal (GTCS) are considered not to have unequivocal generalised or focal features

4. Special syndromes

4.1 Situation-related seizures (Gelegenheitsanfälle)
- Febrile convulsions
- Isolated seizures or isolated status epilepticus
- Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, non-ketotic hyperglycaemia

Table 5.1 *Continued from previous page. Table modified with permission from the Commission on Classification and Terminology of the ILAE (1981).*[3]

Special syndromes

These manifest with situation-related seizures (Gelegenheitsanfälle) such as:[3]
- febrile seizures
- isolated seizures or isolated status epilepticus
- seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia and non-ketotic hyperglycaemia.

Epilepsies with seizures precipitated by specific modes of activation

These are characterised by reflex seizures that are consistently related to specific modes of precipitations, as detailed in Table 16.2 and Chapter 16. Reflex seizures could be focal or generalised, idiopathic, cryptogenic or symptomatic. Also, seizures occur spontaneously in most patients with reflex epilepsies.[3]

Syndromic classification of the new diagnostic ILAE scheme[6,7]

There are significant differences in the syndromic classification between the 1989 ILAE classification and the ILAE Task Force reports that are detailed in the individual syndromes of the relevant chapters in this book.

'Seizures not requiring a diagnosis of epilepsy' are probably synonymous with 'situation-related seizures' (Tables 5.1 and 5.2). 'Diseases frequently associated with epileptic seizures or syndromes' (detailed in Chapter 17) are probably synonymous

Epileptic syndromes in the ILAE Task Force report

Report of 2001[7]	Report of 2006†,[6]
Idiopathic focal epilepsies in infancy and childhood	**Neonatal period**
Benign infantile seizures (non-familial)	Benign familial neonatal seizures (3) – probably a disease
Benign childhood epilepsy with centrotemporal spikes	Early myoclonic encephalopathy (3)
Early onset benign childhood occipital epilepsy (Panayiotopoulos type)	Ohtahara syndrome (3)
Late-onset childhood occipital epilepsy (Gastaut type)	**Infancy**
Familial (autosomal dominant) focal epilepsies	Migrating partial seizures of infancy (3) – now recognised as a syndrome
Autosomal dominant nocturnal frontal lobe epilepsy	West syndrome (3)
Benign familial neonatal seizures	Myoclonic epilepsy in infancy (3) – the word benign has been removed
Benign familial infantile seizures	Benign infantile seizures (3) – now familial and non-familial forms are combined
Familial temporal lobe epilepsy	Dravet syndrome (3)
Familial focal epilepsy with variable foci*	Myoclonic encephalopathy in non-progressive disorders (3) – now recognised as a syndrome
Symptomatic and probably symptomatic epilepsies	**Childhood**
Limbic epilepsies: • Mesial temporal lobe epilepsy with hippocampal sclerosis • Mesial temporal lobe epilepsy defined by specific aetiologies • Other types defined by location and aetiology	Early onset benign childhood occipital epilepsy (Panayiotopoulos type) (3)
	Epilepsy with myoclonic–astatic seizures (3)
	Benign childhood epilepsy with centrotemporal spikes (3)
Neocortical epilepsies: • Rasmussen syndrome • Hemiconvulsion–hemiplegia syndrome • Other types defined by location and aetiology • Migrating partial seizures of early infancy*	Late-onset childhood occipital epilepsy (Gastaut type) (1)
	Epilepsy with myoclonic absences (2)
	Lennox–Gastaut syndrome (3)
Idiopathic generalised epilepsies	Epileptic encephalopathy with continuous spikes and waves during sleep, including Landau–Kleffner syndrome (3) – the two are now combined
Benign myoclonic epilepsy in infancy	Childhood absence epilepsy (3)
Epilepsy with myoclonic–astatic seizures	**Adolescence**
Childhood absence epilepsy	Juvenile absence epilepsy (3)
Epilepsy with myoclonic absences	Juvenile myoclonic epilepsy (3)
Idiopathic generalised epilepsies with variable phenotypes: • Juvenile absence epilepsy • Juvenile myoclonic epilepsy • Epilepsy with GTCSs only	Progressive myoclonus epilepsies (3) – diseases rather than syndromes
Generalised epilepsies with febrile seizures plus*	

Table 5.2 *Continued on facing page.* *Syndromes in development. †The epilepsy syndromes listed were individually discussed by the Core Group and rated on a score of 1 to 3 (3 being the most clearly and reproducibly defined) regarding the certainty with which the group believed each syndrome represented a unique diagnostic entity.

Epileptic syndromes in the ILAE Task Force report *(continued)*

Report of 2001[7]	Report of 2006[†,6]
Reflex epilepsies	**Less specific age relationship**
Idiopathic photosensitive occipital lobe epilepsy	Autosomal dominant nocturnal frontal lobe epilepsy (3)
Other visual sensitive epilepsies	Familial temporal lobe epilepsies (3)
Primary reading epilepsy	Mesial temporal lobe epilepsy with hippocampal sclerosis (2) – probably more than one syndrome
Startle epilepsy	Rasmussen syndrome (3) – disease or syndrome?
Epileptic encephalopathies	Gelastic seizures with hypothalamic hamartoma (3) – probably a disease
Early myoclonic encephalopathy	**Special epilepsy conditions**
Ohtahara syndrome	Symptomatic focal epilepsies not otherwise specified
West syndrome	Epilepsy with GTCSs only – unable to agree on any syndrome with this feature; whether EGTCSW exists is unclear
Dravet syndrome (previously known as severe myoclonic epilepsy in infancy)	Reflex epilepsies (unclear if other reflex epilepsies constitute syndromes): • Idiopathic photosensitive occipital lobe epilepsy (2) • Primary reading epilepsy (3) • Hot water epilepsy in infants (2)
Myoclonic status in non-progressive encephalopathies*	Febrile seizures plus (FS+) (part of generalised epilepsy with FS+, which is broader than a single generalised syndrome)
Lennox–Gastaut syndrome	Familial focal epilepsy with variable foci (3) – now recognised as a syndrome
Landau–Kleffner syndrome	**Conditions with epileptic seizures that do not require a diagnosis of epilepsy**
Epilepsy with continuous spike–waves during slow-wave sleep	Benign neonatal seizures (2)
Progressive myoclonus epilepsies	Febrile seizures (3)
See specific diseases	**Categories that might be considered in future classification systems**
Seizures not necessarily requiring a diagnosis of epilepsy	Autosomal dominant epilepsies
Benign neonatal seizures	Epileptic encephalopathies
Febrile seizures	Generalised epilepsy with FS+
Reflex seizures	Idiopathic generalised epilepsies
Alcohol-withdrawal seizures	Idiopathic focal epilepsies
Drug or other chemically induced seizures	Reflex epilepsies
Immediate and early post-traumatic seizures	
Single seizures or isolated clusters of seizures	
Rarely repeated seizures (oligoepilepsy)	

Table 5.2 *Continued*. *Syndromes in development. †The epilepsy syndromes listed were individually discussed by the Core Group and rated on a score of 1 to 3 (3 being the most clearly and reproducibly defined) regarding the certainty with which the group believed each syndrome represented a unique diagnostic entity. EGTCSW, epilepsy with GTCSs on awakening. Table adapted with permission from Engel (2007)[7] and Engel (2006).[6]

Useful definitions: age-related stages of development

Neonate (baby, newborn): 0–4 weeks (first 28 days of life of a full term baby)

Infant (from the Latin in-fans, "unable to speak"): 4 weeks to 1.5 years

Childhood There is no universally accepted definition of what age defines childhood; different jurisdictions have defined children as anything from under 12 to under 18

- Early childhood (toddler): 1.5–4 years
- Middle childhood (elementary school age): 4–8 years
- Late childhood (preadolescence, preteen): 8–12 years
- Primary school age (prepubescence): 4–12 years

Teenage (adolescence and puberty): 12–18 years

Adolescence (from the Latin adolescere, "to grow up"): the period of development between childhood and adulthood; when a person goes through the physical stages of puberty or when a child begins to develop adult secondary sex characteristics, which often begins before the age of 13 years. Its endpoint varies in different cultures and countries.

Adult (adultus "grown up"): from the end of adolescence to the beginning of old age

Elderly: Most commonly considered to apply to persons over the age of retirement (65 years)

Table 5.2 lists the accepted epilepsy syndromes by the ILAE Task Force in their reports of 2001[7] and 2006.[6] Note that the group classification is by age at onset in the most recent 2006 report, thus avoiding previous grouping by aetiology (e.g. idiopathic, symptomatic and cryptogenic) or likehood of relations between syndromes (IGE, benign childhood focal seizures, epileptic encephalopathies and so on).

The principle of classification of electro-clinical syndromes and other epilepsies by age at onset as the primary organisational factor (Table 5.2)[6,8] creates significant problems and is highly contentious (see Chapter 1, page 15).

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SIX

EEG and brain imaging

EEG in the diagnosis and management of epilepsies

The EEG, which is entirely harmless and relatively inexpensive, is the most important investigative tool in the diagnosis and management of epilepsies. However, for the EEG to provide accurate assessments, it must be properly performed by experienced technologists and carefully studied and interpreted in the context of a well-described clinical setting by experienced physicians.

More than half the patients currently referred for a routine EEG are suspected of suffering from or do suffer from epilepsies. The EEG is indispensable in the correct diagnosis of the type of epileptic seizure or syndrome that these patients may have.

The EEG is an integral part of the diagnostic process in epilepsies. In this sense, it is mandatory for all patients with epileptic seizures, and there is more than enough justification for performing an EEG after the first seizure or in patients suspected of having epilepsy. That the patient may not need treatment is not a convincing argument against such a practice. The prime aim in medicine is the diagnosis, which determines the prognosis and management strategies.

The role of the EEG is to help the physician establish an accurate diagnosis (Table 6.1).[1–6]

In many epileptic conditions, the EEG may specifically confirm or specifically direct the physician towards the correct diagnosis (Table 6.2 and Figure 6.1). In others, it may not be helpful because it is normal or has non-specific diffuse or paroxysmal abnormalities (Table 6.2). These cases may need an EEG to be performed during sleep and awakening, but again it may not reveal specific features in about 10% of patients. However, even a normal EEG in an untreated patient may be useful because it may exclude some of the above conditions where a normal EEG is remotely unlikely (Table 6.2).

An EEG in patients with chronic epilepsies or those who are on appropriate anti-epileptic drug (AED) medication may be uninformative or misleading. Obtaining previous medical and EEG reports is essential.

A request for an EEG should describe the clinical problem well, and the EEG technologist should also obtain and supplement the relevant clinical information.

The value of routine inter-ictal or ictal EEGs in epilepsies

The use of the EEG in epilepsies is overvalued by some and undervalued by others. The truth is somewhere in between.

Reasons why the EEG should not be undervalued

An EEG is the only available investigative tool for recording and evaluating the paroxysmal discharges

Recommendations for the appropriate use of EEG in the diagnosis of epilepsies

Use EEG (in qualified EEG departments):*

- To support a diagnosis of epilepsy in patients in whom the clinical history suggests it
- To help determine seizure type and specific epilepsy syndrome
- To help identify possible precipitants to epileptic seizures
- To detect clinical events during epileptiform paroxysms with video-EEG (obtaining an ictal recording is the best EEG documentation of epilepsy)

Do not use EEG:

- In unqualified EEG departments (high risk of significant errors that outweigh any benefits)
- To exclude a diagnosis of epilepsy (a normal EEG does not exclude epilepsy)
- In syncope, migraine or other definite non-epileptic disorders (risk of false-positive results)

First ask for standard routine EEG in wakefulness:

- With intermittent photic stimulation and hyperventilation, with informed consent

If diagnosis or classification is still unclear, use:

- Sleep EEG (best achieved through partial sleep deprivation)
- Repeated standard EEG (do not use in preference to sleep or sleep-deprived EEG)
- Long-term video or ambulatory EEG

Table 6.1 *Always describe the clinical problem well in the referral form.

EEG sensitivity and specificity

On initial EEG, inter-ictal epileptiform EEG abnormalities are under 30%. The yield is much higher (80–90%) with increasing length of recordings and on repeating the EEG, as well as with sleep EEG

An EEG is unlikely to be normal in untreated:

- Infantile spasms and other epileptic encephalopathies
- Convulsive or non-convulsive status epilepticus
- Idiopathic generalised epilepsies, particularly absence seizures
- Photosensitivity

A single EEG is more likely to be normal (80%) than abnormal in:

- Mesial frontal, mesial temporal and mesial occipital lobe epilepsies
  - In such cases and particularly in simple focal seizures (no impairment of consciousness), even an ictal EEG may not show electrical changes. This is less common in focal seizures in which there is impairment of consciousness (complex focal seizures) but ictal electrical changes may still be absent, particularly when the origin is in the mesial frontal lobe

Some patients with well-documented epileptic seizures may have persistently normal inter-ictal EEGs

Table 6.2

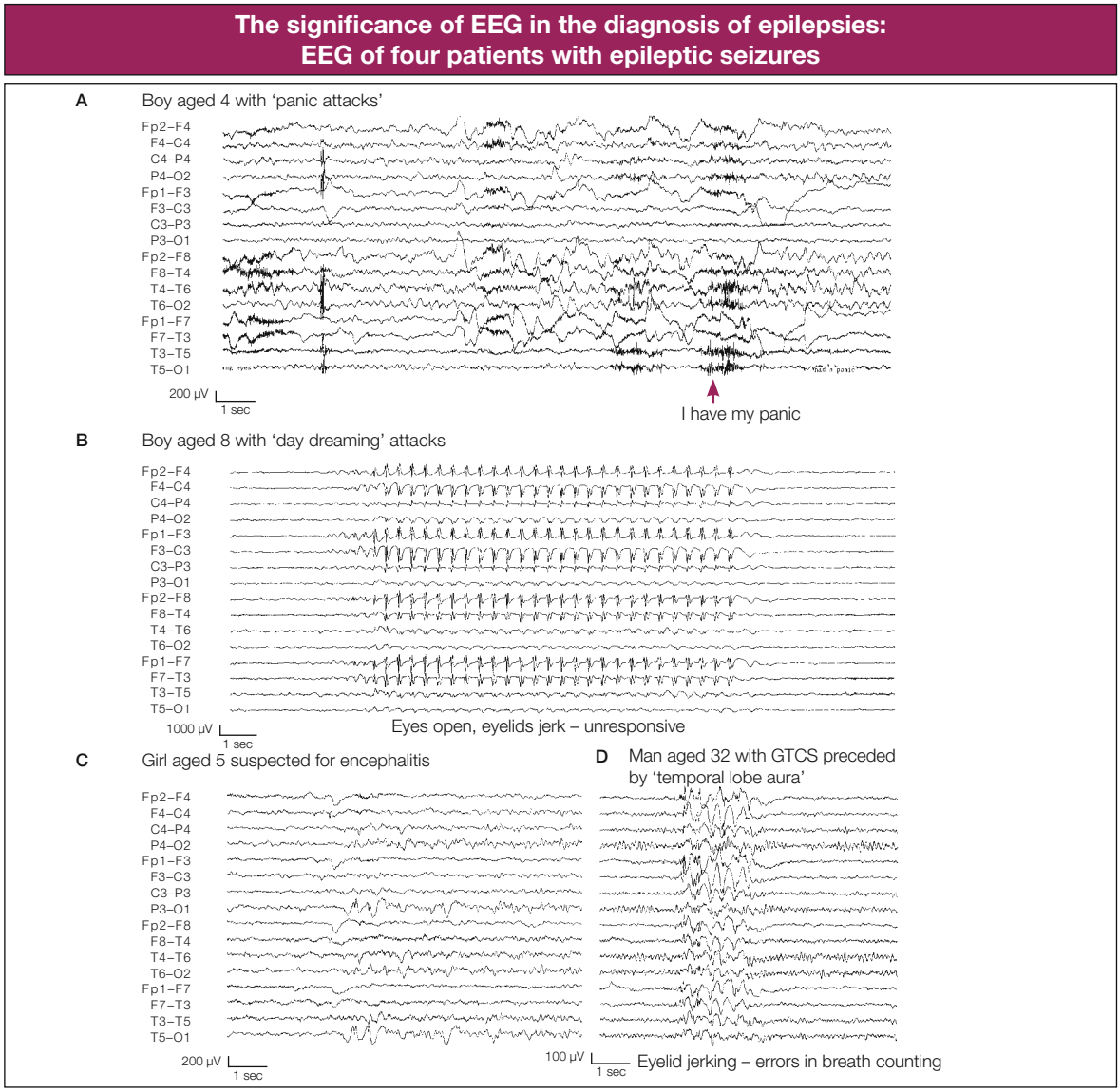

Figure 6.1 (**A**) Ictal EEG of a 4-year-old boy who had frequent brief episodes of 'panic' without impairment of consciousness or convulsive features. The resting EEG was normal but a 'panic' attack was video-EEG recorded with ictal EEG changes of 2 min on the right, mainly involving the right temporal regions. The child accurately answered all questions and communicated well with the technologist during the ictus. This EEG unequivocally established the diagnosis and dictated the appropriate management. MRI showed right hippocampal sclerosis. (**B**) Video-EEG of a child aged 8 years with frequent episodes of 'blanks and day dreaming' for 2 years. Frequent typical absence seizures were recorded and appropriate treatment was initiated with complete control of seizures. (**C**) Inter-ictal EEG of a 5-year-old girl 2 days after a prolonged autonomic status epilepticus who was treated for suspected encephalitis (see case 47 in Panayiotopoulos[7]). EEG showed scattered right central and bi-occipital spikes. The diagnosis of Panayiotopoulos syndrome was established and the child was discharged. (**D**) Video-EEG of a 32-year-old man with three to four GTCSs every year from age 16 (see case 1 in Panayiotopoulos[8]). All GTCSs were preceded by absence status diagnosed as 'prodrome' or 'temporal lobe aura'. Treatment included inappropriate use of phenytoin and even vigabatrin. Brief generalised discharges of 3 to 4 Hz spike/polyspikes and slow-waves were recorded during hyperventilation. These were associated with brief rhythmic myoclonic jerks of the eyelids (which would be impossible to detect without video) and minor errors in breath counting. The correct diagnosis of IGE with phantom absences was established and treatment changed to valproate. No further seizures occurred in the next 5 years of follow-up.

of cerebral neurones that cause seizures. It is often with the help of an EEG that a clinical diagnosis is confirmed, rejected, questioned or documented.

The seizure and epileptic syndrome classifications are based on combined clinico-EEG manifestations. Epileptic syndromes, the most important advance of recent epileptology, were mainly identified because of their EEG manifestations. Focal and generalised epilepsies are often difficult to differentiate without an EEG, even by the most experienced epileptologists.

It is the EEG that will often document, beyond any doubt, the epileptic or non-epileptic nature of paroxysmal events. The EEG is the most powerful investigative tool in neonatal seizures.

Reasons why the EEG should not be overvalued

The EEG is oversensitive in conditions such as benign childhood seizure susceptibility syndrome and of no value in other conditions such as frontal epilepsies. On rare occasions, even ictal events may be undetected in a surface EEG (some frontal seizures are a typical example of this situation).

Patients with mainly focal epilepsies may have a series of normal EEGs, and the EEG localisation is not always in agreement with ictal intracranial recordings. More than 40% of patients with epileptic disorders may have one normal inter-ictal EEG, although this percentage falls dramatically to 8% with a series of EEGs and appropriate activating procedures, particularly sleep.[5]

Severely 'epileptogenic' EEGs may be recorded from patients with infrequent or controlled clinical seizures and *vice versa*. The EEG abnormalities often do not reflect the actual severity of the epileptic disorder.

More than 10% of normal people may have non-specific EEG abnormalities and approximately 1% may have 'epileptiform paroxysmal activity' without seizures.[1] The prevalence of these abnormalities is higher in children (2–4% of normal children have functional spikes) and in patients with non-epileptic neurological or medical disorders, or neurological deficits.[9]

Useful reminder

Conventional EEG 'epileptogenic abnormalities' of focal spikes occur in 2–4% of normal children (Table 12.1) and their prevalence is much higher in children with neurodevelopmental abnormalities, even if they do not have epileptic seizures.

Conversely, EEGs of symptomatic epilepsies (cerebrovascular disease, older patients, fast growing tumours) are commonly void of conventional 'epileptogenic abnormalities'; instead, focal slow waves without spikes are seen.

Sources of error in EEGs

Even the most reliable investigative tools in medicine cannot escape severe errors because of poor technical quality (equipment, personnel or both), interpretation by poorly qualified physicians or both (Figure 6.2). A competent report should not only describe the EEG abnormality accurately, but also provide its significance and meaning in accordance with a well-described clinical setting.[9]

Failing to achieve this leads to severe errors and erroneous criticism such as 'a routine inter-ictal EEG is one of the most abused investigations in clinical medicine and is unquestionably responsible for great human suffering'.[10] Anything in medicine, clinical or laboratory, may be harmful if misinterpreted. Raising standards, not abandoning the service, is the proper response (Figure 6.2).[6,11]

That a patient with a brain tumour may not have clinical signs does not invalidate the clinical examination and the same is true for the EEG.

The main cause of concern and suffering is that physicians, including a few epilepsy authorities, have misunderstood the EEG, its value and its limitations.

Provided that the EEG is technically correct, the following are, in my opinion, the most important factors of error listed in order of significance.

1. The single most significant source of error is that the EEG is often interpreted out of the clinical context. There are two reasons for this. First, the referring physician

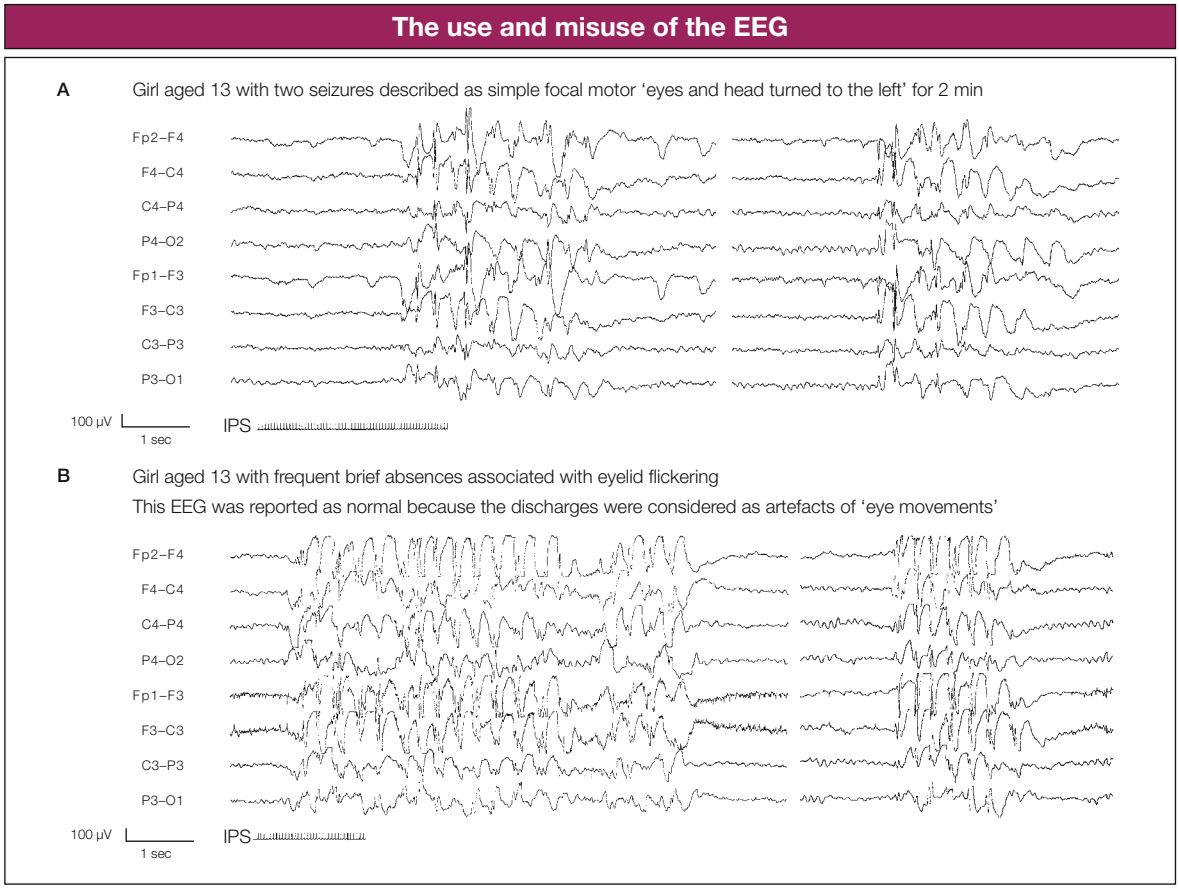

Figure 6.2 Two girls with similar EEG abnormalities of generalised spike/polyspike–slow-wave discharges either spontaneous or elicited by intermittent photic stimulation (IPS). (**A**) shows proper use of the EEG. This girl gave a clear-cut history of two seizures that, on clinical grounds, had all the elements of focal motor seizures. Her eyes turned to the left, followed by her head and she 'could not bring them back to normal' for 2 min. The EEG clearly documented that she had generalised not focal epilepsy. (**B**) shows misuse of the EEG. A 26-year-old woman with juvenile myoclonic epilepsy had onset of seizures at the age of 13 years. These consisted of brief absences with eyelid jerking. Her first EEG documented the epileptic nature of the attacks, but the reporting physician and the EEG technologist considered the discharges as artefacts produced by the concurrent eyelid jerking. The EEG was erroneously reported as normal.

provides inadequate information about the events ('patient with loss of consciousness or grand mal seizures', 'black-outs: epilepsy?' and 'unexplained aggressiveness: temporal lobe epilepsy [TLE]?') and often fails to mention other medical conditions or drugs that may significantly affect the EEG and its interpretation. Second, the reporting clinical neurophysiologist prefers a convenient but rather unhelpful and uncommitted abbreviation of the factual report ('normal EEG', 'an abnormal EEG with generalised discharges of frontal origin', etc).

2. Non-specific EEG abnormalities are overemphasised without suggesting any means of clarifying their significance, e.g. with a sleep-deprived EEG or after obtaining more clinical data.

3. EEG changes, whether developmentally (age) related or induced by physiological drowsiness or sleep and hyperventilation, are significant and impossible for non-specialists to evaluate. EEGs in infants and children are even more complex and demanding.

4. Non-epileptic episodic transients, such as benign epileptiform transients of sleep, 6 and 14 positive

spikes per second, and rhythmic mid-temporal discharges, may often be misinterpreted as evidence of epilepsy by non-specialists.

5. Previous EEG recordings and results are lost, destroyed or not sought. EEGs that are recorded at the initial stages of the disease, and particularly before treatment, are significant not only at first medical presentation, but also in the re-evaluation of patients and diseases.

6. The EEG may be altered by drugs (such as neuroleptics or AEDs) or coexisting medical conditions (migraine, electrolyte disturbances, cerebrovascular disease or a previous head injury).

Physiological activators of EEG abnormalities

Activating procedures are intended to improve the EEG diagnostic yield by inducing or enhancing epileptogenic paroxysms. Intermittent photic stimulation (IPS) and hyperventilation are routinely applied in awake-stage EEGs. Drowsiness, sleep and awakening are also very important activating procedures.

Drowsiness, sleep and awakening

An EEG in drowsiness, sleep and awakening is important for the purposes of increasing the diagnostic yield of specific epileptiform patterns. It is particularly useful in patients who produce a normal routine awake EEG or in those whose seizures are consistently associated with these physiological stages.

To achieve sleep for the purpose of obtaining an EEG during sleep, EEG departments have different practices:

- sleep deprivation (partial or all night)
- drug-induced sleep.

The best practice is to perform a sleep EEG that is as close as possible to the natural state and habits of the patient, and thereby achieve best results with minimal risk to the patient and minimal discomfort to the patient and their family.

Best clinical practice

- Partial instead of all-night sleep deprivation (drug-induced sleep should be reserved only for uncooperative patients).
- The EEG recording should continue to include the awakening state (Figure 6.3).

Partial sleep deprivation is practical, more natural, less disturbing and more rewarding than all-night sleep deprivation. If properly performed, more than 90% of patients (including infants and children) go to sleep and allow a good EEG recording in sleep and awakening.[13]

Patients are asked to sleep 1 or 2 hours later and wake up 1 or 2 hours earlier than their routine practice and remain awake until their appointment time, which is after their lunch hour (around 11.30 a.m. for children and 1.30 p.m. for adults).

This timing does not, however, need to be so rigid but can be adjusted to each patient's sleep habits. Some patients find it easy and others difficult to go to sleep. Patients or their parents should be told that the aim of this procedure is to obtain a natural sleep.

The EEG is performed in a darkened and quiet recording room, usually after application of the EEG electrodes. However, it is often useful for infants and children to go to sleep in their parents' arms in a darkened and quiet waiting room before the EEG. The recording is for 30–60 min, depending on the depth of sleep and EEG abnormalities. Subsequently, the patient is awakened and the EEG continues, including a recording of hyperventilation and IPS. This last phase on awakening lasts for about 15 min, also depending on EEG inter-ictal and ictal abnormalities. Ideally, the whole procedure should be performed with video-EEG, particularly when minor or major seizures are expected on clinical or previous EEG grounds.

All-night sleep deprivation is usually required by most EEG departments. The EEG is performed the next morning with the aim of obtaining a 30- to 40-min recording during sleep. As soon as this is achieved,

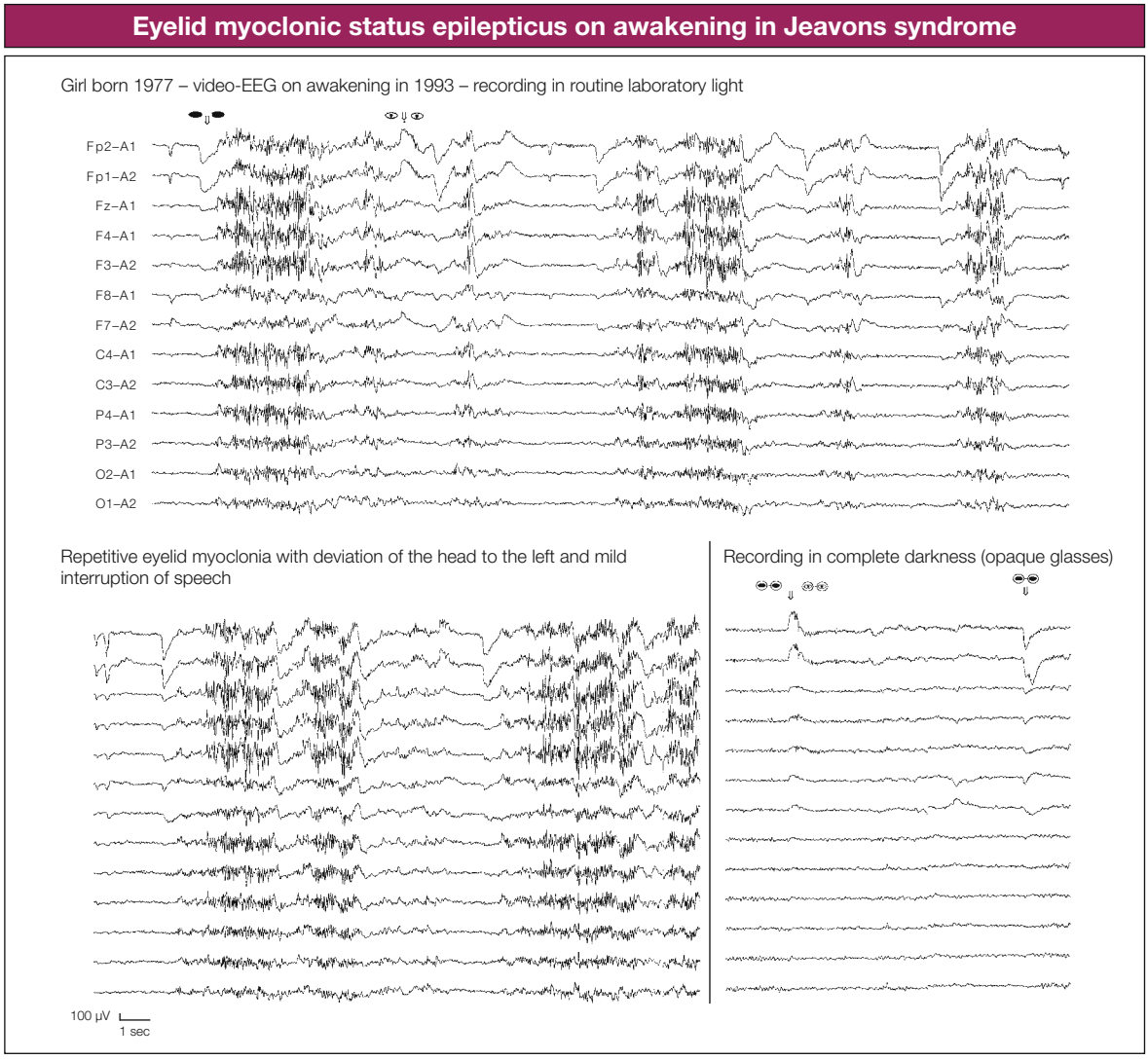

Figure 6.3 The video-EEG was after partial sleep deprivation. The sleep EEG was of good organisation with a few brief generalised discharges that were not associated with clinical manifestations. Repetitive brief seizures started immediately after awakening from 30 min of sleep and lasted for 35 min. Each seizure had a duration of 2–8 s and consisted of violent tonic spasm of the eyelids, eyeballs and head, which were consistently deviated to the left with little interruption of speech. The patient was able to communicate well during the whole episode with entirely intact cognition and speech in between the discharges, which because of their length may constitute discontinuous eyelid myoclonic status epilepticus. All clinical and EEG eye-closure-related abnormalities were eliminated when she wore underwater goggles covered with opaque tape (bottom right).

the recording is stopped and the patient awakened and allowed to go home.

This is unsatisfactory because all-night sleep deprivation:

- is inconvenient for the patient and often the whole family
- may induce seizures in susceptible individuals, particularly after leaving the EEG department in the awakening period; patients with juvenile myoclonic epilepsy are particularly vulnerable because seizures mainly occur on awakening after sleep deprivation.

Furthermore, sleep is achieved in only half the patients when the EEG is recorded in the morning, even after all-night sleep deprivation.[14]

Drug-induced sleep is also applied in some departments either routinely or for children who are uncooperative. Currently, chloral hydrate or, more recently, melatonin is given to the patient before or during electrode placement with the aim of obtaining a sleep EEG, after which the same procedure as above is followed. There is no requirement for an EEG on awakening. However, sleep-inducing drugs may interfere with normal patterns and patients are often drowsy during the rest of the day. They may also have a seizure on awakening.

Hyperventilation

Hyperventilation is a standard procedure in a routine EEG. The patient is instructed to breathe deeply rather than quickly at a rate of 20 deep breaths per min for 3 min. Young children are encouraged to hyperventilate by asking them to blow on a brightly coloured pinwheel or a balloon. Infants often hyperventilate while sobbing.

Hyperventilation is the most powerful activating procedure for eliciting absence seizures and generalised spike–wave discharges in more than 90% of patients who have idiopathic generalised epilepsy (IGE) with absences (see Chapter 13).

The significance of breath counting during hyperventilation: Generalised spike/polyspike–wave discharges are often associated clinically with impairment of consciousness, which can be evaluated with breath counting. This is easily performed by any patient who can count irrespective of age and intelligence. The patient counts each breath at its expiration phase loudly and consecutively. This allows an accurate identification of even mild transient cognitive impairment during generalised discharges, manifested as slurring of the speech, cessation, delay, hesitation, errors in counting with repetitions and counting out of sequence. Mild to moderate impairment of cognition is easily missed by the routine testing of a verbal test stimulus (a phrase, number or rhyme) during the discharge, which the patient is asked to recall (recall or not recall, all or none fashion) (Figure 1.3).

Breath counting is powerful in detecting transient cognitive abnormalities because of the simultaneous testing of attention, concentration, memory, sequential precision and language function. The patient's performance during breath counting acts as its own control.

Intermittent photic stimulation

IPS is primarily for the detection of photosensitive patients and is less important with regard to other parameters such as asymmetrical photic following.[15] An untreated photosensitive patient is unlikely to have a normal EEG during IPS. Conversely, photoparoxysmal responses may occur in more than 1% of healthy individuals. The IPS application should comply with the recommended guidelines and avoid the induction of a seizure (see Chapter 16).

Other forms of appropriate activation of reflex seizures

Other forms of appropriate activation should be used for patients suspected of having reflex seizures such as reading, pattern, musicogenic, proprioceptive and noogenic epilepsy. Their detection is of significance with regard to diagnosis and management. The avoidance of precipitating factors may be all that is needed in certain patients with reflex seizures.

Useful recommendations

The EEG recording should be tailored to the specific circumstances of the individual patient:

- The technologist should be alerted to apply the appropriate stimulus when reading or other forms of reflex epilepsy are clinically suspected (see Chapter 16).
- Patients with IGEs may have a normal or non-specifically abnormal routine EEG. In these patients an EEG after partial sleep deprivation, with video-EEG recording during sleep and on awakening, frequently reveals clinical and EEG ictal events (Figure 6.3).
- The same applies to patients with nocturnal seizures who may have a normal EEG while awake.
- Women with catamenial seizures should have an EEG during their vulnerable periods if EEGs at other times are inconclusive.

Video-EEG recording should be made routine clinical practice

Video-EEG recording is the only means of reaching an incontrovertible diagnosis if clinical events occur during the recording.[13,16,17] These may be incidental or predictable based on circadian distribution and triggering stimuli. Video-EEG machines are relatively inexpensive nowadays because of advances in digital compression and storage technology.

An EEG discharge is of great diagnostic and management significance if it is associated with clinical manifestations. However, these symptoms may be minor and escape recognition without video recordings. Video-EEG recordings are particularly important in the identification of absences, which are easily elicited by hyperventilation, myoclonic jerks or focal seizures, as well as psychogenic or other non-epileptic seizures, particularly those of the hyperventilation syndrome (see Chapter 4).[3]

Seizures or other paroxysmal events may occur at any stage during the EEG. Therefore, it is advisable to start and continue video recording during the whole procedure of an EEG. Vasovagal attacks often occur during EEG electrode placement. Psychogenic or fraudulent non-epileptic seizures often happen at the end of an EEG recording, during the removal of the electrodes, particularly when the patient is told that the EEG is normal.

The role of EEG technologists

The principal responsibility of EEG technologists is a competent EEG recording and a factual report. However, their role should be more than this, when considering the following:

- Currently, about 70% of EEG referrals are for epileptic disorders.
- Referrals commonly come from general paediatricians or general physicians who may not be familiar with the syndromic diagnosis of epilepsies.
- Information in the request form is usually inadequate.
- An EEG technologist spends 15–20 min preparing the patient for the recording, which may be valuably used to obtain information about such things as minor seizures, precipitating factors and the circadian distribution, and other aspects of the particular individual. The interpretation of the EEG depends on a patient's clinical history, which is often poor or missing.
- Currently, non-medical health professionals, such as nurses, are rightly involved in the management of epilepsies.

A well-qualified EEG technologist is expected, and should be trained, to have a thorough knowledge of seizures and epileptic syndromes.[18] In my department the EEG technologists often provide me with the correct syndromic diagnosis of our patients based on such a dual approach. Even interpretation of a normal EEG may be significantly different according to clinical information (see the illustrative cases on pages 139–141).

The significance of the EEG after the first afebrile seizure

A routine EEG recording is an evidence-based standard recommendation of the diagnostic evaluation of a child after a first afebrile seizure,[19] although in the UK, this is not an essential requirement.[20] The main practical reasons for this recommendation are listed in Table 6.3.

Value of EEG in stopping AED treatment

When considering stopping AEDs, an EEG is often requested in order to assess risks of seizure recurrence. It is an abnormal and not a normal EEG that is of value in these circumstances.

A normal EEG is of no value because the patient may still have active epilepsy and high risk of relapse (Table 6.3). In addition, AEDs effective in IGEs usually suppress generalised discharges and photosensitivity; focal spikes are less affected. Most patients with IGE who receive valproate may have a

Reasons for recommending an EEG after a first non-febrile epileptic seizure

- An EEG in an untreated stage of an epileptic syndrome is imperative and this is most likely to happen if the EEG is requested after the first seizure
- With an EEG, it is possible to recognise the features of specific epileptic syndromes in children
- Clinically undetected, minor seizures such as absences, myoclonic jerks or focal fits may be recorded by the EEG
- The EEG may establish seizure-precipitating factors such as video games or television, thus leading to early and appropriate clinical recommendations
- An epileptiform EEG is associated with determining a two- to three-times higher risk of seizure recurrence than a normal EEG

Table 6.3

normal EEG despite a high risk of relapse on valproate withdrawal. Conversely, certain AEDs such as carbamazepine may enhance generalised discharges, and their effect in suppressing focal epileptiform discharges is weak.

An abnormal EEG is of absolute value if ictal events occur. Electrical and/or clinical seizures such as absences, myoclonic jerks and focal seizures document active epilepsy. They indicate the need for continuing AED treatment and that the current medication is ineffective.

An abnormal EEG is of probable value if significant inter-ictal epileptiform paroxysms occur. Generalised, more than focal, abnormalities usually predict a recurrence of seizures. Frequent generalised discharges and photoparoxysmal responses would have a high chance of relapse. Conversely, functional spikes of childhood have no predictive value, even if abundant.

Improving the EEG contribution to the diagnosis of epilepsies

The EEG should be performed only by qualified certified technologists and evaluated only by qualified certified clinical neurophysiologists. The EEG should be interpreted within the overall clinical context, which should be supplied by the referring physician and supplemented by the EEG personnel (technologists or clinical neurophysiologists).[13,18]

Qualified EEG technologists provide a technically almost-perfect EEG tailored to the needs of the particular patient and the particular clinical problem.

Qualified clinical neurophysiologists have extensive knowledge about the following features of the EEG and how to deal with them:

- the EEG age-related developmental changes and limits of normality
- the EEG normal physiological rhythms and their variants during drowsiness, sleep, awakening, hyperventilation and photic stimulation
- the distinction of EEG normal variant patterns from inter-ictal seizure-related or ictal discharges
- the specificity and the limits of an EEG (normal or abnormal) in relation to a particular seizure or syndrome diagnosis
- non-specific abnormality and its significance to the particular question
- the frequency by which certain 'epileptiform' abnormalities are seen in the general population of neonates, children, adolescents and adults
- the influence of AEDs, other medications and concurrent or co-morbid diseases on the EEG.

All this knowledge of the reporting physician should be reflected in the EEG report, the purpose of which is to relate to the particular clinical problem and assist the clinical specialist in diagnosis and management. Otherwise, a conclusion simply stating that the EEG

is normal or abnormal (with or without epileptiform abnormalities) is entirely meaningless.

Conversely, the referring physician should provide precise information with regard to history and medical state (including possible medications) of the patient.

Illustrative cases of good EEG practice

Normal routine EEGs

The following cases are examples of normal routine EEGs, where the clinical information requires a new, appropriately tailored EEG.

Case 6.1

The normal routine EEG of a teenager with a single generalised tonic–clonic seizure (GTCS) on awakening after significant sleep deprivation, fatigue and unaccustomed alcohol consumption.

Conclusion: The EEG is normal but, because the patient's seizure occurred on awakening after significant precipitating factors, we have arranged an EEG after partial sleep deprivation.

The EEG was normal again, but after awakening there were brief (1–2 s), asymptomatic, generalised discharges of spikes and waves of 3 or 4 Hz during hyperventilation. These were consistent with the clinical impression of a low threshold to IGE. The patient was advised about precipitating factors and no drug treatment was given.

Case 6.2

The normal routine EEG of an 8-year-old child with a GTCS during sleep.

Conclusion: The routine awake EEG is normal, but, because this is a child with a nocturnal convulsive seizure, a sleep EEG is indicated.

The sleep EEG showed centrotemporal spikes, thus documenting the diagnosis of rolandic epilepsy and securing an excellent prognosis.

Case 6.3

The normal ictal and inter-ictal EEG of a 20-year-old man referred for frequent brief clusters of bizarre movements, which 'sounds like pseudo-seizures'.

Conclusion: The routine awake EEG is normal. However, in view of the history that the paroxysmal events occurred mainly during sleep, the technologist allowed time for the patient to go to sleep, during which several of his habitual attacks were recorded with video-EEG recording. These were typical hypermotor epileptic seizures, thus documenting the diagnosis of mesial frontal lobe epilepsy (supplementary sensorimotor epilepsy).

Case 6.4

The normal EEG of a 50-year-old man with 'GTCSs from age 12 years, but on remission for 10 years. Stop anti-epileptic medication?'

Conclusion: The EEG is within normal limits. However, stopping medication is not recommended because, according to the information provided to the EEG technologist, the patient continues having brief seizures, consisting of unilateral multicoloured and spherical visual hallucinations lasting for a few seconds to 1 min, often progressing to deviation of the eyes and head. They are identical to those occurring before his GTCSs. The patient suffers from occipital epilepsy with visual seizures and secondarily GTCSs, a situation frequently misdiagnosed as migralepsy.

Despite this report, medication was discontinued. Two months later, the patient had a GTCS at work and lost his job.

Abnormal EEGs

The following cases are examples of patients with abnormal EEGs, showing that the reporting physician may make a significant contribution to the correct diagnosis and management.

Case 6.5

An EEG with brief generalised discharges of spikes and waves in a 30-year-old man referred because of a first GTCS.

Conclusion: The EEG is of good organisation with a well-formed alpha rhythm. It is abnormal because of brief generalised discharges of small spikes and waves of 3 or 4 Hz, which are facilitated by hyperventilation. These are not associated with any ictal

clinical manifestations tested with video-EEG recording and breath counting.

Opinion: The EEG abnormality indicates a low threshold to IGE. This is consistent with the clinical information that the recent GTCS occurred in the morning after sleep deprivation and alcohol consumption. The patient is not aware of absences or myoclonic jerks. There is a remote possibility that these abnormalities are due to frontal lesions[21] or subependymal heterotopia (a distinct neuronal migration disorder associated with epilepsy).[22] This may indicate the need for high-resolution MRI, although I expect it to be normal.

Comment: This patient may not need any drug treatment, but he should be advised about precipitating factors.

The MRI was normal and the patient did not have any other seizures in the next 10 years of follow-up.

Case 6.6

A 35-year-old woman was referred because of prolonged confusional premenstrual episodes.

Conclusion: The EEG is of good organisation with a well-formed alpha rhythm. It is suspiciously but not definitely abnormal because of a brief and inconspicuous generalised burst of larval spikes and theta waves.

Opinion: The EEG abnormality is mild and not conclusive. We organised an EEG during her vulnerable premenstrual period because the confusional episodes may be non-convulsive status epilepticus.

This was performed and showed definite and frequent generalised discharges of spikes/polyspikes and slow waves of 3 or 4 Hz associated with impairment of consciousness and eyelid flickering. No further confusional episodes occurred after treatment with valproate.

Case 6.7

A 17-year-old man was referred because of a 'single episode of loss of consciousness and convulsions. Epilepsy?'

Conclusion: The EEG is of good organisation with a well-formed alpha rhythm. It is abnormal because of brief runs of monomorphic theta waves around the left anterior temporal regions.

Opinion: The EEG abnormality is mild but definite, although it does not show conventional epileptogenic features. However, because the abnormality is strictly unilateral, a high-resolution MRI is indicated. This is also mandated because, according to the information gathered by our EEG technologist, the recent convulsive episode was preceded by an ascending epigastric sensation and fear, which had also occurred in isolation several times over the previous 2 years. These raise the possibility of hippocampal epilepsy.

MRI confirmed left hippocampal sclerosis, and a sleep-stage EEG showed a clear-cut sharp-and-slow-wave focus in the left anterior temporal electrode.

Case 6.8

An EEG with occipital spikes from a 6-year-old child referred because of 'a prolonged episode of loss of consciousness with convulsions'.

Conclusion: The EEG is of good organisation with a well-formed alpha rhythm, which is often interrupted by clusters of high-amplitude, bioccipital, sharp-and-slow waves.

Opinion: The EEG abnormality of occipital spikes is often associated with benign seizures in this age group. From the clinical description, this child may suffer from 'Panayiotopoulos syndrome', whereby seizures are often solitary or infrequent. However, occipital paroxysms may also occur in 1% of normal children and even more frequently in children with congenital visual abnormalities (strabismus and amblyopia) and other conditions with or without seizures.

Comment: 'This EEG should be interpreted in accordance with the clinical manifestations of this child. In particular, was the event nocturnal or diurnal? What were the symptoms that preceded the convulsions and what was their duration? Did he have autonomic disturbances, vomiting or eye deviation? Is this a normal child with normal vision and development? Please let me know, as treatment may not be needed.'

Analysis of the clinical history documented that the child had two typical autonomic seizures of Panayiotopoulos syndrome.

There are numerous similar examples of this type of communication between electroencephalographers

and clinicians being essential for a better diagnosis and management of patients with epilepsies. The problems become even more complicated and demanding in the interpretation of EEGs of patients referred for possible epileptic seizures who also suffer from co-morbid conditions, such as migraine, psychiatric diseases or cerebrovascular insufficiency, and who may also be on various medications. In these cases it is often important to admit that 'the EEG, although abnormal, may be misleading in view of the migraine, cerebrovascular, psychiatric or previous head injuries of the patient. The EEG abnormality cannot be taken as evidence for or against epilepsy'.

Brain imaging in the diagnosis and management of epilepsies

Modern structural and functional brain imaging methodologies have made a colossal impact on the diagnosis and management of epilepsies.[23–46] High levels of anatomical and metabolic data are now provided with different brain imaging techniques. The combination of appropriate new imaging techniques has led to greater insights into the pathophysiology underlying symptomatic epilepsy and can contribute greatly to the elucidation of the basic mechanisms of the various forms of epilepsies. Investigations of larger, more homogeneous genetic disorders, and longitudinal rather than cross-sectional neuroimaging studies, have advanced our knowledge about the cause and effect of epilepsies.[39]

This section is based on the recommendations of the ILAE for the neuroimaging of people with epilepsy in general,[23] the neuroimaging of people with intractable seizures in their pre-surgical evaluation[24] and the functional neuroimaging.[25]

Magnetic resonance imaging

MRI is the most superior of all structural imaging tools.[23,24] Optimal MRI scanning allows *in vivo* visualisation of structural causes of epilepsies and its sensitivity is increasing with technological improvements. MRI abnormalities are identified in 80% of patients with refractory focal seizures and 20% of patients with single unprovoked seizures or epilepsy in remission.

MRI is greatly superior to X-ray CT in terms of its sensitivity and specificity for identifying subtle abnormalities. Even when CT reveals an epileptogenic lesion, MRI often adds new and important data in terms of characterising the nature and extent of the underlying pathology and of identifying other lesions.

The principal role of MRI is in the definition of the structural abnormalities that underlie seizure disorders. Identification of a structural lesion often indicates the site of seizure onset.

Clinical note

Suboptimal MRI application in clinical practice

Current knowledge is still not being optimally applied in clinical practice,[51] e.g. a study in Germany showed that, in patients with focal seizures who had unremarkable MR images at general hospitals, a focal lesion was found in 85% of cases when they later underwent MRI at a specialised centre.[52]

Hippocampal sclerosis may be reliably identified (Figure 6.4), whereas quantitative studies are useful for research and, in equivocal cases, clinical purposes. A range of malformations of cortical development may be determined (Figures 6.5–6.7). The proportion of cryptogenic cases of epilepsy has been decreased with improvements in MRI hardware, signal acquisition techniques and post-processing

Coronal (A) and axial (B) T1-weighted MRI scan showing right hippocampal sclerosis (arrows)

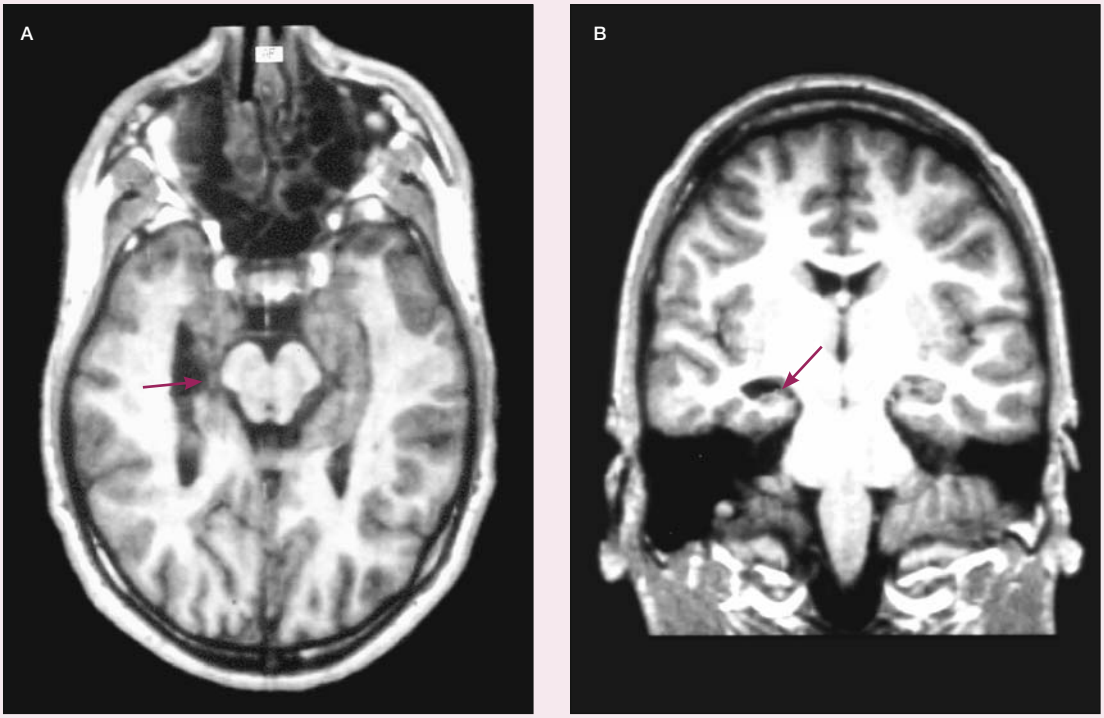

Figure 6.4 *Courtesy of Dr. Rod C. Scott, Institute of Child Health, London, UK.*

methodologies (Figure 6.8). Automated voxel-based analysis can identify subtle changes in the neocortex over time that are not evident on visual inspection.[47] White-matter tracts, including connections of eloquent areas, can be visualised with tractography and thus reduce the risks of surgery.[48]

Both T1-weighted and T2-weighted images should be obtained, with slices being as thin as possible. Three-dimensional volume acquisition is preferable, but coronal as well as axial slices should be obtained in all cases. Gadolinium contrast enhancement is not necessary in routine cases, but may be helpful in selected cases if the non-contrast-enhanced MRI is not definitive. Myelination is incomplete in the first 2 years of life, resulting in a poor contrast between white and grey matter and, thus, producing difficulties in the detection of cortical abnormalities. In contrast, white matter disorders are recognised better, because the normal signal of myelin (which varies according to age) and the topography of the brain are well known. In such young patients, MRI may not reveal lesions and scans may have to be repeated again after 1 or 2 years.[23]

It should, however, be emphasised that certain lesions such as focal cortical dysplasia are not always identified with conventional MRI and may be more easily identified on a fluid-attenuated inversion recovery (FLAIR) sequence by reconstructing the imaging data set in curvilinear planes and by quantitative assessment of the signal and texture (Figure 6.9).[29,50] A FLAIR sequence increases the conspicuousness of lesions (Figure 6.9) that may not otherwise be identified and should be part of

Examples of malformations of cortical development documented with MRI

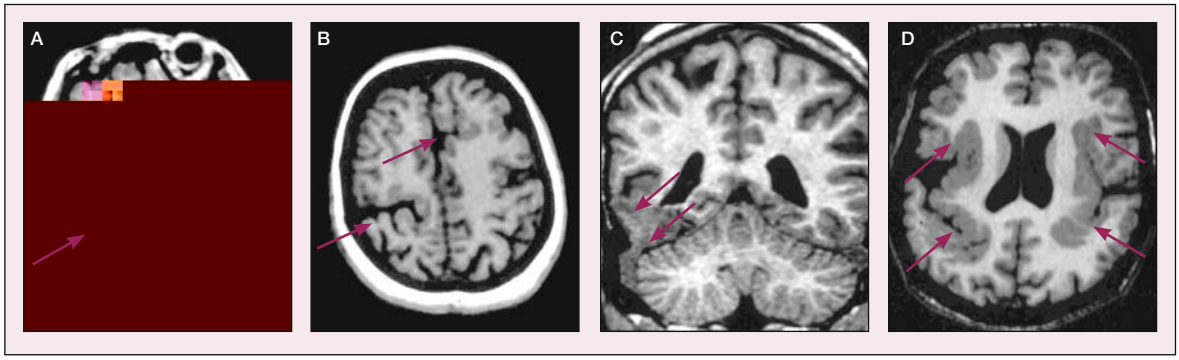

Figure 6.5 (**A,B**) Axial T1-weighted MRI scan showing bilateral schizencephaly (arrows). (**C**) Coronal T1-weighted MRI scan showing right focal cortical dysplasia (arrows). (**D**) Axial T1-weighted MRI scan showing bilateral perisylvian polymicrogyria (arrows). *Courtesy of Professor John S. Duncan and the National Society for Epilepsy MRI Unit, UK.*

Posterior agyria–pachygyria with polymicrogyria documented with MRI scan in two brothers

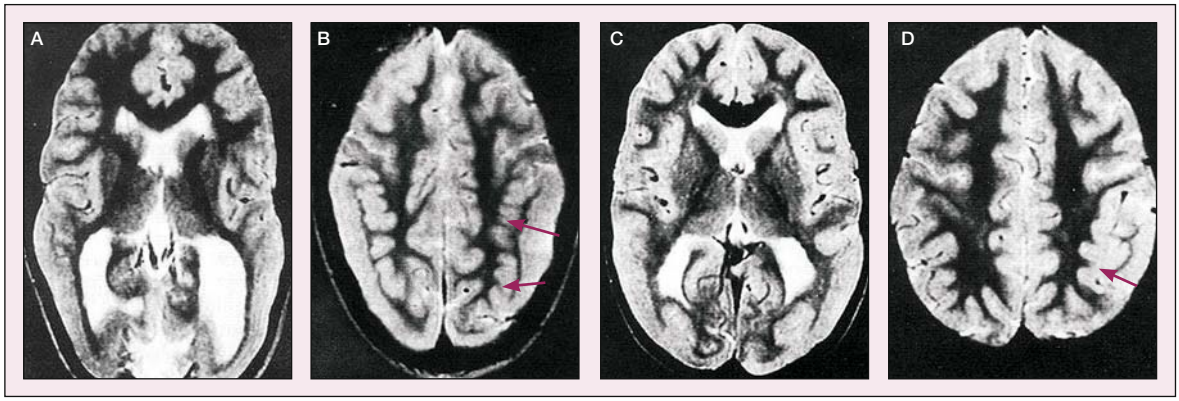

Figure 6.6 Axial T2-weighted MRI scans from the older (**A,B**) and younger (**C,D**) brothers. There is marked posterior agyria–pachygyria with areas of polymicrogyria mainly in the parietal cortex.
Reproduced with permission from Ferrie, et al *(1995).*[49]

a standard MRI protocol for patients with epilepsy. Other sequences, such as T2, may reveal abnormalities such as small cavernous angiomas.

In addition to careful qualitative evaluation of the hippocampus, quantitative assessment can be useful. Hippocampal volumetry requires absolute volumes corrected for the intracranial volume, which must be compared with appropriate controls from the same laboratory, as well as side-to-side ratios. T2-weighted relaxometry also quantitates hippocampal abnormalities and may show evidence of bilateral disease.[23]

X-ray computed tomography

X-ray CT can detect gross structural lesions, but will miss many small mass lesions, including tumours, vascular malformations, hippocampal sclerosis and most malformations of cortical development.[23] A

Small malformations of cortical development documented with MRI

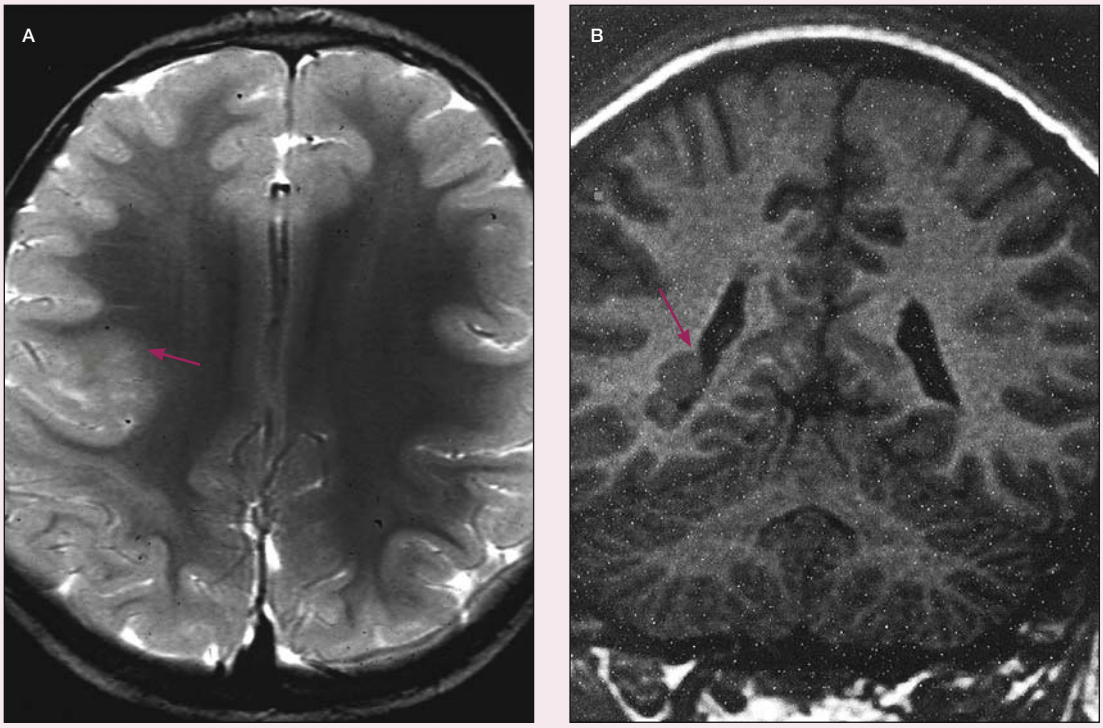

Figure 6.7 (**A**) Coronal T2-weighted MRI scan showing frontal focal cortical dysplasia (arrow). (**B**) Coronal T1-weighted MRI showing nodular subependymal heterotopia in the inferior lateral wall of the right lateral ventricle (arrow).
Figure A courtesy of Dr. Rod C. Scott, Institute of Child Health, London, UK.
Figure B reproduced with permission from Duncan (1997).[26]

negative CT scan conveys little information, and so CT should not be relied on and usually does not need to be performed when MRI is available. Occasionally, CT may be useful as a complementary imaging technique in the detection of cortical calcifications, particularly in patients with congenital or acquired infections (e.g. cysticercosis) or tumours such as oligodendrogliomas.[23]

If MRI is not readily available or cannot be performed for technical reasons (e.g. a patient who has a cardiac pacemaker or a cochlear implant) then a scan is an appropriate initial investigation. It is also useful in the acute situation of seizures developing in the context of a neurological insult, such as head injury, intracranial haemorrhage or encephalitis, particularly if there is a need to have ready access to the patient during the scan.[23]

Functional neuroimaging

Functional neuroimaging has been used for localising cerebral dysfunction, predominantly through disturbances in an individual's metabolism or blood flow. The techniques available include SPECT, PET and functional MRI (fMRI). Functional brain imaging is currently supplementary to MRI, principally in the evaluation of neurosurgical candidates. SPECT and PET are inadequate for the assessment of brain structure.[23]

Conventional isotope brain scans do not provide sufficient information about the brain structure to

Magnetisation transfer ratio maps – axial images

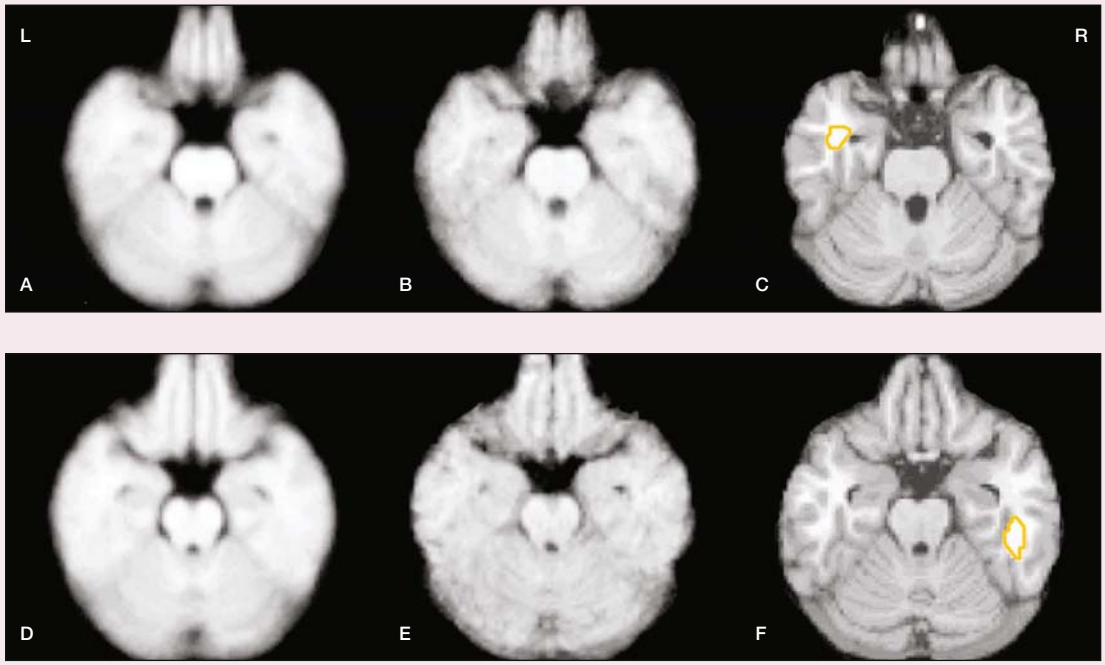

Figure 6.8 Magnetisation transfer ratio maps for 30 control subjects (**A**,**D**), patients with normal conventional MRI and left temporal lobe epilepsy (**B**), and right temporal lobe epilepsy (**E**). Statistical analysis showing areas of a significantly reduced magnetisation transfer ratio in patient groups (**C**) and (**F**).
Courtesy of Professor John S. Duncan and the National Society for Epilepsy MRI Unit, UK.

Series of coronal MRI scans showing increased lesion conspicuity with FLAIR

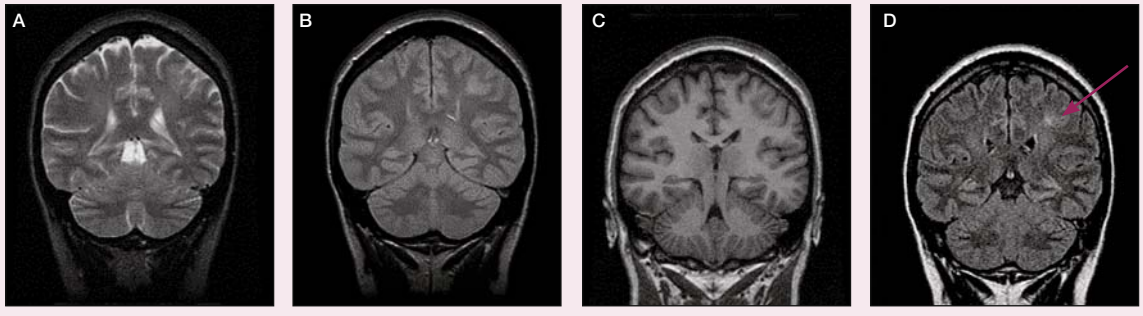

Figure 6.9 The patient's left is on the right of the images. The patient is a 50-year-old man with a 25-year history of focal motor seizures involving the right hand. The T1-weighted (**C**), T2-weighted (**A**) and proton-density (**B**) images were read as normal. On the FLAIR scan (**D**) it is evident that there is an area of increased signal in the brain parenchyma in the left primary sensorimotor cortex (arrow).
Courtesy of Professor John S. Duncan and the National Society for Epilepsy MRI Unit, UK.

identify many lesions associated with seizures and their use is not recommended.[23]

Recommendations for neuroimaging of patients with epilepsy[23]

The aim of neuroimaging is:

1. to identify underlying pathologies such as tumours, granulomas, vascular malformations, traumatic lesions or strokes that merit specific treatment
2. to aid the formulation of syndromic and aetiological diagnoses, and thereby provide an accurate prognosis for patients.

Ideal practice

In the non-acute situation the ideal practice is to obtain structural neuroimaging with MRI in all patients with epilepsy, except in those with a definite electroclinical diagnosis of IGE or benign childhood focal epilepsy.[23]

MRI is particularly indicated in patients with one or more of the following:

- onset of seizures at any age with evidence of focal onset in the medical history or on the EEG
- onset of unclassified or apparently generalised seizures in the first year of life or in adulthood
- evidence of a focal fixed deficit on neurological or neuropsychological examination
- difficulty in obtaining control of seizures with first-line AED treatment
- loss of control of seizures with AEDs or a change in the seizure pattern that may imply a progressive underlying lesion.

Minimum standards

Appropriate minimum standards vary between different countries and societies, according to economic and geographical factors and the system for providing health care.[23]

CT is an alternative procedure if MRI is not available or cannot be performed for technical reasons.

An MRI is essential in a patient with:

- focal or secondarily generalised seizures and apparently generalised seizures that do not remit with AED treatment
- the development of progressive neurological or neuropsychological deficits.

Scans must be interpreted in the context of the entire clinical situation. A specialist in neuroimaging, who has training and expertise in the neuroimaging of epilepsy, must review the images.[23]

Functional neuroimaging in clinical practice[25]

The Neuroimaging Subcommission of the ILAE has assessed the roles of PET, SPECT, MR-based functional imaging methods of fMRI and magnetic resonance spectroscopy (MRS) in clinical practice and research.[25] The following conclusions have been reached.[25]

Functional MRI

There is no currently approved or universally accepted clinical indication for fMRI.[25] However, this situation is changing and in many epilepsy surgery centres fMRI of the blood oxygen level-dependent (BOLD) contrast is being used to localise the primary motor cortex, the functional anatomy of memory tasks, predict deficits after temporal lobe resection and lateralise language function (Figure 6.10).[53] Furthermore, continuous and simultaneous recording of EEG and fMRI (EEG–fMRI) is now possible after the introduction of methods for removing the artefact on the EEG trace caused by fMRI acquisition. EEG–fMRI can visualise the BOLD response to inter-ictal epileptic activity and assist in identifying targets for surgical treatment. Clinically, these methods will aid EEG interpretation and understanding of the pathophysiological basis of epileptic activity.[29,54,55]

Magnetic resonance spectroscopy

MRS has been evaluated primarily in TLE. Proton MRS provides a useful lateralisation of metabolic dysfunction. Sensitivity is of the order of 90%, but

fMRI scan showing an area of cerebral activation in relation to right-hand movement that is anterior to structural lesion (dysembryoplastic neuroepithelial tumour)

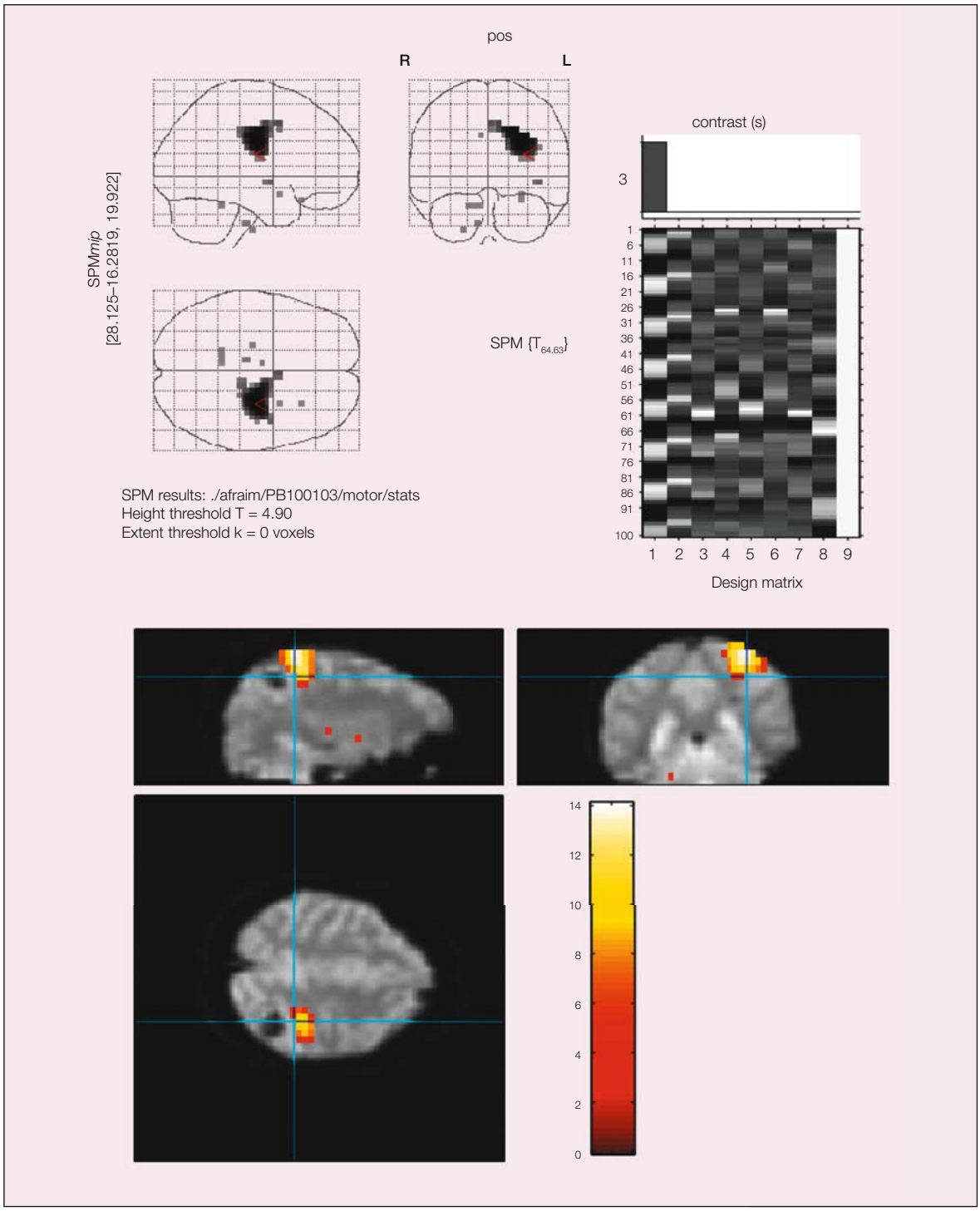

Figure 6.10 *Courtesy of Professor John S. Duncan and the National Society for Epilepsy MRI Unit, UK.*

bilateral temporal abnormalities are common and abnormalities may be reversible. MRS may be useful in patients who have otherwise normal MRI studies. Phosphate (^{35}P)-MRS has moderate sensitivity for lateralisation, based on abnormal elevations of inorganic phosphate, although abnormalities of pH have been controversial and so cannot be considered to be reliable for this. MRS has been reported to be useful in extratemporal epilepsies, but the present limitation of spatial coverage limits its clinical utility.[25] It is evident from studies of malformation of cortical development that metabolic derangements are frequently more extensive than the structural lesion seen on MRI.[56]

Single photon emission CT

SPECT with cerebral blood flow agents is useful for supporting the localisation of focal epilepsy when it is performed in a carefully monitored ictal (Figure 6.11) or early post-ictal examination compared with an inter-ictal scan. This may be used as part of pre-surgical evaluation and help to guide the placement of intracranial electrodes if other data, including structural imaging, are equivocal or not concordant. In apparently generalised epilepsies, ictal SPECT may be helpful to identify a focal component.[25] Recent developments allow patients to inject the isotope themselves at the first warning of a seizure, thus increasing the possibility of capturing a seizure, as well as reducing the interval between seizure onset and trapping of the tracer in the brain.[57]

PET with [^{18}F]fluorodeoxyglucose and ^{15}O-labelled water

Inter-ictal [^{18}F]fluorodeoxyglucose (FDG)-PET may have a role in determining the lateralisation of temporal lobe epilepsy, without intracranial EEG recording of seizures, in patients in whom concordance of MRI, EEG and other data are not good (Figure 6.12). This role has decreased with the wider availability of high-quality MRI. In patients with normal or equivocal MRI or discordance between MRI and other data, such that intracranial electrodes are required, FDG-PET may be useful for planning the sites of intracranial electrode placement for recording ictal onsets in temporal and extratemporal epilepsies. However, caution is needed because the ictal onset zone may be at the border of the hypometabolic area and not at the most hypometabolic area. FDG-PET may have a useful role in apparently generalised epilepsies in trying to define a focal abnormality and when resection may be contemplated. For practical purposes, the clinical and research uses of ^{15}O-labelled water ($H_2{}^{15}O$)-PET for mapping areas of cerebral activation have been superseded by fMRI.[25]

PET with specific ligands

There are no proven indications for ligand PET in clinical epileptological practice. A role that is being evaluated is in the pre-surgical evaluation of patients with refractory focal seizures. In patients with mesial TLE and negative MRI, [^{11}C]flumazenil (FMZ)-PET may have some advantages over FDG-PET, offering more precise localisation of the epileptogenic region, but it does not appear to be superior for lateralisation. In MRI-negative patients with neocortical seizures, the identification of focal abnormalities using FMZ-PET may be useful for guiding the placement of intracranial EEG electrodes.[25] However, caution is needed because the ictal onset zone may be at the border of the area of abnormal binding and not at the area of maximal abnormality. Co-registration with high-quality MRI is essential (Figure 6.13).

Co-registration of SPECT/PET with MRI

The co-registration of post-ictal SPECT images with a patient's MRI improves the anatomical determination of the abnormalities of cerebral blood flow.[58] The objectivity and accuracy of data interpretation are enhanced with co-registration of inter-ictal with either ictal or post-ictal SPECT images, resulting in an 'ictal difference image' that may be co-registered with the individual's MRI. The co-registration of PET images with high-resolution MRI structural images from the same individual has practical value in the anatomical interpretation of functional abnormalities in PET, with account being taken for potential partial volume artefacts. Together with an MR image, PET images with different tracers, e.g. FDG and FMZ, can be co-

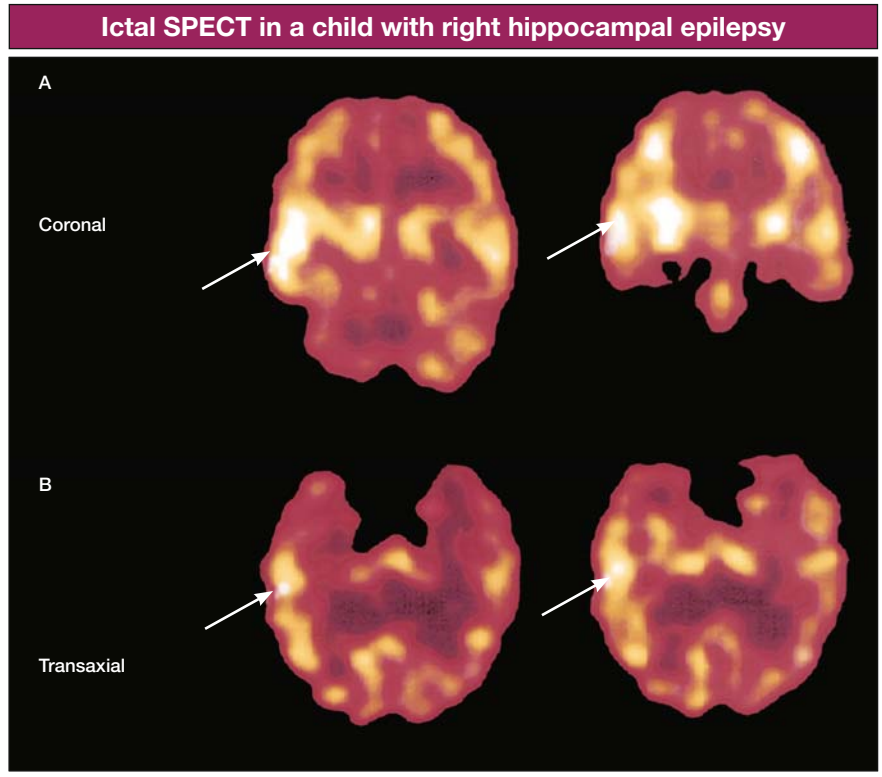

Figure 6.11 Coronal (**A**) and axial (**B**) ^{99}mTc HMPAO SPECT images show increased perfusion in the right anterior temporal lobe (arrows). *Courtesy of Dr. Rod C. Scott, Institute of Child Health, London, UK.*

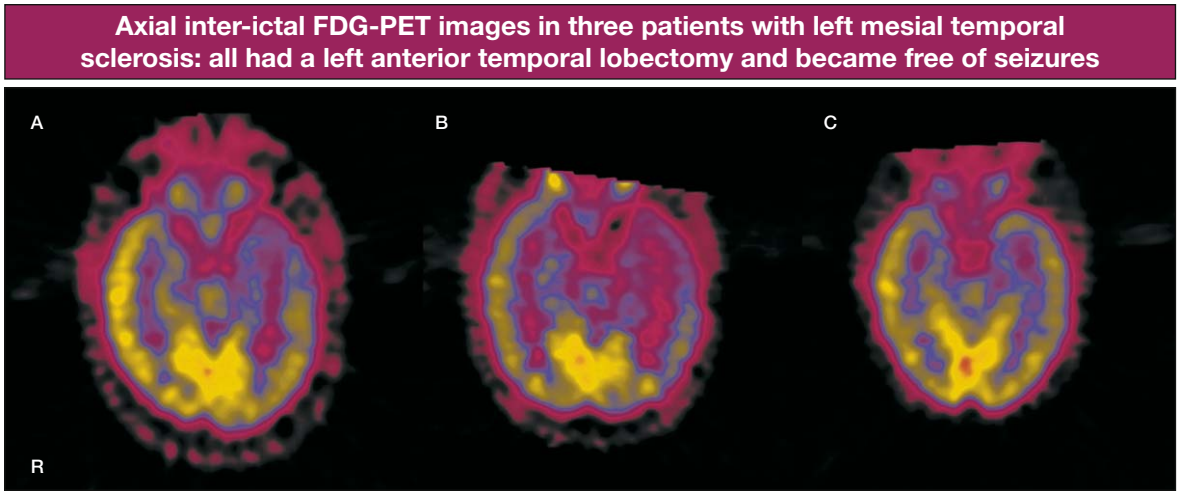

Figure 6.12 (**A**) Unilateral glucose hypometabolism in a 22-year-old male. FDG uptake is reduced in mesial temporal lobe structures and the tip and anterior portion of the temporal neocortex in the left hemisphere. (**B**) Bilateral asymmetrical glucose hypometabolism in a 19-year-old male. Reduction of FDG uptake is observed in both temporal areas, being more remarkable in the left hemisphere. (**C**) Equivocal symmetrical glucose metabolism in a 34-year-old female. There was no laterality in FDG uptake. Semi-quantitative analysis with regions-of-interest methods showed that the asymmetry indices of the mesial and lateral temporal areas were within normal range.
Courtesy of Dr. Nozomi Akanuma, Department of Clinical Neurosciences, Guy's, King's and St Thomas' School of Medicine, UK.

registered, which enables a direct comparison of the location, pattern and extent of each abnormality (Figure 6.13).

Magnetoencephalography[59–67]

Magnetoencephalography (MEG) is a promising non-invasive and non-hazardous technology of functional brain mapping that is still in development. It is used to identify both normal and abnormal brain function 'in action'. MEG records externally, from the scalp, the weak magnetic forces generated by neuronal electrical activity of the brain. It provides localised cortical areas with a great degree of accuracy, generating maps with high spatial and temporal resolution (Figure 6.14).

The primary advantage of MEG over EEG is that magnetic fields are not altered by the skull and other surrounding brain structures, thus permitting greater accuracy as a result of the minimal distortion of the signal. This allows for more usable and reliable localisation of brain function. However, MEG is better at detecting superficial rather than deep mesial temporal lobe epileptogenic foci.

MEG is usually performed with simultaneous EEG recording. Superimposing MEG with CT and MR

Coronal and axial views of structural and functional neuroimages of a 21-year-old male with right mesial temporal sclerosis; a right anterior temporal lobectomy rendered him free of seizures

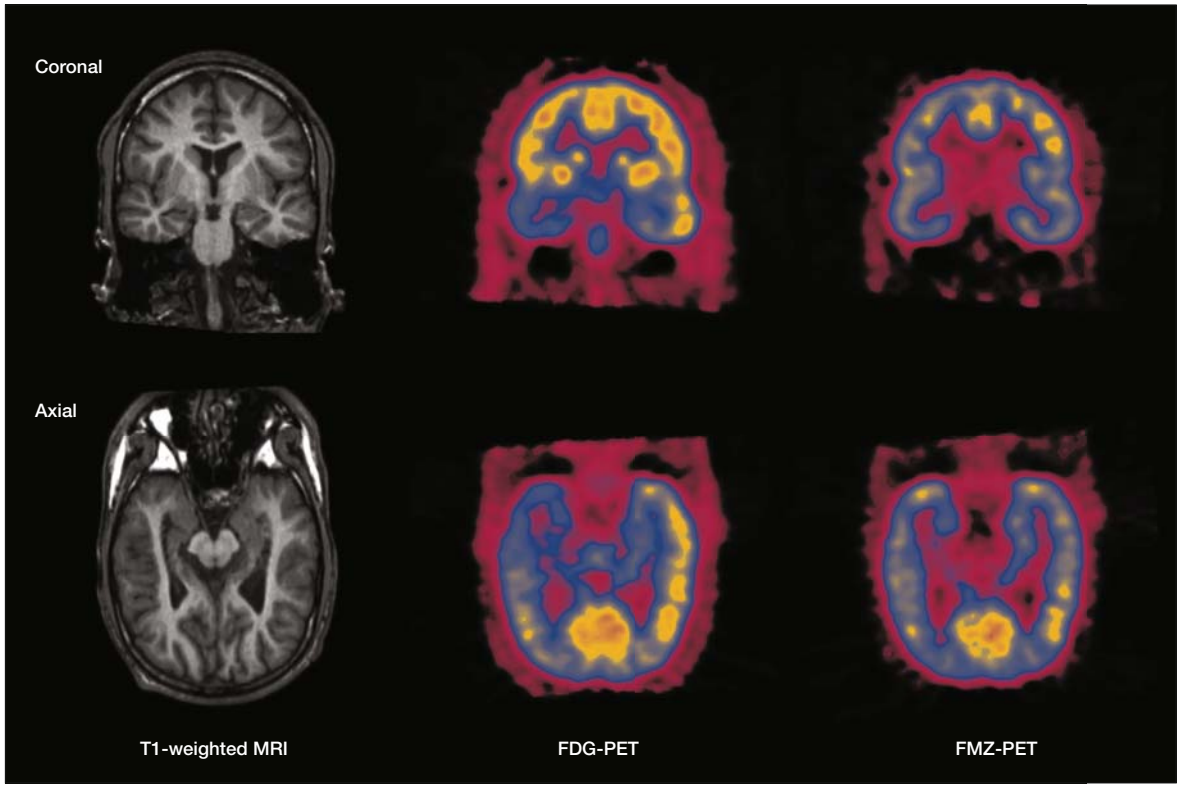

Figure 6.13 FDG-PET and FMZ-PET images were co-registered with a T1-weighted MRI scan. The T1-weighted MRI scan demonstrates hippocampal atrophy on the right. FDG uptake is reduced in the corresponding region extending to the ipsilateral lateral temporal cortex and parietal area. In contrast, the reduction in $GABA_A$ receptor binding is fairly restricted within the right mesial temporal lobe structures.
Courtesy of Dr. Nozomi Akanuma, Department of Clinical Neurosciences, Guy's, King's and St Thomas' School of Medicine, UK.

MEG images of a girl aged 10 years with frequent rotatory seizures to the left; brain MRI was normal

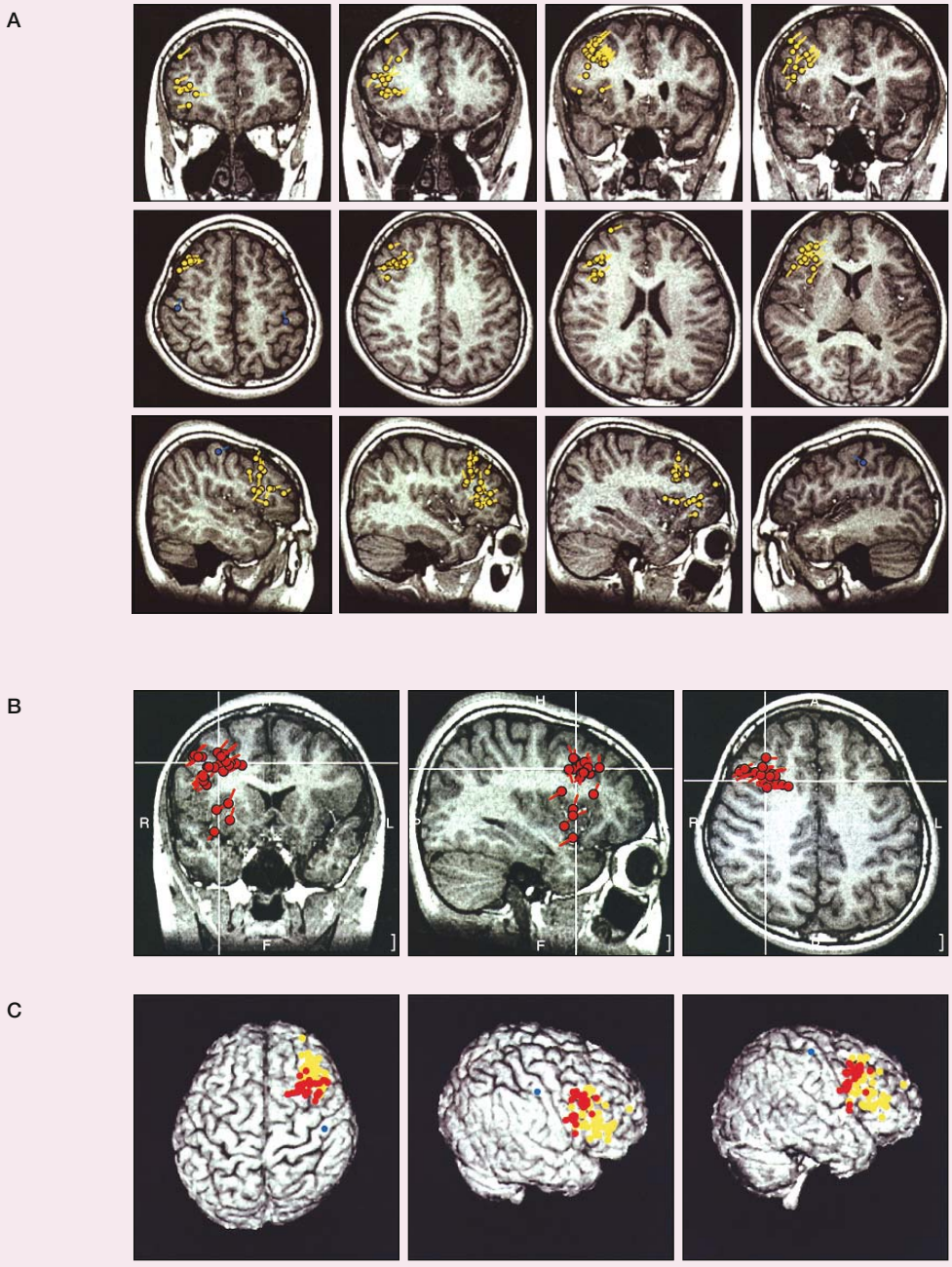

Figure 6.14 (**A**) Inter-ictal MEG showed right frontal dipole sources (yellow dots). (**B**) MEG analysis of the ictal onset also revealed slightly backward right frontal dipole sources (red dots). (**C**) Supperimposed ictal and inter-ictal images. Dipole sources of somatosensory evoked fields-N20 (blue dots).
Courtesy of Dr. Osamu Kanazawa, Department of Psychiatry, Saitama Medical University, Saitama, Japan.

scans produce functional/anatomical images of the brain, referred to as magnetic source imaging (MSI).

The most thoroughly studied clinical applications of MEG/MSI are to detect and localise:

- epileptogenic foci
- eloquent cortices.

The exact localisation of the epileptogenic area is crucial for screening of surgical candidates and surgical planning. MSI has principally been investigated as an alternative to invasive pre-surgical monitoring when there is no concordance of clinical, EEG and MRI findings. Furthermore, in patients who have had past brain surgery, the electrical field measured by EEG may be distorted by the changes in scalp and brain anatomy. If further surgery is needed, MEG may be able to provide necessary information without having to use invasive EEG studies.

Localisation of the 'eloquent' brain areas, such as sensorimotor regions, is critical for their preservation during any type of brain surgery. MEG/MSI is used to map the exact location of the normally functioning areas near the lesion that should be avoided in planning surgical resection, thus minimising post-operative significant neurological deficits. Such use might also obviate the need for other forms of invasive mapping techniques.

MEG and MSI are very expensive and availability is low. Under most health insurance policies MEG and MSI are approved as investigational procedures for neurosurgery patients but not for routine evaluation of a seizure disorder.

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seven

Principles of therapy in the epilepsies

The traditional aim of therapy in epilepsies is total freedom from seizures with no clinically significant adverse effects. This has now been broadened to include optimal outcomes of health-related quality of life with regard to physical, mental, educational, social and psychological functioning of the patient. The mainstay of treatment is usually with anti-epileptic drugs (AEDs) in continuous prophylactic schemes. However, AEDs are ineffective for about 20% of patients. These patients are candidates for neurosurgical interventions, other pharmacological or non-pharmacological treatments.

A prerequisite for any treatment is that the patient truly suffers epileptic seizures; a quarter of patients treated for 'epilepsy' do not suffer genuine epileptic seizures.[1,2]

Correct seizure and often syndrome diagnosis is a precondition for the success of therapeutic decisions because the choice of AED primarily depends on seizure type, whereas length of treatment is mainly determined by syndrome type.

AED prophylactic treatment

AED treatment is the mainstay of the management of epilepsies. The laudable aim is freedom from seizures with minimal, if any, adverse drug reactions (ADRs). This is achieved in about 50–70% of patients with a single, appropriately selected AED at target therapeutic doses. This seizure-free rate varies significantly with seizure type and epileptic syndrome. Polytherapy should be avoided if possible, but it is inevitable in about 30–50% of patients who fail to respond to single-drug therapy. Freedom of seizures should not be pursued at any cost and, in particular, at the expense of ADRs.

There is no point in treating epilepsy at the expense of drug-induced disease.

For some patients, a few minor and often harmless seizures may be allowed to occur instead of increasing the number of AEDs or their doses, which may jeopardise the quality of life of the patient. The identification of ADRs, although sometimes difficult, is a crucial part of the management.

Useful information

The 'package insert' (FDA in the USA) and the 'summary of product characteristics' (EMEA in the EU) are the most complete single sources of information on a drug. The package insert can be obtained from http://dailymed.nlm.nih.gov/dailymed/about.cfm. The summary of package characteristics can be obtained in any European language from http://www.emea.europa.eu/htms/human/epar/a.htm. In UK these are also available from http://emc.medicines.org.uk

The drug treatment of epilepsies requires thorough knowledge of the AEDs with regard to seizure-specific

Efficacy of main AEDs in seizure types

AED	Focal seizures (simple or complex)	Secondarily GTCSs	Primarily GTCSs	Myoclonic jerks	Absence seizures
Carbamazepine	Effective	Effective	Effective	–†	–†
Clobazam‡	Effective	Effective	Effective?	Effective?	Effective?
Clonazepam¶	Effective?	Effective?	Ineffective?	Effective	Effective
Eslicarbazepine	Effective	Effective	Unknown	Unknown	Unknown
Ethosuximide	–	–	–	Effective?§	Effective
Gabapentin	Effective	Effective	–	–¶¶	May exaggerate
Lacosamide	Effective	Effective	Unknown	Unknown	Unknown
Lamotrigine	Effective	Effective	Effective	May exaggerate**	Effective
Levetiracetam	Effective	Effective	Effective	Effective	Effective††
Oxcarbazepine	Effective	Effective	Effective	–‡‡	–‡‡
Phenobarbital	Effective	Effective	Effective	Effective	–
Phenytoin	Effective	Effective	Effective	–	–
Pregabalin	Effective	Effective	–	Exaggerates¶¶	–
Tiagabine	Effective	Effective	–	–	Exaggerates
Topiramate	Effective	Effective	Effective	Effective?	Effective?
Valproate	Effective	Effective	Effective	Effective	Effective
Vigabatrin	Effective	Effective	–	–	Exaggerates
Zonisamide	Effective	Effective	Effective?§§	Effective?§§	Effective?§§

Table 7.1 This table is based predominantly on information obtained from the SmPCs[3–19] and PIs (see Useful Information on page 173). AEDs in blue are, in general, contraindicated for the treatment of idiopathic generalised epilepsies. However, carbamazepine, oxcarbazepine and phenytoin may be used in the rare pure forms of primarily generalised tonic–clonic seizures (GTCSs). –, the cited AED is not indicated for this seizure type, either because it is not licensed or it is ineffective or may exaggerate the seizure. †According to the SmPC 'carbamazepine is not usually effective in absences and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences'. However, many observational reports have shown the deteriorating effect of carbamazepine in these types of seizure.[20–25] ‡Clobazam is licensed only as adjunctive therapy in 'epilepsy'. Its efficacy is not the same as that of clonazepam. It may be more efficacious in focal than generalised epilepsies.[26–28] ¶Clonazepam is licensed for any type of epileptic seizure, but it is mainly used as one of the most efficacious AEDs in myoclonic jerks. It may not suppress GTCSs of juvenile myoclonic epilepsy and patients may be deprived of the warning jerks, which herald the onset of GTCS.[29] §Ethosuximide may be effective in negative myoclonus.[30] **Lamotrigine may aggravate myoclonic jerks in juvenile myoclonic epilepsy and some progressive myoclonic epilepsies.[25,31–34] ††The effect of levetiracetam on absences is not well documented, although clinical series have shown a significant beneficial effect in childhood and juvenile absence epilepsy.[35,36] ‡‡Oxcarbazepine, like carbamazepine, may aggravate myoclonic jerks[37] and absence seizures.[38,39] ¶¶Myoclonus is a treatment-emergent type of seizure in patients with focal seizures treated with pregabalin as an adjunctive medication[40] or even in non-epileptic patients receiving this drug for pain relief.[41] Gabapentin may have a similar promyoclonic effect.[24,42] This may signify the need for extreme caution in the use of pregabalin and gabapentin in epilepsies with myoclonus. §§Zonisamide, although licensed for focal seizures only, appears to be a broad-spectrum AED.[43]

Main adverse reactions of AEDs, which may sometimes be serious and rarely life threatening

AED	Main adverse reactions	Life threatening
Carbamazepine	Idiosyncratic (rash), sedation, headache, ataxia, nystagmus, diplopia, tremor, impotence, hyponatraemia, cardiac arrhythmia*	AHS†, hepatic failure, haematological
Clobazam	Severe sedation, fatigue, drowsiness, behavioural and cognitive impairment, restlessness, aggressiveness, hypersalivation and coordination disturbances. Tolerance and withdrawal syndrome	No
Clonazepam	As for clobazam	No
Eslicarbazepine	Idiosyncratic (rash), dizziness, somnolence, headache, ataxia, inattention, diplopia, tremor, nausea, vomiting, hyponatraemia, PR prolongation in ECG	No
Ethosuximide	Idiosyncratic (rash), gastrointestinal disturbances, anorexia, weight loss, drowsiness, photophobia, headache	AHS†, renal and hepatic failure, haematological
Gabapentin	Weight gain, peripheral oedema, behavioural changes, impotence, viral infection*	Acute pancreatitis, hepatitis, Stevens–Johnson syndrome, acute renal failure‡
Lacosamide	Dizziness, headache, diplopia, nausea, vomiting, blurred vision, PR prolongation in ECG	No
Lamotrigine	Idiosyncratic (rash), tics, insomnia, dizziness, diplopia, headache, ataxia, asthenia*	AHS†, hepatic failure, haematological
Levetiracetam	Irritability, behavioural and psychotic changes, asthenia, dizziness, somnolence, headache*	Hepatic failure, hepatitis‡
Oxcarbazepine	Idiosyncratic (rash), headache, dizziness, weakness, nausea, somnolence, ataxia and diplopia, hyponatraemia*	AHS†, haematological
Phenobarbital	Idiosyncratic (rash), severe drowsiness, sedation, impairment of cognition and concentration, hyperkinesia and agitation in children, shoulder–hand syndrome	AHS†, hepatic failure, haematological
Phenytoin	Idiosyncratic (rash), ataxia, drowsiness, lethargy, sedation, encephalopathy, gingival hyperplasia, hirsutism, dysmorphism, rickets, osteomalacia	AHS†, hepatic failure, haematological
Pregabalin	Weight gain, myoclonus, dizziness, somnolence, ataxia, confusion*	Renal failure, congestive heart failure, AHS†,‡
Tiagabine	Stupor or spike–wave stupor, weakness*	Status epilepticus
Topiramate	Somnolence, anorexia, fatigue, nervousness, difficulty with concentration/attention, memory impairment, psychomotor slowing, metabolic acidosis, weight loss, language dysfunction, renal calculi, acute angle-closure glaucoma and other ocular abnormalities, paraesthesiae*	Hepatic failure, anhidrosis
Valproate	Nausea, vomiting, dyspepsia, weight gain, tremor, hair loss, hormonal in women*	Hepatic and pancreatic failure
Vigabatrin	Irreversible visual field defects, fatigue, weight gain	No
Zonisamide	Idiosyncratic, drowsiness, anorexia, irritability, photosensitivity, weight loss, renal calculi*	AHS†, anhidrosis

Table 7.2 This table is based predominantly on information obtained from the SmPCs[3–19] and PIs (see Useful Information on page 173). It is an assessment of common ADRs and/or those of clinical importance. It is not an exhaustive list of all ADRs; for these, readers should refer to the relevant chapters of this book and, mainly, to the SmPC or PI of each AED. For more details, see "Considerations of adverse antiepileptic drug reactions in the treatment of epilepsies" (page 197) and the pharmacopoeia (Chapter 18). *FDA warning for suicidal ideation (see page 198). †AHS, anticonvulsant hypersensitivity syndrome. ‡Post-marketing experience.

efficacy, acute and chronic ADRs, pharmacokinetics, doses and titration, drug interactions and contra-indications. This information is widely available in books, journal reviews, manufacturers' prescribing information and credible internet sources.

As with all drugs, AEDs may be therapeutic when appropriately used (Table 7.1), but they also possess toxic properties (Table 7.2). A balance between the therapeutic and toxic effects of an AED is a primary responsibility and the crux of epilepsy management. This treatment goal cannot be achieved satisfactorily without a thorough evaluation of the patient's seizures, medical history, possible co-medication for other diseases and the individual patient's circumstances.

Patients and parents should be well informed about the purpose of AED medication, and its efficacy, ADRs and possible length of treatment. Otherwise, there are failures in compliance, disenchantment and breaking down of patient/physician trust.

Special groups of patients with epileptic disorders require particular attention and management. Children, elderly people, women (particularly of childbearing age) and patients with mental, physical and other comorbidities are vulnerable and their treatment is more demanding. A special section on women (page 204) and the elderly (page 219) has been added in this revision.

Key points of AED treatment

- The aim of AED treatment is to achieve seizure-freedom without ADRs.
- The first-option AED is the most likely to be efficacious and the most unlikely to cause ADRs.
- The correct AED dose is the smallest one that achieves seizure control without ADRs.
- An AED appropriate for one type of seizure may be deleterious for another type.
- Titrating to the limit of tolerability may improve AED efficacy, but often at the cost of ADRs.
- Optimal efficacy of an AED may be lost by exceeding tolerability limits.

Cost should not be an issue in medicine, but with most of the global population living in poverty and often in conditions of starvation, options are frequently limited to the older AEDs, which are often life-saving agents.

Clarifications on terminology of AED treatment

Efficacy is not synonymous with effectiveness.

Efficacy is the ability of a medication to produce a clinically measurable beneficial effect aiming at seizure freedom.[44] It is a relative term defined by the designers of a study, but is usually a specific effect of a treatment. A drug can be highly efficacious yet not very clinically useful; i.e., not clinically effective.

There is no formal definition or the exact limits of the term '*spectrum of efficacy*'. In clinical practice, broad spectrum AEDs are those that are efficacious in all or most of focal and generalised epileptic seizures, while narrow spectrum refers to those with efficacy in one or few types of either focal or generalised seizures.

Effectiveness, in contrast to efficacy, is meant to be a more pragmatic measure that addresses the utility of a drug as it is actually employed in practice.[44,45] Effectiveness encompasses both AED efficacy and tolerability, as reflected in retention on treatment.[44] Effectiveness encompasses many potential components including tolerability, cognition, mood or quality of life.

Tolerability involves the incidence, severity and impact of ADRs.[44]

Thus, an AED efficacious in controlling seizures may not be effective because of high incidence or severe ADRs as, for example, with vigabatrin in focal seizures because of irreversible visual field defects (see page 191) or felbamate, which has not been licensed by the EMEA because of a high incidence of aplastic anaemia and hepatic failure.

ADRs are not synonymous with adverse drug effects or side effects.

According to the International Conference on Harmonisation of Definitions and Standards:

> *ADR* is a response to a drug which is noxious and unintended, and which occurs at doses normally used for prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function. The phrase

'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a possibility.

An *adverse event* is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

See www.fda.gov/cber/gdlns/ichexrep.htm.

Choosing the best AED option

The ideal profile of a first-choice AED in the prophylactic treatment of epilepsies is determined by a number of factors (Table 7.3).

The importance of these factors varies significantly according to whether the AED is used in monotherapy or polytherapy.

Properties of AEDs to consider in prioritising their use

- Seizure specificity
- Strength of efficacy
- Spectrum of efficacy
- Safety
- Tolerability
- Adverse reactions (particularly if these are severe and life threatening)
- Pharmacokinetics
- Phamacodynamics
- Drug–drug interactions
- Mechanisms of action
- Speed of titration (time needed to reach effective dose)
- Need for laboratory testing
- Frequency of administration and ease of use
- Cost of treatment

Table 7.3 Factors highlighted in red are of particular importance in polytherapy (see page 187).

Seizure specificity

The first-choice AED should primarily be in accord with the seizure type. Some AEDs may be very efficacious in some epileptic seizures and syndromes, but contraindicated in others (Table 7.1). Carbamazepine, for example, is a first-choice AED in focal seizures but should be avoided in idiopathic generalised epilepsies (IGEs).

Strength of efficacy

The more efficacious a drug the more likely it is to control seizures. Seizure-free status is the ultimate, often achievable, goal of treatment. That an AED may achieve more than 50% seizure reduction is not the best option, although this is a common outcome measurement in randomised controlled trials (RCTs).

Spectrum of efficacy

This is significant in the treatment of patients when the differentiation between focal and generalised epileptic seizures cannot be certain. In such cases broad-spectrum AEDs are recommended (Table 7.1), which are those that are efficacious in a wide range of focal and generalised epileptic seizures, and include valproate, levetiracetam, lamotrigine, topiramate and zonisamide.

Useful clinical notes

Women are more sensitive than men to specific ADRs

- Valproate: reproductive ADRs.
- AEDs that are associated with weight gain (Table 7.4): polycystic ovarian syndrome.
- AEDs that are associated with aesthetic changes (phenytoin).
- AEDs that are associated with increased risk of teratogenicity (pregnancy category D).
- AEDs that interact with hormonal contraception or pregnancy (enzyme inducers and lamotrigine).

Children are more susceptible than adults to specific ADRs

- Valproate: hepatotoxicity.
- Lamotrigine: AHS.
- Phenobarbital: hyperkinetic behaviour and cognitive impairment.
- Topiramate and zonisamide: hypohidrosis (anhidrosis).

Safety, tolerability and adverse reactions

These vary significantly between AEDs (Table 7.2) Adverse drug reactions may outweigh any beneficial effect achieved by reduction of the seizures. Currently, with so many efficacious AEDs, it is possible to avoid those with significant ADRs and particularly those associated with sometimes fatal ADRs, teratogenicity or significant impairment of quality of life. Carbamazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital and zonisamide are associated with frequent idiosyncratic reactions and anticonvulsant hypersensitivity syndrome (AHS), which may be fatal. Women, children and elderly patients are more vulnerable to ADRs from certain AEDs; for example, valproate in babies and women of childbearing age. In children, documented or potential ADRs on growth, height and weight should be meticulously considered. Treatment-emergent weight changes should also be a significant concern (Table 7.4).

Clinical pharmacokinetics[47–49]

Pharmacokinetics is the study of the time course of a drug and its metabolites in humans. Absorption, distribution, metabolism and excretion are the primary parameters of pharmacokinetics and these significantly influence efficacy, ADRs and interactions with hormones and other drugs. AEDs with high pharmacokinetic profile scores should be preferred (Table 7.5).[47–49] Most commonly used AEDs are

Main AEDs that are likely to affect body weight

The risks of obesity are emphasised routinely in the media in the USA, UK and other industrialised countries where obesity has become epidemic

Patients, particularly women (e.g. see increased risk for polycystic ovarian syndrome), should be informed of the following AEDs that are likely to cause weight gain:

- Gabapentin
- Pregabalin
- Valproate
- Vigabatrin

Significant weight loss, which can be relentless, may be caused by:

- Topiramate
- Zonisamide

Note: Levetiracetam may be associated with a decrease[46] or increase of body weight

Table 7.4 This table is based predominantly on information obtained from the SmPCs[7,10,14,16–19] and PIs (see Useful Information on page 173).

Pharmacokinetic profile rating of AEDs
Superior
Lacosamide (96), levetiracetam (96), vigabatrin (96), gabapentin (89), pregabalin (89)
Moderate
Topiramate (79), ethosuximide (77), oxcarbazepine (77), lamotrigine (73)
Inferior
Tiagabine (67), zonisamide (67), phenobarbital (57), valproate (52), carbamazepine (50), phenytoin (50)

Table 7.5 Numbers in parenthesis are the scores derived from a semi-quantitative rating system based on 16 pharmacokinetic parameters. The maximum possible score is 100.[48,49]

eliminated through hepatic metabolism catalysed by cytochrome P450 (CYP) and uridine diphosphate glucuronosyltransferase (UGT) enzymes (Table 7.6). Hepatic enzyme modifiers have low priority over others, particularly in patients who are receiving co-medications. Carbonic anhydrase inhibitors (Table 7.7), such as topiramate, reduce urinary citrate excretion and increase urinary pH, resulting in an increased risk of metabolic acidosis (which increases the risk for nephrolithiasis and osteomalacia/osteoporosis, and reduces growth rates in children). Different formulations of the same AED may have different bioavailability, which explains the loss of efficacy or emerging signs of toxicity when switching from one preparation to another. This is also the case with some controlled-release formulations such as that of carbamazepine, which has a more variable bioavailability than the conventional forms. Major metabolic pathways and elimination of AEDs are important to consider, particularly in patients with any type of hepatic or renal impairment (Table 7.8).

Hepatic enzyme induction and inhibition

Hepatic enzyme induction stimulate the production and increase the amount of CYP enzymes (Table 7.6). This, in turn, increases the rate of metabolism of drugs metabolised by the CYP enzymes, thus resulting in lower plasma concentrations. Conversely, hepatic enzyme inducers may increase the bioavailability of drugs that require metabolism for their activation. The effect of hepatic induction, unlike hepatic inhibition,

AEDs that are hepatic enzyme inducers and/or inhibitors

AED	Enzyme induced	Enzyme inhibited
Carbamazepine	CYP2C, CYP3A, CYP1A2, microsomal epoxide hydrolases, UGTs	–
Lamotrigine	UGTs	–
Oxcarbazepine	CYP3A4, UGTs	CYP2C19
Phenobarbital	CYP2C, CYP3A, microsomal epoxide hydrolases, UGTs	–
Phenytoin	CYP2C, CYP3A, microsomal epoxide hydrolases, UGTs	–
Topiramate	Dose-dependent enzyme inducer CYP3A4, β-oxidation	CYP2C19
Valproate	–	CYP2C9, microsomal epoxide hydrolases, UGTs

CYP (cytochrome P450 system) is a superfamily of isoenzymes that are responsible for the oxidative metabolism of many drugs, exogenous compounds and endogenous substrates. They are located in the membranes of the smooth endoplasmic reticulum, mainly of the liver. CYP enzymes are classified into families (designated by the first Arabic number), subfamilies (designated by the capital letter after the Arabic number) and isoenzymes according to the similarities in their amino acid sequences

UGTs (uridine diphosphate glucuronosyltransferases) are a superfamily of enzymes that are responsible for the formation of hydrophilic drug metabolites, which are mainly excreted via renal or biliary routes. They catalyse the glucuronidation of drugs and endogenous substrates. They are located in the endoplasmic reticulum of cells in the liver, kidneys and other organs, including the brain. Glucuronidation, mainly hepatic glucuronidation, represents one of the main detoxification pathways in humans

Table 7.6

Carbonic anhydrase inhibitors
Acetazolamide
Sulthiame
Topiramate
Zonisamide

Table 7.7

Major metabolic and elimination pathways of AEDs	
Hepatic	
Carbamazepine	Phenobarbital
Clobazam	Phenytoin
Clonazepam	Tiagabine
Ethosuximide	Topiramate
Lamotrigine	Valproate
Oxcarbazepine	Zonisamide
Renal	
Gabapentin	Pregabalin
Lacosamide	Vigabatrin
Levetiracetam	

Table 7.8

persists for several days following the withdrawal of the enzyme inducer drug.

Useful clinical notes

For AEDs that are eliminated renally (Table 7.8), either completely unchanged (e.g. gabapentin, pregabalin and vigabatrin) or mainly unchanged (e.g. lacosamide, levetiracetam and topiramate), the pharmacokinetic variability is small and usually predictable. However, the dose-dependent absorption of gabapentin increases its pharmacokinetic variability. Interactions with other drugs can affect their plasma concentration markedly, and individual factors such as age, pregnancy and renal function will contribute to the pharmacokinetic variability of all renally eliminated AEDs.

If the affected drug has an active metabolite the impact of an inducer may be reduced, but this depends on the subsequent metabolism of the metabolites; for example, induction may increase metabolite concentrations and enhance toxicity without elevation of the parent drug.

Enzyme inducers, by speeding up the elimination of other substances that are metabolised in the liver, have significant disadvantages:

- Drug–drug interactions make them undesirable in polytherapy.
- Some hormones critical to sexual function are metabolised in the liver and levels of these hormonal substances may be reduced. Thus, long use of hepatic enzyme inducers can lead to significant changes in sex hormones in women and may potentially result in long-term endocrine effects in children. Furthermore, CYP3A4 enzyme inducers increase clearance of oestrogen and also of the progestational component of hormonal contraception, thus decreasing their plasma levels and effectiveness.
- Increased metabolism of vitamin D, which is metabolised through the liver, may result in hypocalcaemia, osteomalacia (rickets in children) and osteoporosis. It is reasonable to advise taking calcium and vitamin D supplements.

Useful clinical notes

AEDs that are carbonic anhydrase inhibitors

Avoid concomitant administration of carbonic anhydrase inhibitors because of the increased risk of:

- metabolic acidosis
- heat-related adverse events during exercise and exposure to warm environments
- nephrolithiasis.

Do not use them with anticholinergic drugs or a ketogenic diet.

Diseases or therapies that predispose to acidosis, such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet or certain drugs, may add to the bicarbonate-lowering effects of carbonic anhydrase inhibitors.

Manifestations of acute or chronic metabolic acidosis may include hyperventilation, non-specific symptoms such as fatigue and anorexia, or more severe sequelae, including cardiac arrhythmias or stupor.

Hepatic enzyme inhibition usually occurs because of competition at the enzyme site.

In enzyme inhibition, the added drug inhibits or blocks drug-metabolising enzymes, which in turn decreases the rate of metabolism of the other drug, causing higher plasma concentrations.

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors (Table 7.7) reduce urinary citrate excretion and increase urinary pH. They need particular attention in clinical practice because they may induce hyperchloraemic, non-anion gap, metabolic acidosis (i.e. decreased plasma bicarbonate below the normal reference range in the absence of respiratory alkalosis). Chronic, untreated metabolic acidosis may:

- increase the risk of nephrolithiasis or nephrocalcinosis
- result in osteomalacia (rickets in children) and/or osteoporosis with an increased risk for fractures
- reduce growth rates in children and eventually decrease the maximal height achieved.

The effect of topiramate and zonisamide on growth and bone-related sequelae is unknown and has not been systematically investigated.

Pharmacodynamics

Pharmacodynamics refers to the biochemical and physiological effects of drugs and their mechanisms of action. They may be additive, synergistic or antagonistic. They may be beneficial, detrimental or both, as exemplified by lamotrigine combined with valproate (increased therapeutic efficacy but also increased risk of ADRs and teratogenicity).

Drug–drug interactions

These refer to phamacokinetic and pharmacodynamic changes that occur through concomitant use of drugs (Table 7.6). They are frequent causes of therapeutic failures and ADRs. Most AEDs are associated with a wide range of drug interactions, including hepatic enzyme induction and inhibition, and protein-binding displacement. Anticipation of induction or inhibition interactions and careful clinical monitoring may alleviate potential problems. Occasionally, drug–drug interactions may be beneficial (increased effectiveness, reduced risk of unwanted adverse reactions or both).

Useful clinical notes

Pharmacokinetic and pharmacodynamic interactions as exemplified by lamotrigine

Lamotrigine demands significant clinical attention in polytherapy, hormonal contraception and pregnancy.

Lamotrigine is metabolised predominantly in the liver by glucuronic acid conjugation. The major metabolite is an inactive 2-*N*-glucuronide conjugate. UGT1A4 is the major enzyme responsible for *N*-glucuronidation of lamotrigine. Lamotrigine is a weak UGT enzyme inducer.

Lamotrigine dose and titration schemes are different in co-medication with valproate or enzyme inducers. The reason for this is that valproate is a potent inhibitor of UGT-dependent metabolism of lamotrigine, whereas enzyme-inducer AEDs are potent inducers of UGT-dependent metabolism of lamotrigine.

Lamotrigine undergoes important changes in conjunction with initiation or withdrawal of hormonal contraception and before, during and after pregnancy. The reason for this is that pregnancy and hormonal contraception significantly lower (by more than half) lamotrigine levels. Patients may suffer breakthrough seizures mainly during the first trimester of pregnancy (if lamotrigine levels are not corrected) or have toxic effects post partum (if lamotrigine levels had been adjusted during pregnancy but not after delivery).[50]

Lamotrigine also has significant pharmacodynamic interactions with valproate that are beneficial (increased therapeutic efficacy),[51] although they may also be detrimental as result of an increased risk of ADRs[52] and teratogenicity.[53]

Mechanisms of action

Mechanisms of action vary significantly among AEDs (Table 7.9)[54–57] and they have not been fully elucidated for most of them. The main mechanisms of action of the available AEDs are thought to be:

- blockade of voltage-dependent ion channels (K^+, Na^+ and Ca^{2+} channels)
- increasing the activity of the inhibitory GABAergic system
- decreasing the activity of the excitatory glutamatergic system.

The mechanism of action of levetiracetam – modulating the function of the synaptic vesicle 2A protein

AEDs: main mechanisms of actions

Blocking voltage-dependent Na^+ channels ($\downarrow Na^+$)
- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Phenytoin

Multiple, mainly or including blocking voltage-dependent Na^+ channels
- Phenobarbital ($\downarrow Na^+$, $\downarrow Ca^{2+}$, $\uparrow$ GABA, $\downarrow$ glutamate)
- Topiramate ($\downarrow Na^+$, $\downarrow Ca^{2+}$, $\uparrow$ GABA, $\downarrow$ glutamate)
- Valproate ($\downarrow Na^+$, $\downarrow Ca^{2+}$, $\uparrow$ GABA, $\downarrow$ glutamate)
- Zonisamide ($\downarrow Na^+$, $\downarrow Ca^{2+}$)

Increasing GABA inhibition ($\uparrow$ GABA)
- Clobazam ($GABA_A$)
- Clonazepam ($GABA_A$)
- Tiagabine (inhibitor of GABA uptake into neurones and glial cells)
- Vigabatrin (selective, irreversible GABA transaminase inhibitor)

Blocking T-type Ca^{2+} channels ($\downarrow Ca^{2+}$)
- Ethosuximide

Modifying Ca^{2+} channels and neurotransmitter release
- Gabapentin
- Pregabalin

Novel: binding to synaptic vesicle protein SV2A
- Levetiracetam

Novel: (1) selectively enhancing slow inactivation voltage-gated Na^+ channels; (2) may be binding to collapsin response mediator protein-2 (CRMP-2)*
- Lacosamide

Table 7.9 Based on data taken from the SmPCs[3–19] and PIs (see Useful Information on page 173) and references.[54–57]
*More recent experiments did not confirm binding of lacosamide with CRMP-2.

(SV2A) – is likely to be distinct from that of all other AEDs[58]. Lacosamide also has novel mechanisms of action (see Figure 7.1 and page 184).

In clinical practice, knowledge about the mechanism of action is significant particularly in the treatment of seizure types with known pathophysiology; for example, primarily GABA-ergic AEDs such as tiagabine and vigabatrin are contraindicated in absence seizures that are facilitated by $GABA_B$ activation. Furthermore, in polytherapy, combining AEDs with the same action is ill-advised because their combination is unlikely to have a better success and more likely to have additive ADRs.[59,60]

Need for as little titration as possible

AEDs of fast titration should have priority over those demanding slower titration (Table 7.10). Slow titration may mean more seizures (which may also be hazardous) and be more difficult for patients to follow (compliance may be lessened). Starting with small doses and a slow titration rate is mandated for lamotrigine (increased risk of skin rash) and topiramate (increased risk of cognitive impairment), which need 6–8 weeks in order to reach reasonable therapeutic levels. It is of less concern in others, such as gabapentin and levetiracetam (Table 7.10)

Need for less laboratory testing and other monitoring (Table 7.11)

Patients on AEDs may need laboratory testing and other monitoring for: (1) the detection of ADRs associated with certain AEDs, such as oxcarbazepine or valproate; and (2) therapeutic drug monitoring

Titration of AEDs: the recommendation of 'start low and go slow' is AED dependent	
AEDs that do not need slow titration; the first dose may be therapeutic[7,10]	**AEDs that need very slow titration of 6–8 weeks to reach therapeutic dose[9,12,16]**
Gabapentin*	Lamotrigine
Levetiracetam*,†	Phenobarbital
	Topiramate

Table 7.10 All other AEDs need slow titration of approximately 4 weeks. *Results from studies on adjunctive therapy.[7,10] †Slow titration may be needed when used as adjunctive therapy.[10]

Need for laboratory testing and TDM	
Minimal	**Maximal**
Clobazam	Carbamazepine (haematological toxicity, hyponatraemia, TDM)
Clonazepam	Lamotrigine (idiosyncratic reactions, TDM)
Gabapentin	Oxcarbazepine (hyponatraemia)
Lacosamide	Phenytoin (haematological and liver toxicity, TDM)
Levetiracetam	Topiramate (metabolic acidosis, TDM)
Pregabalin	Valproate (hepatotoxicity)
Tiagabine	Zonisamide (metabolic acidosis, TDM)

Table 7.11 TDM, therapeutic drug monitoring.

(TDM), as for lamotrigine in pregnancy and hormonal contraception, and carbamazepine, oxcarbazepine, lamotrigine, topiramate and zonisamide in co-medication when polytherapy is needed or for co-morbid disorders. More laboratory testing may also mean less compliance, more expense and more uncomfortable situations for patients.

Frequency of administration and ease of use

AEDs that need dosing more than twice a day are not practical for patient use and may lessen compliance. The frequency of administration is often determined by the plasma half-life. Most AEDs are given twice daily. Phenytoin and phenobarbital are the more advantageous, needing one dose per day before sleep. Doses three-times per day may be needed for gabapentin and sometimes for carbamazepine, pregabalin and oxcarbazepine. In large doses, some AEDs may need to be given three times daily to avoid ADRs associated with high peak plasma concentrations.

Patient-friendly formulations are particularly important for children or adults who may have difficulties in swallowing tablets or capsules, some of which may be very large.

Parenteral formulations are significant when oral administration is temporarily not feasible (Table 15.3). Levetiracetam and lacosamide are the only newer AEDs with oral and parenteral formulations.

Useful clinical note

Dosing of AEDs in children

Young children metabolise AEDs more rapidly than adults and therefore require more frequent dosing and a higher amount per kilogram of body weight.

Cost of treatment

Cost is often a significant factor, particularly in resource-poor countries and when medication is not freely provided by national health systems or personal health insurance. All newer AEDs are very expensive in relation to older generation AEDs.

Newest generation AEDs licensed in the treatment of focal epilepsies: lacosamide and eslicarbazepine

Despite the explosion of new therapeutic options in the last 15 years, there is still a great need for new AEDs for improving seizure control and the quality of life of patients with treatment-resistant epilepsies.

Lacosamide (Vimpat®) is the first of the newest AEDs to be licensed for prescribing this year by the EMEA and FDA. Lacosamide is indicated for the adjunctive treatment of focal seizures with or without secondarily generalised tonic–clonic seizures in patients with epilepsy aged 16 years (17 years in the USA) and older.[8] The indication has been granted for the oral tablet, oral syrup and intravenous formulations.[8]

This decision is supported by data from three multicentre, double-blind, placebo-controlled clinical trials that evaluated the efficacy, safety and tolerability of lacosamide (200, 400 and 600 mg/day given in two divided doses) in a total of over 1300 adults with uncontrolled focal seizures. Patients in these trials were taking at least one to three AEDs and many of the patients had previously tried at least seven AEDs. Across these studies significantly greater than 50% responder rates and reductions in median seizure frequency were seen versus placebo. Lacosamide was also generally well tolerated with the most common adverse events of lacosamide (⩾10% and greater than placebo) reported in these trials including dizziness, nausea, diplopia and headache.[61]

Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilisation of hyperexcitable physiological neuronal excitability (Figure 7.1). In addition, it may bind with collapsin response mediator protein-2 (CRMP-2), a protein mainly expressed in the central nervous system and involved in neuronal differentiation and axonal outgrowth.[61]

The evidence so far is that lacosamide has proven efficacy and long retention rates in difficult to treat patients.[61] It is particularly important in adjunctive AED therapy because of minimal drug to drug interactions, good safety and tolerability, parenteral formulations and novel mechanism/s of action different than any other AED co-medication.[61]

Mechanism of action of lacosamide

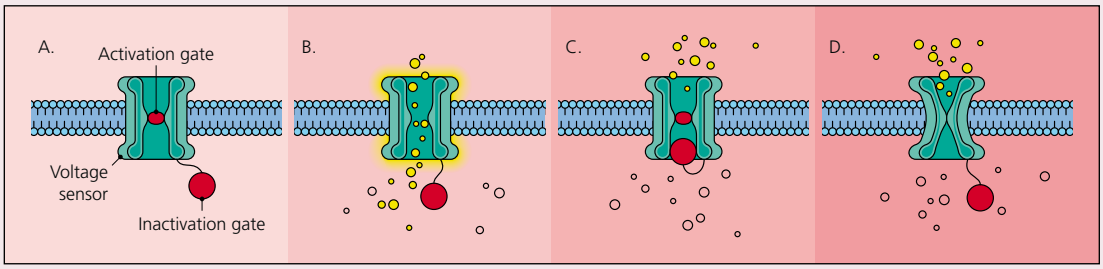

Figure 7.1 (A) Voltage gated sodium channel (B) activated VGSC (C) traditional fast inactivation as with most AEDs and (D) slow inactivation as with lacosamide.

Eslicarbazepine (Exalief® and Zebinix®) acetate, a derivative of carbamazepine, is the second AED licensed this year (April 2009) by the EMEA (it is not yet approved by FDA) as adjunctive therapy in adults (≥ 18 years of age) with focal seizures with or without secondarily GTCS. It was developed with the intention to have no auto-induction and less interaction potential with other drugs than its parent drug carbamazepine by preventing the formation of toxic epoxide metabolites such as carbamazepine-10,11 epoxide. However, this promise does not appear to have been fulfilled because eslicarbazepine acetate is associated with significant interactions with drugs eliminated by metabolism through CYP3A4 (carbamazepine, phenytoin, phenobarbital, topiramate) or conjugation through the UDP-glucuronyltransferases (lamotrigine) and with oral hormonal contraception. Such interactions make the use of an AED problematic in adjunctive therapy and particularly when taken concomitantly with drugs of the same mechanism of action (carbamazepine, lamotrigine, phenytoin). Of benefit is that the rate of rash (1.1%) and hyponatraemia (less than 1%) with eslicarbazepine acetate is less than with carbamazepine and oxcarbazepine.

Newly diagnosed epilepsy

'Newly diagnosed epilepsy' (or newly identified epilepsy) is a general term for encompassing all types of epilepsy that are newly identified and firmly diagnosed by physicians irrespective of cause and prognosis. It includes any patient of any age with any form of seizure who seeks medical attention for the first time because of paroxysmal events that are diagnosed as epileptic seizures. Newly diagnosed epilepsy is not a diagnostic or therapeutic entity. Its purpose should be to emphasise that these patients require meticulous medical support with regard to diagnosis and treatment, which is thoroughly demanding. At this stage of first confirmation of diagnosis, medical decisions may affect the rest of the patient's life and often the lives of their families. Social and psychological support for the impact that such a diagnosis may have is a significant aspect of proper management. AED efficacy and ADRs are not determined by how long before the onset of treatment a diagnosis of seizures has been established.

'Newly diagnosed epilepsy' is not synonymous with 'new-onset epilepsy' with which it is incorrectly equated. Many patients have onset of seizures several years before seeking medical attention.

The management of patients with newly diagnosed epilepsy demands a precise diagnosis of both seizures and syndrome. Unifying them as a single therapeutic category[62] discourages diagnostic precision and encourages the use of inappropriate AED trial strategies (see Table 7.1).

Starting AED treatment in newly diagnosed epilepsy

The decision to start AED treatment needs to be thoroughly considered. It should not be a knee-jerk reaction to a crisis about a dramatic convulsive event that may not even be an epileptic seizure. Starting an AED often implies continuous daily medication for many years, which is sometimes life-long. Therefore, this should be strictly initiated in those with an unacceptably high rate of seizure recurrence or high risk of seizure injury. Some patients do not need prophylactic treatment, as in febrile and benign childhood focal seizures. In others the avoidance of precipitating factors may be sufficiently prophylactic, as in some reflex seizures or in individuals with a low threshold to seizures. For those in need of prophylactic treatment, the first-choice AED should primarily be in accordance with the seizure type (Table 7.1). AEDs beneficial for focal epilepsy may be detrimental for IGEs (Table 7.1). Even among IGEs, an AED beneficial in one type may be ineffective or aggravate another seizure type (Table 7.1).

Before starting prophylactic anti-epileptic medication in a patient with newly diagnosed seizures, a physician should be confident of the following:

1. *The patient unequivocally has epileptic seizures.*
   This requires definite exclusion of any imitators of epileptic seizures.
2. *The epileptic seizures of the patient need treatment.*
   This requires precise diagnosis of the epileptic syndrome and the type of seizures, their frequency

and severity, their likelihood of relapse or remission, precipitating factors and the patient/family concerns and understanding of the risks versus benefits of the AED. Hard and fast rules are not always applicable.

3. The most appropriate AED is selected for this particular patient with this particular type of seizure(s). The appropriate AED is that which is the most likely of all others to be truly prophylactic as monotherapy (single-drug treatment) for the seizures of the patient without causing undue ADRs (Tables 7.1 and 7.2). Carefully consider and exclude AEDs that may worsen or be ineffective in this particular type of seizures.

An AED is contraindicated not only when it exaggerates seizures, but also when it is ineffective in controlling the seizures that it is supposed to treat. It may cause unnecessary ADRs and deprive the patient of the therapeutic effect that could be provided by another appropriate AED.

4. The starting dose and titration of the selected drug should be in accordance with the appropriate recommendations, the age and, primarily, the particular needs of the treated patient.

All these should be thoroughly explained to the patient/guardian and it should be ensured that this is well understood.

The following should also be taken into consideration in deciding how to start and escalate the selected AED:

- patients, particularly with newly identified epilepsy, respond to their first-ever AED at low dosage and are prone to develop ADRs (biological, cognitive or behavioural), which in 15% of them lead to AED discontinuation
- some patients develop ADRs easily even at an AED dose below the minimal limit of the target (therapeutic) range, whereas others are resistant to AEDs even at the maximum limit of the target range
- even for patients with the same type of seizures and the same AED, seizure control may be achieved with a drug concentration below, within or above the target range.

Useful clinical notes

Steps from titration to maintenance AED dose

- Explain and give in writing the recommended dose to be used and the rate of escalation of the AED.
- Allow the patient to self-regulate the rate of dose and time escalation in terms of both the dose of and the time intervals for taking the AED.
- The first dose (test dose) should be taken at night before sleep. If ADRs cause significant discomfort the test dose should be decreased to half and tried again the next night.
- The patient should be at liberty to prolong the escalation time and reduce the escalation dose to suit his or her own reaction to the AED.
- Warn that any type of idiosyncratic reactions such as rash (even if mild) should be reported immediately so as to prevent more serious and sometimes life-threatening events.
- Clarify that minor ADRs such as fatigue or somnolence are usually dose related and should not discourage escalation unless they interfere with the patient's daily activities.
- If seizures are controlled at some stage during the escalation, this should be the maintenance dose (irrespective of whether this is smaller than the recommended dose).

Monotherapy

Patients should be treated with a single AED (monotherapy) because of better efficacy, minimisation of ADRs and drug interactions, and improved compliance. Monotherapy with an appropriately selected AED at an appropriate target dose achieves complete control of seizures in 50–70% of patients. In one study, almost half the newly diagnosed patients of any type (symptomatic or idiopathic) became seizure free on their first-ever AED, with more than 90% doing so at modest dosing.[63] If seizures continue, titrating to the limit of tolerability will achieve additional seizure control in about 20% of patients, but be aware of the increased risk of ADRs.

The selected AED should be considered as a failure if unacceptable ADRs occur, seizures continue or

new treatment-emergent seizures appear. In any of these events, another AED that fulfils therapeutic expectations for success should be initiated. The first AED should be gradually withdrawn so as to re-establish monotherapy. Switching between AEDs must be carried out cautiously, slowly withdrawing the first drug only after the second drug has reached an adequate therapeutic dosage.

Important practical note

Non-compliance or failing to understand and follow the instructions for AED treatment is a major cause of therapeutic failure. This can often be improved with the use of AED-dispenser systems, which are widely available through pharmacies. These usually come in small boxes for a weekly or longer supply of each individual patient's tablets or capsules to be taken at the time and date shown. These are useful even for patients who comply well, but who often may be uncertain whether or not they have taken their medication.

Rational polytherapy

Polytherapy (combination, adjunctive or 'add-on' therapy) should be considered only when attempts at monotherapy with an AED have not resulted in freedom from seizures. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or polytherapy) that has proved most acceptable to the patient in terms of providing the best balance between effectiveness in reducing seizure frequency and the tolerability of ADRs.

The risks of polytherapy include

- more ADRs
- frequent unwanted interactions with other drugs,
- an increased risk of teratogenicity,
- inability to evaluate the efficacy and ADRs of individual AED agents, and
- poor compliance.

However, polytherapy is infrequently more desirable than monotherapy; for example, in JME patients on valproate, adding small doses of clonazepam for continuing disturbing myoclonic jerks or small doses of lamotrigine for continuing serious absences may be more beneficial than increasing the dose of valproate.

Rational polytherapy is often needed for 30–50% of patients who are unsatisfactorily controlled with a single AED. This is much higher in patients with symptomatic focal epilepsies than in patients with IGEs. A recent study showed that the chance to become seizure free declines by 75% after every 3 lifetime used AEDs, leaving up to 16.6% of patients uncontrolled after failure of three previous AEDs.[64] Similarly, the chance to be a 50% responder also declines by 50% after every 2 lifetime used AEDs.[64] Almost all epileptic encephalopathies require polytherapy. Initially, a second drug is added to the agent, which showed better efficacy and tolerability in monotherapy. The choice of a second or sometimes a third drug depends on many factors such as efficacy, ADRs, interactions with other drugs, mode of action and the need for laboratory testing (Table 7.3).

The addition of an AED to other AEDs that have partially or totally failed or have made the situation worse is a formidable task for a physician, especially when faced with a disappointed and frustrated patient. Polytherapy with more than three drugs is discouraged because adverse reactions become more prominent, with little if any seizure improvement.

Polytherapy can be *irrational* and *hazardous* if a diagnosis is incorrect and AED indications/contraindications are violated.

The decision for polytherapy should first scrutinise the possible/probable reasons why the monotherapy failed. These should thoroughly examine the following possibilities, which often require re-evaluation of diagnosis (genuine epileptic seizures? what type of seizures?):

- the patient does not suffer from epileptic seizures
- the patient has both genuine epileptic and non-epileptic seizures
- the patient has focal and no generalised seizures or *vice versa*
- the AED used as monotherapy was not suitable for the particular type of seizures in this patient because of contraindications (tiagabine or carbamazepine in absences or myoclonic jerks, and lamotrigine in myoclonic epilepsies), weak efficacy (valproate or

gabapentin in focal seizures) or total ineffectiveness (gabapentin in primarily GTCSs)
- non-compliance, which varies from unwillingness to take medication to occasionally forgetting or missing the AED dose; violation of particularly eminent seizure-precipitating factors such as photic stimulation, sleep deprivation and alcohol or drug abuse.

The ideal profile of an AED for polytherapeutic purposes includes all the factors that are important for monotherapy (Table 7.3), but with particular emphasis on the following points.

Strength of efficacy which may be increased or weakened by pharmacokinetic and pharmacodynamic interactions.

Safety and tolerability (Table 7.2), which are often worsened by pharmacokinetic and pharmacodynamic interactions.

Interactions with other AEDs, whether pharmacokinetic, pharmacodynamic or both, are particularly unwanted in polytherapy (Tables 7.6 and 7.7). Raising the levels of concomitant AEDs and pharmacodynamic interactions may lead to toxic effects. Conversely, decreasing their levels may increase and worsen seizures causing a vicious cycle in clinical management. With the exception of lacosamide, levetiracetam and gabapentin, all other newer AEDs exhibit sometimes complex, undesirable, drug–drug interactions. Of the newer AEDs, lamotrigine is probably the worst of all. Lamotrigine:
- requires different dosage and titration schemes when combined with hepatic enzyme inducers and when combined with valproate
- pharmacodynamic interactions enhance toxicity and teratogenicity (although pharmacodynamic interactions have a beneficial effect on efficacy)
- its levels lower more than half during pregnancy or hormonal contraception.

Different mechanisms of action in relation to other concurrent AEDs (Table 7.8). Anti-epileptic drug–drug interactions may be purely additive, antagonistic or synergistic. AEDs with the same mechanism of action would be expected to be additive, while combining AEDs with different mechanisms of action may have synergistic effects.[65] A sodium channel blocker AED combined with another that increases the GABA-ergic neurotransmission or that has multiple mechanisms is generally more effective than a combination of two sodium channel blockers.[66] An AED is unlikely to have better success and more likely to have additive ADRs if added to another AED with the same mechanism of action.[66] Lacosamide and levetiracetam appear to have novel modes of action.[61,67]

Converting from polytherapy to monotherapy

Evidence from studies with older and newer AEDs shows that a significant number of patients can be converted successfully from polytherapy to monotherapy without losing seizure control and, in some cases, with improved seizure control. In these cases the AED that appears, after careful consideration, to be the least effective is gradually withdrawn. 'Gradually' sometimes means in steps of weeks or months. This should be particularly slow for certain AEDs, such as phenobarbital and benzodiazepines, in order to avoid withdrawal seizures.

Total AED withdrawal

Consideration of total withdrawal of AEDs is needed in the following patients:
- patients who do not suffer from epileptic seizures
- patients suffering from age-related and age-limited epileptic syndromes who have reached an appropriate age of remission
- patients who are seizure free for more than 3–5 years, provided that they do not suffer from epileptic syndromes requiring long-term treatment such as JME.

Discontinuation of AEDs should be extremely slow, in small doses and in long steps of weeks or months. The rate of relapse increases with a faster rate of AED discontinuation. Furthermore, with fast discontinuation of AEDs there is a risk of seizures that are directly related to the withdrawal effects of certain AEDs (phenobarbital and benzodiazepines).

Before AED withdrawal, there is a need for a thorough re-evaluation of the patient. The presence

of even minor and infrequent seizures specifies active disease. Conversely, the occurrence of such seizures in the process of AED discontinuation mandates restoration of AED medication.

Over-medication in terms of the number of AEDs and doses and length of exposure is undesirable but common. Treatment should be reviewed at regular intervals to ensure that patients are not maintained for long periods on drugs that are ineffective, poorly tolerated or not needed, and that concordance with prescribed medication is maintained.

A normal EEG does not mean that AED withdrawal is safe. Conversely, ictal EEG abnormalities associated with clinical manifestations (e.g. jerks or absences) is a definite indicator for continuing proper AED treatment.

Generic versus brand or generic to generic AED prescribing

A patient who is stabilised with an AED in terms of seizure control and minimal ADRs should remain in the same brand or the particular generic product, which are not interchangeable without risks.

When an AED is first prescribed, this can be a brand or a generic product providing that the latter has been truly tested in regard to the credibility of its manufacturers and bioequivalence with the brand product. Titration and maintenance should be with the same AED product.

It is unreasonable to switch from one to another AED, either from an expensive branded AED to a cheaper bioequivalent generic product or vice versa. It is unnecessary and may impose significant risk to the patient.

When such substitution is attempted the patient should be well informed of possible consequences, such as seizure relapse or ADRs.

Prescriptions should clearly indicate the type of AED formulation to be used even for generic products.

AEDs are first licensed and used with their brand name and this is protected by granted patents and exclusivity. Patents are granted anywhere along the development lifeline of a drug and can encompass a wide range of claims. Exclusivity is a term describing marketing rights granted upon approval of a drug and can run concurrently with a patent or not. Exclusivity was designed to promote a balance between new drug innovation and generic drug competition. Generic AEDs are usually introduced after patents and exclusivity have been expired with the single aim to reduce the cost of the medication.

There is considerable concern amongst physicians and patients about the efficacy and safety of brand to generic AED substitution or vice versa and also from one to another generic drug of different manufacturers.[68–76]

These concerns have been reasonably raised because of well documented breakthrough seizures, emergency treated epilepsy-events and toxicity as a result of such substitutions. These unwanted and preventable adverse effects are well documented from the time of Epanutin® to phenytoin[77] and Mysoline® to primidone substitutions.

Substitution from one to another AED of the same active substance is safe only when these are of therapeutic equivalence: "Drug products are considered to be therapeutic equivalents … if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." However, even when the generic product is from a reliable source (something that is beyond the role of prescribing physicians) there may be problems with their therapeutic equivalence particularly in terms of bioavailability and pharmacokinetic profiles.

AEDs are particularly vulnerable in these changes, because most have a narrow reference concentration index between drug levels that are therapeutic and those that may cause ADRs.

It is because of these problems that formal recommendations worldwide uniformly warn against such substitutions of AEDs (see citations in reference):[69]

"Changing the formulation or brand of any AED is not recommended because different preparations may vary in bioavailability or have different pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side-

effects." (National Institute for Health and Clinical Excellence-UK).[2]

"For AEDs, small variations in concentrations between name-brands and their generic equivalents can cause toxic effects and/or seizures when taken by patients with epilepsy. The AAN believes that the authorities should give complete physician autonomy in prescribing AEDs." (American Academy of Neurology).[75]

In regard to the implications of changing AED formulations for TDM the recent ILAE position paper recommends:[78]

(a) When an AED formulation is changed, e.g., when switching to/from generic formulations, measuring the plasma concentration of the AED before and after the change may help in identifying potential alterations in steady-state drug concentrations resulting from differences in bioavailability.

(b) When patients are switched to a formulation with modified-release characteristics (for example, from an immediate-release to a sustained-release formulations), or when dosing schedule is changed (for example, from twice daily to once daily administration), interpretation of TDM data should also take into account the expected variation in diurnal drug concentration profile. In some instances, collection of two or more blood samples at different intervals after drug intake may be desirable to fully assess the concentration profile change.

Evidence for AED treatment recommendations in clinical practice

In clinical practice a physician faces a colossal task not only to make the correct diagnosis for a patient but also to correctly identify which is the best AED option for both the patient and their particular type of seizure and syndrome. However, such judgement requires huge, extensive, continually updated and multilevel knowledge, which even expert clinical epileptologists may not have. Therefore, it is fundamental for physicians to be informed about the best existing evidence for AED treatment in clinical practice.

> Clinicians need advice – they always have, but with the multiplicity of therapies now available, this need is pressing.[79]

Recommendations and guidelines should be clear for each AED: what priority and for what type of seizures they are effective, potentially useful, ineffective, contraindicated or harmful. Ideally, these recommendations should be based on unequivocal documentation but often this is limited to probable, possible or purely anecdotal evidence.

Evidence-based recommendations

Evidence-based medicine (EBM),[80,81] which was introduced in 1991, is a welcome healthcare practice that is based on integrating the knowledge gained from the best available research evidence and clinical expertise with patients' values and circumstances.

EBM is defined as 'the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients' and the practice of EBM means 'integrating individual clinical expertise with the best available external clinical evidence from systematic research'.[80]

In therapy, EBM aims to treat patients according to the best available evidence and its purpose is to protect patients from treatments based on untested ideas. The way to test which treatment is best is usually by appropriate RCTs, which are typically double-blind. In many instances when solid evidence is lacking or not directly applicable to a given patient, EBM endorses lower levels of evidence (e.g. ongoing importance of fundamental clinical skills, sound clinical reasoning, accumulated experience and common sense).

Problems with RCTs include:

- bad quality; the Consolidated Standards for Reporting of Trials (CONSERT) statement was developed in an attempt to combat this problem
- designs for regulatory purposes and of no clinical relevance
- their high cost, which often makes RCTs unapproachable or limited
- their misuse by special interest groups.[81]

Approximately a fifth of drugs approved by regulatory authorities are subsequently withdrawn due to post-marketing evidence of imposing health risk.

> The results of EBM often clash with the agenda of special interest groups… We need to alert clinicians and patients to studies showing that reviews sponsored by the industry almost always favour the sponsor's product, whereas those that aren't sponsored by such companies do not. We also need to provide patients and the general public with the tools to enable them to understand and evaluate systematic reviews.[81]

The problems with RCTs in epilepsies are similar to those of other treatments and I quote protagonists of RCTs:

> These studies are almost always sponsored by the pharmaceutical company that manufactures the newer drug, and almost always conclude that the newer drug is equally as effective but better tolerated than the established drug.[82]

> Unfortunately, methodological problems, including small sample size, questionable selection of patients, titration schedules, dose and dose form, and short duration of study, have limited the acceptance of the results.[82]

> Rating classification schemes for RCTs have the sole purpose of eliminating bias in studies. They do not address whether the study results are clinically valid.[83]

> Results were potentially confounded by errors in seizure classification and failure to measure seizures other than tonic clonic during follow-up.[84]

> Misclassification of patients may have confounded the results… The age distribution of adults classified as having generalized seizures indicated that significant numbers of patients may have had their seizures misclassified.[85]

Diagnostic uncertainties and methodological pressures confound the analysis of these studies.

The school of clinical epileptology that I follow may find some RCTs unacceptable both in their methodology and in their proposals on the use of AEDs in clinical practice for the principal reason that they examine AED response in a unified definition of 'epilepsy' irrespective of the type of epileptic seizures or patient group. Children's epilepsies and management differ from adults in many respects. Women of childbearing age mandate a different approach.

One RCT[62] promotes the detrimental, indiscriminate use of carbamazepine and valproate because 'neither of them is regarded as the single drug of choice for all patients with newly diagnosed epilepsy'[62] despite established documentation that these are two different AEDs with different indications and contraindications in partial and generalised epilepsies.

Another, more recent RCT unifies *all* patients (normal or neurodevelopmentally impaired children, women, men and elderly) with *all* types of seizures. The physician's intention to treat with carbamazepine or valproate is the only differentiating question in the quest of what is the best AED treatment.[84]

We have also seen some disasters. Numerous RCTs showed that vigabatrin was a relatively safe drug with a relatively benign adverse-effect profile. A RCT in 1999 found vigabatrin 'less effective but better tolerated than carbamazepine in patients with partial epilepsies'.[86] This was 2 years after the first report of vigabatrin-emergent irreversible peripheral visual field defects,[87] which occur in 40% of the patients receiving vigabatrin and ended its use in epilepsies other than the West syndrome.

These issues with RCTs may compromise purely evidence-based recommendations[88] and for multiple reasons there are significant difficulties in extrapolating data from RCTs to clinical practice.[89] This is well reflected in the discrepancies between guidelines derived from the same data.[79,90] Partly as a result, such influential recommendations may mislead physicians in the appropriate use of newer AEDs and inadvertently perpetuate suboptimal practice in new clinical trials.

> One striking result of the increasing plethora of guidelines is the apparent paradox that recommendations differ from one guideline to another, although each usually purports to use the same evidence base and to exhibit scientific objectivity.[79]

Furthermore, in some of these formal recommendations there is a conspicuous bias in favour of the newer AEDs. A formal guideline emphasises that:

> The older AEDs as a class have complex pharmacokinetics. Four of the six AEDs available prior to 1990 (phenytoin, carbamazepine, phenobarbital and primidone) are hepatic enzyme inducers. Induction not only complicates combination AED therapy but also changes internal hormonal milieu in possibly important

ways. Intrinsic compounds, such as sex steroids and vitamin D, are hypermetabolised. This can lead to reproductive dysfunction and osteopenia. Enzyme-inducing AEDs produce important interactions with many commonly used medications, such as warfarin, oral contraceptives, calcium channel antagonists and chemotherapeutic agents, to name a few. Valproate, in contrast, is a potent hepatic inhibitor. There is controversy about the impact of valproate on the hormonal milieu and inhibition leads to important drug interactions with AEDs as well as other classes. The newer agents are involved in many fewer drug interactions. Many of the newer agents have little if any effect on the CYP450 enzyme system and other metabolic pathways.[91]

However, such a generalisation, although correct if older and newer AEDs are considered as two different 'classes', is inadequate without specifying that certain newer AEDs have similar or even worse drug–drug interactions in comparison with certain older AEDs. Newer AEDs are not innocent. All newer AEDs but levetiracetam (characterised as ideal),[92,93] lacosamide, pregabalin, and gabapentin sometimes exhibit complex undesirable drug–drug interactions.

A recent editorial by Simon Shorvon in *Epilepsia – We live in the age of the clinical guideline* – should be read by all physicians.[79] It is the most objective, wise and brave paper published on these important issues as evident by the following extracts[79] with which I fully agree:

> An avalanche of guidelines risks burying the clinician in a white snow of double-talk and humbug, and is not wholly in the best interests either of medicine or of patients.
>
> Political interference, personal ego and prejudice are common in guideline committees.
>
> Commercially funded systematic reviews are prone to bias in favour of the sponsor and have been shown to score badly on scientific validity.
>
> Other inherent limitations further reduce the practical value of clinical guidelines. One (obvious) issue is the fact that knowledge advances: time is no friend to the clinical guideline.
>
> The blanket advice of many restrictive guidelines, based on a limited number of RCTs that are narrow in their scope, almost invariably ignores the fact that optimal therapy can differ in different syndromes and in different clinical settings.

On medicolegal aspects Shorvon also emphasises:[79]

> Guidelines are not regulations but often are treated as such.
>
> Tailoring therapy to individual patients, whether within or outwith a guideline recommendation, remains a prerogative that doctors should not sacrifice.

Poverty of reliable RCTs in epilepsies

The 2006 ILAE report[44] is the most authoritative evidence-based review and analysis of the efficacy and effectiveness of AEDs as initial monotherapy for epileptic seizures, although myoclonic seizures have not been assessed. It also reviews evidence-based AED efficacy and effectiveness as initial monotherapy in JME, childhood absence epilepsy and rolandic epilepsy. The analysis applied a rating scale of evidence of class I (best) to class IV (worst) to potentially relevant reports from 1940 until July 2005. The level of evidence for the conclusions was also graded from A (a high degree of reliability) to F (a low degree of reliability).

The ILAE report concluded that:

> It is clear that an alarming lack of well-designed, properly conducted epilepsy RCTs exist… the absence of rigorous comprehensive adverse effects data makes it impossible to develop an evidence-based guideline aimed at identifying the overall optimal recommended initial monotherapy AED. There is an especially alarming lack of well-designed, properly conducted RCTs for patients with generalized seizures/epilepsies and for children in general. The majority of relevant existing RCTs have significant methodologic problems that limit their applicability to this guideline's clinically relevant main question.[44]

The following recommendations were made:

> Multicenter, multinational efforts are needed to design, conduct and analyze future clinically relevant RCTs that can answer the many outstanding questions identified in this guideline. The ultimate choice of an AED for any individual patient with newly diagnosed or untreated epilepsy should include consideration of the strength of the efficacy and effectiveness evidence for each

AED along with other variables such as the AED safety and tolerability profile, pharmacokinetic properties, formulations, and expense. When selecting a patient's AED, physicians and patients should consider all relevant variables and not just efficacy and effectiveness.[44]

Based on available efficacy and effectiveness evidence alone and only for RCTs published before July 2005, recommendations at levels A and B were possible for:

- adults with newly diagnosed or untreated focal seizures: carbamazepine (A), phenytoin (A) and valproate (B)
- children with newly diagnosed or untreated focal seizures: oxcarbazepine (A)
- elderly with newly diagnosed or untreated focal seizures: lamotrigine (A) and gabapentin (A)
- adults with GTCSs: none has reached level A or B
- children with GTCSs: none has reached level A or B
- children with absence seizures: none has reached level A or B
- rolandic epilepsy: none has reached level A or B
- JME: none has reached level A or B.

Note

Levetiracetam has not been considered in the above recommendation because the relevant RCT of Brodie *et al*[94] has only recently been published. The results of this class 1 with A level of evidence RCT earned levetiracetam approval as a first-line monotherapy in the treatment of focal epilepsy.

Evidence-based recommendations in this book

The recommendations made in this book are based on a thorough review of the efficacy, tolerability, safety and interactions, and other essential parameters involved in the choice of AEDs (Tables 7.3 and 7.12). The following sources were used:

- evidence-based reports, RCTs, reviews and expert assessments and guidelines of AED treatment in children and adults
- post-marketing open studies, and observational and case reports that appeared in full papers or abstract forms
- expert physicians' experiences of the clinical use of AEDs, which were obtained through critical discussions or personal correspondence with them
- pathophysiology of seizures and mechanisms of actions in animal models as supportive rather than conclusive evidence of clinical usefulness.

It is reassuring that important conclusions made in my previous publications proved to be correct, in particular with respect to the following recommendations:

- valproate is the superior AED for generalised epilepsies but its use as monotherapy in focal epilepsies is unwise
- vigabatrin and tiagabine are pro-absence AEDs that induce rather than treat absence epilepsies
- gabapentin has the least efficacy of the newer AEDs in focal epilepsies and is ineffective in IGEs
- pregabalin does not appear to have a promising profile as an AED
- lamotrigine may not be appropriate for monotherapy in JME (it may aggravate myoclonic jerks), where its beneficial effect is mainly seen when combined with valproate
- levetiracetam is a very effective broad-spectrum newer AED in focal[94] and generalised[95] epilepsies; it is the only one of the newer AEDs licensed for myoclonic seizures of JME.

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM), in which plasma concentrations of AEDs are measured, can have a valuable role in guiding patient management provided that concentrations are measured with a clear indication and are interpreted critically, taking into account the whole clinical context.[78]

Useful recommendation

The recent ILAE position paper of 2008[78] is a practice guideline for TDM and is highly recommended for further reading and citations. It also provides pharmacokinetic details, interactions with other AEDs, and reference ranges for each AED and discusses the role of TDM in children and the elderly and during pregnancy.

Pragmatic recommendations for AED treatment with older and newer AEDs for epileptic seizures and main epileptic syndromes

Seizures/syndromes	First-line AEDs* (in order of priority)	Second-line AEDs* (in order of priority)
Focal (simple and complex) seizures with or without secondarily GTCSs	Carbamazepine, phenytoin, phenobarbital *Levetiracetam, oxcarbazepine, lamotrigine, topiramate*	Clobazam, valproate, *Lacosamide, gabapentin, zonisamide, pregabalin, tiagabine*
Primarily GTCSs only	Valproate, phenobarbital, phenytoin *Levetiracetam, lamotrigine, topiramate*	Carbamazepine *Oxcarbazepine*
Myoclonic seizures only	Clonazepam, valproate, phenobarbital *Levetiracetam*	Phenytoin, ethosuximide *Topiramate, zonisamide*
Absence seizures only (typical and atypical)	Valproate, ethosuximide *Lamotrigine*	Clonazepam *Levetiracetam, zonisamide, topiramate*
Negative myoclonic and atonic seizures	Ethosuxide, valproate *Levetiracetam*	Clonazepam *Zonisamide, topiramate*
Tonic seizures	Valproate, phenytoin, phenobarbital *Topiramate, lamotrigine*	Clonazepam, clobazam *Zonisamide*
Benign childhood focal seizures and syndromes	Carbamazepine, valproate, sulthiame, clobazam *Levetiracetam, oxcarbazepine, lamotrigine*	*Gabapentin, lacosamide, zonisamide*
All symptomatic and cryptogenic syndromes of focal epilepsies	Carbamazepine, phenytoin, phenobarbital *Levetiracetam, oxcarbazepine, lamotrigine, topiramate*	Clobazam, valproate *Lacosamide, gabapentin, zonisamide, pregabalin, tiagabine*
Childhood absence epilepsy	Ethosuxide, valproate *Lamotrigine*	Clonazepam
Juvenile absence epilepsy	Valproate, ethosuximide *Lamotrigine*	Clonazepam *Levetiracetam, zonisamide, topiramate*
Juvenile myoclonic epilepsy	Valproate, phenobarbital *Levetiracetam, topiramate*	Clonazepam, ethosuximide *Zonisamide, lamotrigine*
Photosensitive and other reflex seizures	Valproate *Levetiracetam*	Clonazepam *Lamotrigine*
Lennox–Gastaut syndrome and other epileptic encephalopathies (AEDs largely depend on predominant seizure type)	Valproate *Lamotrigine, levetiracetam, rufinamide, topiramide, zonisamide*	Clobazam, clonazepam, ethosuximide, phenytoin *Felbamate, stiripentol (Dravet syndrome only)*

Table 7.12 *Older AEDs are shown in roman; newer AEDs are shown in blue italics. The table is only indicative of AEDs to use in each of the epileptic seizures or syndromes. Priority depends on AED properties, whether monotherapy or polytherapy is used, and the needs of individual patients, as detailed in this book. In choosing an AED from this table, the order of priority is between the first in the list of older or newer AEDs in the middle column.

Reference ranges which laboratories can quote and which clinicians can use as a guide are not synonymous with therapeutic ranges.[78]

The "reference range" of an AED is a statistical standard of the AED concentration. It is derived from population studies and indicates the level

at which most patients achieve optimal seizure control. It specifies a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur.[78,95] Concentrations lying within the reference range are not "normal" because the "normal" concentration of a drug in a living organism is zero.

Reference range is the optimal drug concentration range at which most patients achieve the desired therapeutic effect with no undesirable side effects.

Reference range is a useful guideline, but effective AED maintenance dosing should be based mainly on clinical criteria because the inter-patient variability is considerable. Many patients can achieve therapeutic benefit at plasma drug concentrations outside these ranges. Some patients are well controlled below the low range-limit, whereas others achieve seizure freedom above the upper range-limit. Some patients are free of adverse reactions even at 'toxic' target levels, whereas others may develop adverse reactions that are unacceptable for them at trough levels, which are just measurable. Thus, concentrations lying within the reference range may not necessarily be "therapeutic", "effective", or "optimal" and therefore it is recommended that these adjectives not be used when reporting the results.[78] The correct reporting terminology should be "The result lies within/above/below the reference range".[78] It is because of these reasons that the term therapeutic range has been introduced.

The "therapeutic range" is defined as the range of drug concentrations that is associated with the best achievable response in a given person, and therefore can only be determined for the specific individual.

Plasma and saliva TDM

Serum or plasma represents the matrix of choice for TDM, and although they can be used interchangeably it is preferable to use one or the other.[78] Saliva is a matrix of increasing utility, but only for some AEDs.

Useful practical note

TDM: rule of thumb for individual patients

The level is 'therapeutic' when, and only when, the patient is free of seizures and free of ADRs regardless of numbers in TDM. The dose of an AED is adequate if seizures are controlled and if ADRs are not present or these are mild. The dose is high if intolerable adverse reactions are present irrespective of seizure control.

Routine TDM measures the total (free and protein-bound) plasma concentration of an AED in a blood sample. The values provided do not discriminate between the amount of the protein bound drug and that which is free (unbound) and pharmacologically active.[78] Thus, monitoring free plasma concentrations is useful in clinical settings when protein binding is altered, such as in hypoalbuminemia (e.g. in pregnancy, in old age, and in liver disease, renal disease, and many other pathological conditions), in conditions associated with accumulation of endogenous displacing agents (e.g., uraemia), and following administration of drugs which compete for plasma protein binding sites. Phenytoin and valproate are highly protein-bound and consequently susceptible to variable binding.

Saliva TDM is rarely used in clinical practice because samples are often contaminated in the mouth, thereby making the results unreliable. Advantages of saliva TDM of AEDs as an alternative to plasma TDM include:

- collection is simple and non-invasive
- it can be especially useful in patients with disabilities and is preferred by children and their parents
- for most AEDs, measured concentrations reflect the free (pharmacologically relevant) concentration in blood.

Disadvantages of saliva TDM include:

- the difficulty in measuring concentrations that may be lower than total plasma concentration
- the possibility of contamination and unreliable results due to the presence of drug residues in the mouth or leakage of drug-rich exudate, particularly in patients with gingivitis. To minimise contamination from drug residues,

saliva sampling is best done before the next dose and after a good wash of the mouth

AEDs for which there are substantial data suggesting useful correlations between saliva concentrations and free plasma concentrations include carbamazepine, ethosuximide, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, primidone, topiramate, and vigabatrin. For drugs with pK values close to physiological pH (e.g., valproate and phenobarbital), salivary concentrations can be highly variable or erratic; saliva TDM should not be used for these drugs.

Clinical applications

Monitoring the plasma levels of AEDs is useful in clinical practice for maximising seizure control and minimising adverse reactions, provided that it is selectively and appropriately used in response to a patient-specific pharmacokinetic or pharmacodynamic issue or problem.[78,97,98]

Of the older AEDs, phenytoin, phenobarbital and carbamazepine are more likely to necessitate TDM; valproate has a number of peculiarities and variability. The usefulness of TDM has been initially questioned for most of the newer AEDs because a wide range of plasma concentrations are associated with clinical efficacy and no useful or considerable overlap is reported between 'concentration–effect' and 'concentration–toxicity'. This view has been recently revised, particularly in women, because plasma concentrations of some newer AEDs are significantly influenced by hormonal contraception and pregnancy (see forthcoming section of the management of women with epilepsy). In co-medication also enzyme-inducers significantly affect plasma levels of lamotrigine and topiramate levels.[99] Current tentative reference ranges for each of the newer AEDs have been reported and these are stated in the pharmacopoeia and in references.[78,94,100]

Solid evidence for the usefulness of TDM in improving clinical outcome is scarce and debated.[78,101]

In clinical practice TDM is recommended:[78,100]

- for establishing 'baseline' effective concentrations (therapeutic range) in patients who have been successfully stabilised, enabling future comparisons to assess potential causes for a change in drug response, for example if seizures recur, in pregnancy or in patients in need of polytherapy or other medications
- for evaluating potential causes for lack or loss of efficacy
- for evaluating potential causes for toxicity
- to assess compliance, particularly in patients with uncontrolled seizures or breakthrough seizures
- to guide dosage adjustment in situations associated with increased pharmacokinetic variability (e.g., children, the elderly, patients with associated diseases, drug formulation changes) when a potentially important pharmacokinetic change is anticipated (e.g., in pregnancy, or when an interacting drug is added or removed)
- to guide dose adjustments for AEDs with dose-dependent pharmacokinetics, particularly phenytoin.

TDM is complicated in polytherapy because it is unlikely that the reference range is the same when an AED is taken alone or in combination with other AEDs; for example, the toxicity from carbamazepine or valproate appears at higher plasma levels when these AEDs are used in monotherapy than when they are used in combination.

Useful clinical note

Regularly repeating TDM in patients who are controlled and with no sign of adverse reactions 'just to make sure that everything is ok' is totally discouraged.

Trough AED plasma levels are important with regard to efficacy, whereas peak AED plasma levels are important with regard to toxicity.

In treatment with carbamazepine or oxcarbazepine, diplopia is a sign of exceeding the drug dosage, irrespective of TDM levels.

Time of sampling

Sampling time and a meticulous dosage history is imperative for proper TDM utility in clinical practice.[78]

Sampling should be done at steady state, which occurs at 4–5 half-lives after starting treatment or a dose change. Half-life values and other pharmacokinetic parameters of AEDs can be found in the Pharmacopeia of this book (Chapter 18) and in the recent ILAE position paper.[78] Patient noncompliance within a period of 3–4 half-lives before the blood sample is drawn can significantly affect the plasma concentration and cause misinterpretation of the result. Plasma concentration may be underestimated when blood sampling is taken before a drug steady-state plasma is reached. Conversely, it may be overestimated when blood sampling is taken before auto-induction of carbamazepine is complete.[78]

For AEDs with a long half-life (e.g. ethosuximide, phenobarbital, phenytoin) timing is not important because fluctuations in plasma concentration are negligible in the course of a day; samples can be collected at any time.

For AEDs with a short half-life (e.g. carbamazepine, gabapentin, lamotrigine, levetiracetam, pregabalin, topiramate, valproate) it is important to standardise sampling time in relation to dose. For these AEDs it is recommended that blood samples are obtained before the first dose when the concentration is at its trough (which is useful for assessing ineffectiveness) and/or at a time of expected peak concentrations (which is useful for assessing toxicity).

Useful clinical note

There is no point to attempt TDM before a time interval of 4–5 half-lives of starting treatment or a dose change.
TDM is useful for assessing ineffectiveness when the AED plasma concentration is at its trough (before the next dose)
TDM is useful for assessing toxicity at times of expected peak concentrations

Considerations of adverse antiepileptic drug reactions in the treatment of epilepsies

Adverse drug reactions (Table 7.2) should be thoroughly sought in patients treated with AEDs. Despite their significance, identifying ADRs is often neglected because of time constraints, confounding factors and the multiplicity of potential symptoms. Patients may also be reluctant to report them or they may confuse them with a consequence of their illness.

ADRs may be minor or severe, transient or progressive, reversible or irrevesrible, known, unknown or suspected. They vary significantly between AEDs and with dose, length of exposure, individual susceptibility, age, sex and comorbitidies. Emphasis is given to ADRs associated with use of older AEDs, though ADRs may also be highly significant with the use of newer AEDs. They are more likely to occur with polytherapy than monotherapy.

Patients, particularly with newly identified epilepsy, are prone to develop ADRs (biological, cognitive or behavioural), which in 15% of cases lead to AED discontinuation. Some patients develop ADRs readily even at an AED dose below the minimal limit of the reference (therapeutic) range, while others are resistant to ADRs even at the maximum limit of that range.

ADRs may be very common (≥1/10 per patient exposed to an AED), common (≥1/100 to <1/10) or uncommon (≥1/1000 to <1/100).

ADR associated with each AEDs and their particular effects in children, women and elderly are frequently emphasised in this book and are also detailed in the Pharmacopoeia (Chapter 18).

Life-threatening ADRs

These are the most dreadful of all ADRs and carry a black box warning in their package inserts.

Anticonvulsant hypersensitivity syndrome (AHS), though rare, is the most common potentially fatal ADR linked with AEDs, occurring at a rate of 1000–10000 exposures.[102–109] Carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital and zonisamide are associated with frequent idiosyncratic reactions and anticonvulsant hypersensitivity syndrome (AHS). The main clinical manifestations of AHS consist of skin rashes, fever, tender lymphadenopathy, eosinophilia, and hepatic and other systemic organ involvement. Diagnosis

is primarily based on the recognition of clinical symptoms.

The appearance of a rash is an early indicator that mandates the immediate discontinuation of the responsible agent because it may progress to AHS and Stevens–Johnson syndrome.

The underlying mechanisms of AHS are thought to have at least three components: (a) deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine AEDs, (b) reactivation of herpes-type viruses, and (c) ethnic predisposition with certain human leukocyte antigen subtypes.[103] To reflect recent advances in pharmacogenetics, the FDA has issued an alarm on dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis) that can be caused by carbamazepine, which are significantly more common in patients with the leukocyte antigen subtype HLA-B*1502. This particular human leukocyte antigen allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Genetic tests for HLA-B*1502 are already available.

There is usually a high degree (40–80%) of cross-sensitivity for AHS between AEDs. Thus, patients with a history of AHS should avoid use of AEDs which have the potential to cause AHS. Also, there is an increased risk of AHS amongst family members of patients with AHS. AHS is nore common in children than adults.

AEDs that are unlikely to cause AHS are benzodiazepines, levetiracetam and valproate (but the latter has been associated with increasing the AHS risk of lamotrigine).[9]

Other life threatening ADRs to AEDs and their preferential occurrence in age groups or women are detailed in the description of each one of the AEDs and the relevant sections. These include valproate-related hepatic and pancreatic failure in young children, topiramate and zonisamide-related anhidosis and so forth. Little is known about the cardiac ADRs of AEDs though these may also be potentially fatal, particularly in elderly and patients with pre-existing cardiological abnormalities (see page 200).

Suicidal ideation that may lead to suicide has also attracted significant attention recently with another alert issued by FDA[111]. This was based on pooled analyses of 199 clinical trials of eleven AEDs (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate and zonisamide) used as mono- and adjunctive therapies. Patients who were randomised to receive one of the AEDs had almost twice the risk of suicidal behaviour or ideation (0.43%) compared to patients randomised to receive placebo (0.24%). This risk was generally consistent among the eleven drugs, was observed as early as one week after starting AED and throughout the observed duration of AED treatment and was higher in the clinical trials for epilepsy compared to trials for psychiatric or other conditions.

> The increased risk of suicidal thoughts or behavior was generally consistent among the eleven drugs with varying mechanisms of action and across a range of indications. This observation suggests that the risk applies to all antiepileptic drugs used for any indication. All patients who are currently taking or starting on any AED for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behavior or depression.[111]

However, the problem of suicide and depression in epilepsies, which both have a high incidence, is complicated by a number of factors such as pre-existing psychopathology, social, personal, family and occupational difficulties, teenage onset, and others that have been recently detailed.[112–116] There is no evidence that one AED is more prone than another AED to cause suicidal ideation and suicide.

Common CNS-related ADRs

CNS-related ADRs are common and primarily affect vigilance (somnolence, sedation), cognition, the brain stem and vestibulocerebellar system (leading to dizziness, vertigo, incoordination, ataxia, diplopia or nystagmus), the extrapyramidal system (causing chorea and dystonia, parkinsonism or tremor), or the psychiatric and psychological state of the patient (leading to anxiety, depression, psychosis, and psychological and behavioural disturbances).[117,118]

Headache and fatigue are among the commoner CNS-related ADRs of AEDs.

Most of the common CNS ADRs such as sedation, dizziness, incoordination and fatigue are often dose related and occur early after the introduction of an AED. They are reversible, improve with time and can be lessened with slow titration. However, others, such as phenytoin-induced ataxia, appear with long use and are progressive if the responsible agent is not withdrawn. The sedative effect of most older generation AEDs such as phenobarbital and benzodiazepines are well known.

A meta-analysis of the most frequent treatment-emergent CNS ADRs of some new AEDs in adult patients[118] showed significant association of:

- somnolence with gabapentin, levetiracetam, pregabalin , topiramate and zonisamide
- dizziness with gabapentin, lamotrigine, pregabalin, topiramate and zonisamide
- ataxia with lamotrigine and pregabalin
- diplopia with lamotrigine
- fatigue with pregabalin and topiramate
- cognitive impairment with topiramate

Cognitive impairment is common in epilepsies as the result of the seizures, their underlying cause and ADRs to AEDs.[119–123] Cognitive impairment is often of more concern and more debilitating than the actual seizures with a severe impact on quality of life. AEDs may affect any domain of cognition (intelligence, language, visuoperceptual, verbal and nonverbal memory, or executive function) and influence the functional ability of the patient in communication, verbal fluency, problem solving, memory, psychomotor speed and dexterity.

Cognitive ADRs are well known for the older AEDs; it is because of these the use of phenobarbital has been practically prohibited in industrialised countries and particularly the UK. Carbamazepine and valproate are considered to be better than phenytoin in this respect but worse than most of the newer AEDs in RCTs. The relative incidence of cognitive ADRs to newer AEDs are not well known, primarily because of the scarcity of comparative large-scale studies, though topiramate and zonisamide have been associated with significant diffuse cognitive as well as specific ADRs on language and memory. In a recent study attempting to determine the relative prevalence and predictors of subjective cognitive impairment in adult outpatients with epilepsy taking commonly used AEDs (carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, valproate and zonisamide), overall 320 of 1694 (18.9%) patients experienced cognitive ADRs to AEDs at any point.[119] The average rate of such ADRs for a given AED was 16.6%, with 12.8% leading to dosage change or discontinuation (intolerability). The highest rate of intolerable ADRs was attributed to topiramate (21.5% intolerability) followed by zonisamide (14.9%), oxcarbazepine (11.6%), levetiracetam (10.4%), carbamazepine (9.9%), lamotrigine (8.9%), valproate (8.3%) and gabapentin (7.3%).

Rates of intolerable ADRs were lower in monotherapy than polytherapy. The highest rate of intolerable cognitive impairment attributed to AEDs in monotherapy was seen with topiramate (11.1%), and was significantly higher than that of carbamazepine (1.5%) or valproate (0.0%).[119]

Significant predictors of ADRs with AEDs are older age, female gender, focal epilepsy, and presence of CNS infection, chronic obstructive pulmonary disease, or other comorbid conditions. Interestingly, the presence/history of static encephalopathy was negatively correlated with such ADRs.[119]

To minimise the risk of drug-induced cognitive dysfunction, "topiramate should be lowest on the list followed by zonisamide and phenytoin, whereas lamotrigine, levetiracetam, gabapentin, valproate and carbamazepine should be higher on the list".[119] Avoidance of phenobarbital is a well known recommendation, which may now be updated to include topiramate and zonisamide.

Behavioural and psychiatric ADRs to AED[124–131]

Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. (FDA warning for all AEDs)[111]

Evaluating the psychiatric and behavioural ADRs of AEDs is complicated by several factors including the relatively high rate of psychiatric comorbidities in epilepsies, the lack of reliable face to face comparisons and the variety of quality and methods used to assess the occurrence and severity of psychiatric symptoms with AEDs.[124] It is possible that such ADRs are related to the epilepsy itself, to clinical characteristics of more vulnerable patients and some particular properties of the AED itself either alone in monotherapy or in combination with another AED.[125,132]

A current expert opinion is that most psychiatric ADRs primarily occur with rapid titration and high doses for most AEDs.[124] However, such events may happen at any dose, specifically with barbiturates, topiramate, levetiracetam and zonisamide. With the latter AEDs, psychiatric ADRs seem not to occur at random but they are most likely to affect patients with an inherent vulnerability to psychiatric disorders who have a personal or family history of psychiatric illness. In a recent report,[125] the risk of depressive illness associated with topiramate was fivefold higher in patients who underwent rapid titration and this was increased to 23.3-fold in patients with a history of depression.

The paradox is that AEDs are commonly utilised for nonepileptic psychiatric disorders, though there is, in general, a paucity of published RCTs.[133] The overall view is that lamotrigine has antidepressant properties; carbamazepine, valproate, lamotrigine, and oxcarbazepine have mood stabilising properties; and gabapentin, pregabalin, and tiagabine have anxiolytic benefits. Barbiturates, topiramate, and possibly phenytoin may precipitate or exacerbate depression. Underlying depression and anxiety symptoms may be exacerbated by levetiracetam, while psychotic symptoms have rarely been reported with topiramate, levetiracetam, and zonisamide.[133] However, this contradicts firstly with the FDA view that "there is no evidence that one AED is more prone than another AED to cause suicidal ideation and depression"[111] and secondly with the finding that "well-defined DSM-IV disorders are more frequent with topiramate than levetiracetam".[125]

Another paradox is what is known as *forced normalisation* (or alternative psychosis). This is the rare occurrence of psychotic symptoms when the EEG is normalised and seizures have significantly reduced or undergone remission in some patients treated with AEDs for intractable epilepsies.[134] Paranoid psychosis or episodes of major depression are the most frequent manifestations. Forced normalisation has been reported following the use of various AEDs, including phenytoin, carbamazepine, ethosuximide, lamotrigine and levetiracetam.

This is another significant area in which there are more unknowns than knowns and where clinical practice is influenced by reputation rather than concrete evidence.

Non-CNS ADRs of AEDs

ADRs affecting organs outside the CNS are less common and less predictable than those affecting the CNS system but are equally important to recognise because of their impact on physical health and the brain. They affect any body system, including the cardiovascular, integumentary, hematopoetic, hepatic and digestive, renal, metabolic, endocrine, and peripheral nervous systems. They are sometimes difficult to differentiate from other diseases prior to attributing them to a specific AED medication. I have seen many patients investigated invasively and treated for symptoms typical of ADRs to AEDs prior to their recognition as such and their remission after withdrawal of the offensive agent.

Non-CNS ADRs to AEDs may occur soon after the introduction of an AED but they may also happen at a slow and progressive pace during chronic AED treatment. Non-CNS ADRs may also be inconspicuous for many years before they become manifest, sometimes with horrendous consequences.

Adverse cardiac effects of AEDs

There is a conspicuous poverty of information and recommendations on cardiac ADRs of AEDs and their effect on the electrocardiogram (ECG).

The situation may now change in view of the increasing number of studies on SUDEP and the

attention now given to cardiac function when assessing drug safety during the regulatory process, particularly with respect to ventricular repolarisation as reflected in the prolongation of the ECG QT interval (see Useful Information box on the next page). Premarketing investigation of the safety of a new pharmaceutical agent now includes rigorous characterisation of its effects on the QT/QTc interval labelled "Thorough QT/QTc Study".

The QT interval represents the duration of ventricular depolarisation and subsequent repolarisation, and is measured from the beginning of the QRS complex to the end of the T wave (see Figure 7.2). Prolongation of the QT/QTc interval indicates delay in cardiac repolarisation, which is associated with increased susceptibility to cardiac arrhythmias such as torsade de pointes (torsades) and other ventricular tachyarrhythmias. Torsades is a polymorphic ventricular tachyarrhythmia that can degenerate into ventricular fibrillation, leading to sudden death. Patients with the long QT syndrome may suffer torsades and sudden death. Long QT syndrome is an ion channelopathy that may imitate epileptic seizures (see page 105); not all carriers of mutated ion channel genes will manifest QT/QTc interval prolongation and polymorphisms can affect ion channels, leading to an increased sensitivity to drugs that affect ventricular repolarisation.

QT prolongation is a rare adverse effect that is seen with many psychotropic drugs including tricyclic antidepressants (with whom carbamazepine is chemically related).[135] There are no AEDs in the long list of drugs implicated in long QT,[136] though carbamazepine and phenytoin have been cited in some reports.[137]

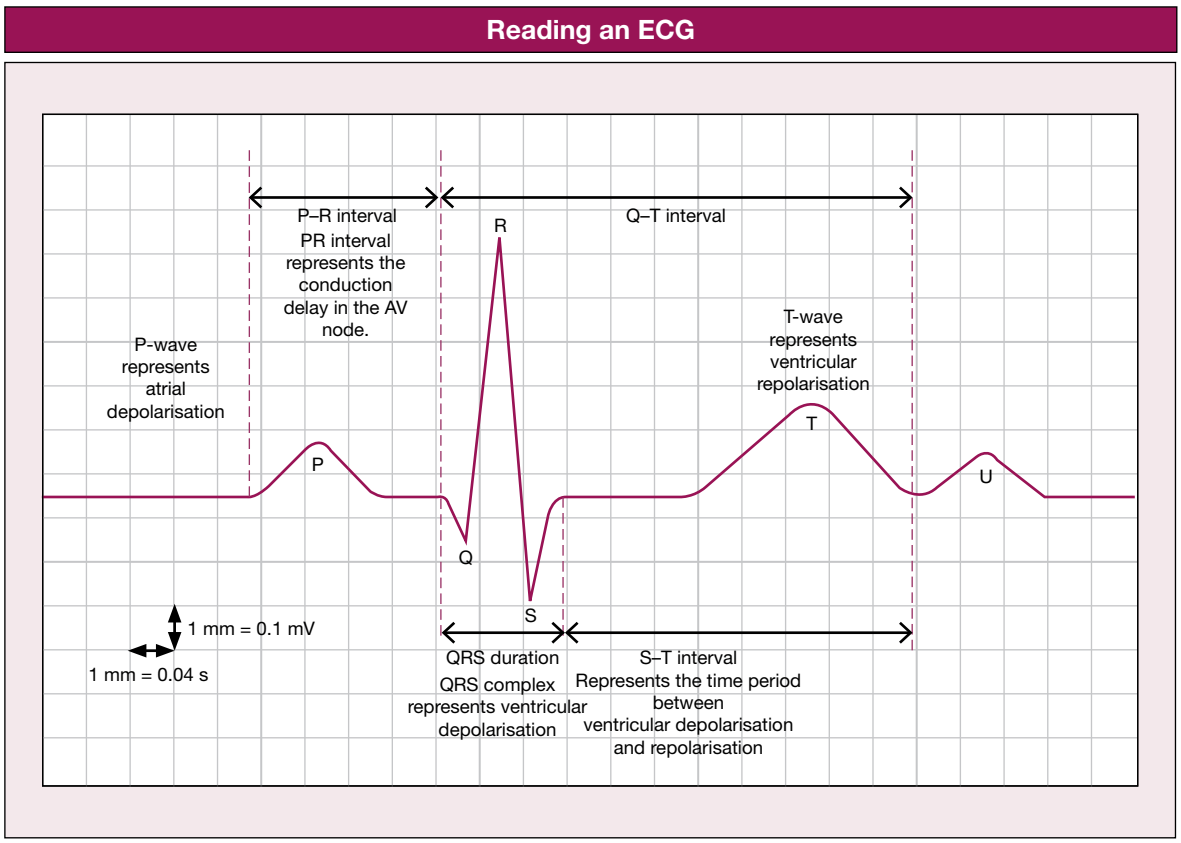

Figure 7.2 The surface ECG represents the different electrophysiological events occurring during normal cardiac conduction. 5 mm = 0.2 s and 0.5 mV.

Useful information

Recent regulatory requirements for cardiac safety of drugs

The regulatory concerns regarding cardiac safety of drugs is addressed with the introduction of the International Conference on Harmonisation topic E 14 (ICH-E14) now required by both FDA (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf) and EMEA (http://www.emea.europa.eu/pdfs/human/ich/31013308en.pdf).

The ICH-E14 requires a thorough premarketing investigation of the safety of a new pharmaceutical agent that should include rigorous characterisation of its effects on the QT/QTc interval.

Also, questions have been recently raised regarding the safety and proarrhythmic consequences of drugs that shorten the QT interval.[138] QT shortening has been reported for primidone,[139,140] lamotrigine and rufinamide.[141] As with QT/QTc prolongation, there are genetic syndromes and pharmaceutical agents which cause shortening of QT/QTc. However, currently it is unclear whether QT/QTc shortening is a suitable biomarker for cardiac arrhythmias and how much shortening of QT/QTc is required before it might be considered a safety issue.[138,141]

The PR interval extends from the onset of atrial depolarisation (beginning of the P wave) and ends at the onset of the QRS complex (beginning of ventricular depolarisation) and represents the time the impulse takes to reach the ventricles from the sinus node. The normal values of PR interval are between 0.12 to 0.20 s.

Prolongation of the PR interval of more than 0.20 s (first-degree atrioventricular block) is usually asymptomatic and frequently encountered in clinical practice.[142] Adverse events with first degree atrioventricular block include syncope and bradycardia, which are usually considered of good prognosis. AEDs that are implicated in the prolongation of PR interval are carbamazepine, eslicarbazepine acetate, lacosamide, and pregabalin. Also "a small increase in PR (0.005 seconds)" has been reported in a RCT with lamotrigine.[143]

The newest AEDs, including eslicarbazepine acetate, lacosamide and rufinamide, have been tested after the implementation of ICH-E14, which may explain why an effect on ECG has been shown in all of these, in contrast

ECG changes and cardiac adverse reactions of AEDs

AED	Adverse cardiac reactions to AEDs as cited in the SmPCs
Carbamazepine	Cardiac conduction disorders, hypertension or hypotension, bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thrombo-embolism (e.g. pulmonary embolism)
Eslicarbazepine acetate	PR prolongation
Gabapentin	Palpitations
Lacosamide	PR prolongation
Pregabalin	Tachycardia, atrioventricular block first degree, sinus tachycardia, sinus arrhythmia, sinus bradycardia, congestive heart failure
Rufinamide	Shortening of the QT interval
Lamotrigine, levetiracetam, phenytoin,topiramate, valproate, zonisamide	None is reported in the SmPCs

Table 7.14 Effects of AEDs on ECGs and cardiac ADRs as cited in SmPCs.

with most other AEDs, which were approved before the ICH-E14 requirements came into force (Table 7.14).

Despite their significance in clinical practice, no recommendations on the ECG and cardiac effects of AEDs are made, even in formal guidelines, including those from the National Institute for Health and Clinical Excellence (which only states that ECG is recommended when a diagnosis of epilepsy is suspected)[2] and the AES/AAN.[144,145]

Neurologists treating patients with epilepsies have little information on the possible adverse effects of AEDs on cardiac conduction. A common practice is to refer those patients with a known or suspected cardiac or ECG abnormality to a cardiologist when the diagnosis of epilepsy is uncertain or when these 'vulnerable' patients need AED treatment, particularly with carbamazepine.

I find it difficult to draw any firm conclusions from the actual documentation for AEDs (old and new) on ECG changes and cardiac abnormalities; most are anecdotal, hypothetical (based on their mode of action), or based on animal data, case reports or series of case reports. The only relevant review, which just refers to carbamazepine and phenytoin, was published 10 years ago.[146] Even in RCTs, ECG methodology, assessment and results are often unclear. The best one can usually find is the observation that "ECG changes were not of clinical significance". The ECG and cardiac effects of AEDs in neonates and infants are even more difficult to assess. This is reflected even in the carbamazepine publications (the AED in which ECG/cardiac effects are most discussed) as cited by Saetre et al.[147] In one recent report purposely designed to compare effects of lamotrigine with carbamazepine in newly diagnosed elderly patients with epilepsy,[147,148] the main conclusion was that "clinically significant ECG changes are not common during treatment with either of these drugs in elderly patients with no pre-existing significant AV conduction defects" and that the ECG changes were minor and comparable in the two groups. Target maintenance doses were relatively low (400 mg/day for carbamazepine and 100 mg/day for lamotrigine). Nearly 20% of the patients' ECGs were "nonevaluable due to incomplete ECG data" despite the fact that "the highest quality ECG recording equipment had to be used, and that a repeat ECG could be obtained immediately if the quality of the recording was deemed inadequate".[148] No ECG results are reported in the final RCT report of this study.[148]

There is little information on the effect of AEDs in patients with cardiac co-morbidities or those also taking other medications or substances that affect the ECG (including alcohol). Indeed, such patients may be included in RCTs of AEDs and may affect the results one way or the other depending on how many are in the active drug and placebo groups. Another point is that the active drug may have a synergistic effect with other AEDs (such as carbamazepine), which may affect the ECG in add-on RCTs.

Most studies of the ECG/cardiac ADRs of AEDs point out those drugs that inhibit voltage-gated sodium channels, such as phenytoin, carbamazepine and lamotrigine. Also, particular attention has been drawn to drugs (including AEDs)[149] that inhibit the rapid component of the cardiac delayed rectifier potassium ion current (Ikr) expressed by the human hERG gene, because this may increase the risk of cardiac arrhythmia and SUDEP.[150–153] The IKr is also of major importance for embryonic cardiac repolarisation and therefore AEDs that affect the IKr may increase teratogenicity.[154]

Principles of management in women with epilepsies

In medicine, the differences between male and female extend beyond the reproductive hormones and organs. Certain diseases affect women exclusively or predominantly, and there can be significant differences between the sexes in the expression of the same medical problem, and in the response and adverse reactions to drugs.

The way in which epilepsies affect many aspects of a woman's life differs from how they affect men. Women are predisposed towards certain seizure disorders, and antiepileptic drugs (AEDs) can affect physical appearance, the menstrual cycle, contraception, fertility, pregnancy, the unborn baby and the menopause. There is a significant lack of knowledge about and even misunderstanding of many of these issues that are specific to women. These topics have been detailed by expert authors in *Epilepsies in girls and women* (2008), which I co-edited with Pamela Crawford and Torbjörn Tomson,[155] and in "*The XX factor. Treating Women with Antiepileptic Drugs*" by Jim Morrow.[156] This chapter deals only with the clinical implications and demands of AED treatment in women of childbearing age. These issues have also been addressed by a recent practice parameter of the American Academy of Neurology (AAN) and the American Epilepsy Society (AES), which is a three-part evidence-based review focusing on pregnancy in women with epilepsy,[157–159] by an Italian consensus conference on epilepsy and pregnancy, labour and the puerperium,[160] and by other excellent, recently published reviews.[161–178]

The decision to start AED treatment and the choice of AEDs in women with epilepsy requires careful assessment of individual risk in terms of both seizures and adverse (short- or long-term) drug reactions in the patient and her offspring. The main challenge is to offer her an accurate and holistic estimate of the individual risks. Stopping AED medication is equally challenging and often necessary, although it may involve risks of seizure recurrence. The ultimate decision should be taken by a well-informed patient.

Oral hormonal contraception and AEDs[179–181]

Many AEDs interact with oral hormonal contraception with two main consequences:

- contraceptive failure leading to an unplanned pregnancy
- deterioration of seizure control.

Effect of AEDs on oral hormonal contraception

The most commonly used current oral hormonal contraceptives contain 20–35 µg of ethinyloestradiol and less than 1 mg of progestogen. The major part of the oestrogen compound is hydroxylated to inactive metabolites by the hepatic CYP3A4 enzyme or directly conjugated. Hepatic enzyme inducers (see Table 7.6) accelerate hepatic elimination of oral hormonal contraception, which may lead to contraceptive failure. Intramenstrual bleeding is an indicator of contraceptive failure, but does not always occur. There is no substantial risk of contraceptive failure with AEDs other than the hepatic enzyme-inducing drugs.

Women taking hepatic enzyme-inducing AEDs who require contraception should be advised to use:

- high-dose preparations containing at least 50 µg or more of the oestrogen compound
- barrier or other methods of contraception.

Progesterone-only contraception is not an option, because of high failure rates.

During treatment with lamotrigine, the levonorgestrel (synthetic progestogen) component of the oral contraceptive is reduced by about 18%, but this interaction is considered to have no clinical significance; the pharmacokinetics of ethinyloestradiol are unaffected.

Effect of oral hormonal contraception on AEDs

The main AED affected by oral contraception is lamotrigine. Increased glucuronidation of lamotrigine, largely by the progestogen component of oral hormonal contraception, leads to increased elimination of lamotrigine and therefore a decrease in plasma levels of more than 50%. In the pill-free period, plasma lamotrigine levels increase rapidly by 25–50%, which may lead to seizure deterioration and toxicity (see page 181), but with minor, if any, risk of contraceptive failure. The effect of oral hormonal contraception on other currently used AEDs that undergo glucuronidation is probably of no clinical significance.

Pregnancy

The outlook for pregnant women with epilepsy and their offspring is excellent. The risks to mothers and their babies are small and often preventable. Overall, 95% of women with epilepsy have uncomplicated pregnancies and deliver normal babies. This rate can be significantly improved with proper management; any serious harm to the baby or mother, particularly if it is avoidable, is too much for the family that is affected.

AED treatment during pregnancy is considered necessary for most women with epilepsy, because uncontrolled maternal convulsive seizures pose a greater risk to the fetus than the use of AEDs and may also harm the mother.[161,182] It is also important to remember that the concentration of AEDs may change significantly during pregnancy and the puerperium resulting in an increase in seizures or toxicity.[183,184]

Prescribing AEDs for women with epilepsy may be influenced by marketing and publishing practices that are more likely to favour the newer AEDs.

Recent studies have not indicated any increased risk of obstetric complications in women with epilepsy.

Teratogenicity

It is generally accepted that AED treatment during the first trimester of pregnancy is associated with a small, but significant, increase in the risk of major congenital malformations (MCM) (Tables 7.14 and 7.15). The following statements are as close to reality as I could assess through an extensive review of the literature, which is often unclear. The risk of MCM is:

- probably no different or only slightly higher than the background rate (around 1–2%, see below) in women with epilepsy who are not taking AEDs
- probably less than twice the background rate with commonly used AEDs (other than valproate) as monotherapy, although the relative risk may vary with individual AEDs
- certainly increased with valproate monotherapy to 3–5 times the background rate
- likely to be high with topiramate, though the relevant studies are still inadequate
- certainly higher with polytherapy than monotherapy; valproate is a significant contributor to the high risk of MCM in polytherapy, particularly in combination with lamotrigine (10%)
- likely to be dose dependent, at least for valproate and lamotrigine (i.e. the higher the plasma AED concentration, the higher the relative risk of MCM).

Teratogenicity, teratogenesis and teratogenic (teras = monster) are terms that should be discouraged as inaccurate and derogatory. The expansion of this term to '*cognitive teratogenesis*' as adopted by the AAN/AES[158] is even more inappropriate.

The reported incidence of MCM varies significantly by around 20-fold, mainly because of methodological differences and deficiencies. Earlier studies usually rely on small numbers of recruited patients and lack statistical power. To understand the extent of the difficulties, a total of 722 drug-exposed pregnancies is needed to identify a seven-fold increase in the rate of occurrence of a specific abnormality, such as spina bifida, with a frequency of 1 in 1000[187] or if drug A has a 3% risk for MCM and drug B doubles the risk to 6%, then 750 patients on monotherapy are needed in each group to reach $p < 0.05$ at 80% power. Several large prospective pregnancy registries throughout the world are collecting data on AED-related MCM and other pregnancy-related outcomes in women with epilepsy.[163] However, even these registries have important methodological

differences in recruitment, ascertainment, inclusion/exclusion criteria, malformation classification and follow-up that may influence the results and prevent meaningful pooling of data.[177]

Useful clarification on pregnancy C and D categorisation of AEDs

Category D drugs are those drugs for which teratogenicity was seen in both animal and human pregnancies; phenytoin, carbamazepine and valproate are category D drugs. Category C drugs have demonstrated teratogenicity in animals, but the risk in humans is not known. However, this categorisation may be misleading if it is not understood that it is based on changing evidence and that most of the newer AEDs have not been assessed. For example, carbamazepine is a class D drug though the risk of MCM may be equal or less than that with lamotrigine or topiramate.

It may be too early to draw definite conclusions for the new-generation AEDs, all of which are classified as category C, with the exception of lamotrigine, which is downgraded to category D in Australia.[185] Also, with the exception of topiramate and vigabatrin, the newer AEDs do not appear to be teratogenic in animals when administered in subtoxic doses.[186]

Background rate of MCM is generally considered to be 1–2%, but reports vary. The Active Malformation Surveillance Program at Brigham and Women's Hospital in Boston, USA, estimates the background rate to be 1.6% after exclusion of genetic and chromosomal anomalies.[188] Some use the higher rate of 3.2%[189] determined by the Metropolitan Atlanta Congenital Defects Program,[190] but this population-based registry uses active case identification from multiple sources, undertakes direct chart review of potential cases and includes all malformations identified up to the age of 5 years.[191]

Commonly used older generation AEDs and major congenital malformations

Valproate is definitely associated with an elevated risk for MCM (tables 7.14 and 7.15), including a 10-fold increase in spina bifida aperta (1–2% of infants exposed). The risk is dose-related, particularly at doses of more than 1000 mg/day. Polytherapy with valproate and any other AED is highly teratogenic and appears to be even worse in combination with lamotrigine (1 of 10 infants exposed).[189,192] Considering that valproate is possibly also associated with cognitive impairment of infants exposed to this drug during pregnancy,[193] it should be avoided in women with epilepsy of childbearing age. This is not a setback for women with focal epilepsies as there are many other AEDs that are more effective and less teratogenic than valproate; valproate should never have been promoted as equivalent to carbamazepine for the treatment of women with focal seizures (see Chapter 15, page 484). The real problem is for women with generalised epilepsies such as JME in whom very few other AEDs are effective; alternatives are probably restricted to levetiracetam (most likely to be effective and less likely to be teratogenic) and lamotrigine (most popular but associated with

MCM rates after exposure to commonly used older AEDs[178]

AED	Range (%)	Mean ± SD (%)
Carbamazepine	1.4–11.4	4.9 ± 1.5
Phenobarbital	2.8–16.7	7.0 ± 4.2
Phenytoin	0.0–16.0	5.0 ± 3.0
Valproate	5.7–17.4	10.9 ± 3.9

Table 7.14

significant problems to be considered in women with epilepsy and worsening of myoclonic seizures). Some authorities also consider that small doses of valproate may be recommended in some women of childbearing age with uncontrolled primarily GTCS and JME.

Avoid entirely valproate polytherapy in any combination and particularly with lamotrigine. The risks are high and outweigh any benefits.

Carbamazepine is classified as a pregnancy category D drug, but recent evidence indicates that the rate of MCM is not a significant concern in relation to other AEDs (Tables 7.14 and 7.15).[158] Therefore, the previously emphasised[194] association of carbamazepine with a significant increase in spina bifida aperta (0.5%)has to be reassessed. Carbamazepine probably does not increase poor cognitive outcomes compared to unexposed controls.[158]

Phenobarbital and phenytoin are considered to have definite, but relatively low, teratogenicity in relation to valproate (Tables 7.14 and 7.15).[158] However, both drugs have also been implicated as possibly causing cognitive impairment in exposed infants,[158] though this was based on a few class II and III studies and has not been replicated in a more recent study (see cognitive teratogenesis below).[193] Nevertheless, phenytoin should be avoided in women with epilepsy, because of aesthetic and other ADRs.[194]

Clonazepam and clobazam. There is no evidence of a significant increase in teratogenicity in women with epilepsy receiving monotherapy with clonazepam or clobazam.[195–198]

Commonly used new generation of broad spectrum AEDs and major congenital malformations

The risks for MCM with most new generation AEDs have not been assessed. Based on existing evidence, the risks associated with three of the more widely used broad spectrum AEDs – lamotrigine, levetiracetam and topiramate (Table 7.15) – are as follows.

MCM in the UK Epilepsy and Pregnancy Register

	Number of women with epilepsy	MCM (%)	95% CI
No exposure to AEDs	445	2.2	1.2–4.1
Exposure to AEDs	5475	3.9	3.4–7.2
Monotherapy	4276	3.4	2.9–4.9
Polytherapy (> 130 AED combinations)	1199	5.8	4.6–7.2
Polytherapy with valproate*	451	8.6	6.4–11.6
Polytherapy with carbamazepine	526	4.9	3.4–7.1
Polytherapy with lamotrigine	644	5.3	3.8–7.3
Polytherapy with levetiracetam	229	3.9	2.1–7.3
Polytherapy with topiramate	162	8.6	5.2–14.0
Monotherapy with valproate	1097	5.8	4.5–7.4
Monotherapy with carbamazepine	1444	2.4	1.7–3.3
Monotherapy with lamotrigne	1524	2.4	1.7–3.3
Monotherapy with levetiracetam	177	0	0.0–2.3
Monotherapy with topiramate	92	4.8	1.9–7.6

Table 7.15 ***Polytherapy with valproate had a significantly higher rate of MCM (8.6%) than regimens without valproate (odds ratio 2.3; 95% CI 1.4–3.7). Monotherapy data updated to November 2009; all others are up to July 2009. Data courtesy of Dr Jim Morrow and the UK Epilepsy and Pregnancy Register.** For recent monotherapy data from the North American AED register (which do not differ significantly from those of the UK) please see http://www2.massgeneral.org/aed/newsletter/Winter2009newsletter.pdf.

Lamotrigine. Significant differences in the risk for MCM have been reported by two of the largest pregnancy registries, though the rate of MCM was similar (2.3–2.4%).[187,192,199] The UK Epilepsy and Pregnancy Register noted a positive dose-response relationship for MCMs with lamotrigine ($p = 0.006$) with a MCM rate of 5.4% (95% CI 3.3–8.7%) for total daily doses of more than 200 mg. This MCM rate was similar to that in those receiving valproate at a dose of 1000 mg or less (5.1%; 95% CI 3.5–7.3). While there was a trend towards lamotrigine being associated with fewer MCMs than valproate, the differences were minimised in those infants exposed to a dose of lamotrigine of more than 200 mg each day.[192] The North American AED pregnancy registry reported a 10.4-fold increase (95% CI 4.3–24.9) in isolated cleft palate or cleft lip deformity,[187] but this has not been confirmed in the UK[199] and the European Surveillance of Congenital Anomalies (EUROCAT) registers.[200]

The international lamotrigine pregnancy registry concluded that "the risk of all major birth defects after first trimester exposure to lamotrigine monotherapy (2.9%) was similar to that in the general population",[189] but this was considered to be an overestimate by other authorities, who suggested that a more accurate conclusion may be "the risk for major malformations associated with first trimester exposure to lamotrigine is only about twice that of the general population... when similar definitions, inclusions and case identification strategies are used".[191] Furthermore, it would be even more difficult to assess the risks of MCM with lamotrigine precisely without TDM, if the finding of a dose-related effect[192] is replicated, because of the significant decrease in plasma levels of lamotrigine (nearly by 50%) in the first trimester of pregnancy.

In polytherapy with lamotrigine and other AEDs, the risk of MCM is 5.3% (95% CI 3.8–7.3) (Table 7.15) and this doubles to around 10% in combination with valproate.[189,192]

Alarmingly, lamotrigine and valproate is the most frequently used AED combination in pregnancy according to the recent EURAP report,[201] despite the fact that it may harm 1 in 10 exposed babies. This is twice the frequency seen with any other combination and indicates a lack of information reaching those prescribing AEDs for women; the messages either do not get through or are unclear.

Lamotrigine has been downgraded to pregnancy category D by the Australian regulatory administration.[185]

Levetiracetam. The number of women treated with levetiracetam in pregnancy registries is still too small to draw definite conclusions, but the data from the UK Epilepsy and Pregnancy Register are very encouraging (Table 7.15).[202] Not a single MCM has been seen in the offspring of 133 women receiving levetiracetam monotherapy (95% CI 0.0–2.8) and the risk of MCM was relatively small (3.9%) in 229 women receiving polytherapy with levetiracetam and other AEDs (95% CI 2.1–7.3).

Topiramate. The use of topiramate in women of childbearing age is uncertain but in my assessment it should probably not be given to this group of patients unless absolutely necessary. This is because topiramate is (a) teratogenic in animals even at subtoxic doses (equivalent to 0.2–10 times the therapeutic doses recommended in humans)[186,203] and (b) has serious ADRs that are likely to affect the fetus, because of the extensive transplacental transfer of the drug. Preliminary results may indicate that such precautions are justified.[203,204] In the UK Epilepsy and Pregnancy Register (Table 7.15), the MCM rate in 79 women receiving topiramate monotherapy was 3.8% (95% CI 1.3–10.6) and in 162 women receiving polytherapy was 8.6% (95% CI 5.2–14). The rate of MCM was even higher (9.8%) in one report of 41 live births from 52 pregnancies during topiramate treatment (29 on monotherapy and and 23 on polytherapy);[203] this finding has, however, been undermined by statistical deficiencies.[205] However, animal studies are not certain predictors of human teratogenicity and the numbers of women studied are still small and need to be statistically verified in pregnancy registries. At the risk of being overcautious, it may be too dangerous to wait for the outcome in thousands of women receiving topiramate in order to validate the teratogenic potential of this drug.

Oxcarbazepine. There is practically no evidence of the teratogenic potential with oxcarbazepine, though preliminary results indicate that this may not be significant.[176] However, oxcarbazepine is associated with an increase in seizure frequency during pregnancy, probably because of the significant 26–38% decrease in levels of its active monohydroxy derivative.[206]

Clarifications and limitations of the AAN/AES report

The AAN/AES review is a laudable endeavour by leaders in the field to provide us with an evidence-based assessment of this important and difficult topic. However, such reports have significant limitations in clinical practice as detailed in "evidence based recommendations" (pages 190–193). In this occasion, the AAN/AES report has the following drawbacks:

(a) It is already outdated, because the assessed evidence was published from December 2005 through to February 2008. More recent evidence-based reports cited in this book have not been included, although some of them that contradict or reinforce the AAN/AES conclusions would probably require an Addendum. An example of this is detailed in the next page of the section "Post-natal cognitive effects of foetal exposure to AEDs."

(b) Evidence of "an increased risk of isolated oral clefts in infants born to mothers exposed to lamotrigine monotherapy in the first trimester of pregnancy" was not considered, despite the warnings from the manufacturer issued in April 2006, which prompted its degrading to category pregnancy D by the Australian authorities.[185] Nor did the report consider other data on levetiracetam and topiramate reviewed in this book.

The AAN/AES assessments of AED-related MCMs

The recent AAN/AES assessments made the following key conclusions.[158]

- AEDs taken during the first trimester probably increase the risk of MCMs in the offspring of women with epilepsy, but it cannot be determined if the increased risk is imparted by all AEDs, or only one or some AEDs.
- Valproate monotherapy during the first trimester possibly increases the risk of MCMs in the offspring of women with epilepsy.
- Valproate used in polytherapy probably increases the risk of MCMs in the offspring of women with epilepsy.
- Carbamazepine probably does not substantially increase the risk of MCMs in the offspring of women with epilepsy.
- There is insufficient evidence to determine whether lamotrigine or other specific AEDs increase the risk of MCMs in the offspring of women with epilepsy.

Foetal anticonvulsant syndrome and minor anomalies

Many reports associate intrauterine exposure to a specific AED with a cluster of foetal abnormalities constituting a specific foetal anticonvulsant syndrome (e.g. phenytoin, carbamazepine, valproate foetal anticonvulsant syndrome).[207] The foetal anticonvulsant syndrome manifests with various abnormalities including intrauterine growth retardation, MCM, cognitive and behavioural impairment, and a number of minor anomalies such as craniofacial dysmorphisms (hypertelorism, flat nasal ridge, low-set ears, microcephaly, short neck) and digital anomalies (hypoplasia of the distal phalanges or nails). Though some of these features are more prominent in association with one AED compared with another, it is now generally accepted that the separation of the various syndromes of embryo-foetal exposure to AEDs is not as clear-cut as previously thought; genetic factors contribute more than individual AEDs to the foetal anticonvulsant syndrome. Minor anomalies are difficult to evaluate prospectively and may occur in isolation from other features.

The finding that some MCMs occur more frequently following exposure to a specific AED also needs to be viewed in context. MCMs seen more frequently with valproate, such as neural tube defects, can also occur following exposure to other AEDs, demonstrating that this is not an AED-specific MCM.

Like other teratogens, AEDs produce a pattern of MCMs with overlap among the individual AEDs.[158]

Post-natal cognitive effects of foetal exposure to AEDs

There is significant uncertainty about the effect of epilepsy and AED therapy on cognition in children born to mothers with epilepsy.[178] In the conclusions of the AAN/AES practice parameter,[158] first, I am discouraged by the term 'cognitive teratogenesis', which is derogatory and inaccurate, and secondly, I, like others,[178] caution that their recommendations may not precisely represent the true dimension of this problem and its route (see blue box, page 209). By the nature of an evidence-based assessment, the AAN/AES conclusions come mainly from class II and III studies, the confounding factors have not been analysed, the recommendations are probable or possible, and older AEDs have mainly been examined although more should now be known about the newer AEDs with increasing numbers of mothers participating in the pregnancy registries. The influence of AEDs with a high rate of adverse cognitive impairment (e.g. topiramate)[119] may be of particular concern (see page 199).

In the AAN/AES practice parameter,[158] the outcome measure was an assessment of the child's intelligence quotient (IQ) at age 2 years or older. Because maternal IQ is an important influence on child IQ, studies were downgraded if they did not control for maternal IQ. It was also assumed that the cognitive risk was related to AED exposure throughout pregnancy and was not confined to the first trimester. The main conclusions of this AAN/AES report are:

1. Cognition is probably not reduced in children of women with epilepsy who are not exposed to AEDs in utero.
2. There is insufficient evidence to determine whether the children of women with epilepsy taking AEDs in general are at increased risk for reduced cognition.

- Cognitive outcomes are probably reduced in children exposed to AED polytherapy compared with monotherapy in utero.
- Carbamazepine probably does not increase poor cognitive outcomes compared with unexposed controls.
- Valproate is probably associated with poor cognitive outcomes compared with unexposed controls.
- Phenytoin is possibly associated with poor cognitive outcomes compared with unexposed controls (the results are, however, conflicting; see below[193]).
- Phenobarbital is possibly associated with poor cognitive outcomes in the male offspring of women with epilepsy compared with unexposed controls (the results are, however, conflicting; see below[193]).
- Cognitive outcomes are probably reduced in children exposed to valproate during pregnancy compared with carbamazepine and possibly phenytoin.

It is difficult to assess how severely cognition is impaired in these children, but the differences, though significant, may not be extreme. A recent interim report of a prospective, observational, multicentre study in the USA and UK detailed the cognitive outcomes in 309 children at 3 years of age.[193] Contrary to the conclusions of the AES/AAN practice parameters, there were no significant differences between children exposed to phenytoin (IQ 98), carbamazepine (IQ 99) or lamotrigine (IQ 101). However, valproate was associated with a significantly lower IQ (92). The association between valproate use and IQ was dose dependent. Children's IQs were significantly related to maternal IQs among children exposed to carbamazepine, lamotrigine or phenytoin, but not among those exposed to valproate.

Children with intrauterine exposure to high doses of valproate may suffer cognitive impairment, but it would be speculative to state anything further until prospective studies including the newer AEDs are carried out. Such studies also need to consider a significant number of confounding factors, including the occurrence of convulsive seizures that appear to cause cognitive impairment of the infant (see page 213).

Change in seizure frequency and status epilepticus during pregnancy

In most women with epilepsy, seizure frequency in pregnancy is similar to that before pregnancy. Existing findings do not suggest a great increase in the frequency of seizures or status epilepticus during pregnancy or an increased risk of seizure relapse during

Change in seizures during pregnancy. Analysis of data from five studies (n=537) described by the AAN/AES[159]

	Range (%)	Mean±SD
Seizures unchanged	54–80	69 ± 12
Seizures decreased	0.3–24	12 ± 7
Seizures increased	14–32	19 ± 7
Seizure-free rate in 948 women previously seizure-free for > 9 months	74–92	84 ± 8

Table 7.16

pregnancy for women who are seizure-free.[159] This is another compelling reason to strive for improvement and possibly seizure freedom in women with epilepsy who are planning pregnancy.[159]

Significant progress has been made in our understanding of the factors that may predict seizure deterioration or improvement, and recurrence or remission, though they have not been fully elucidated. In most patients (69%), epilepsy largely follows the same pattern as before pregnancy (Table 7.16).[159] Furthermore, most women (84%) who are seizure-free for at least 9 months before pregnancy do not experience any recurrences (Table 7.16). In the minority of women whose epilepsy changes during pregnancy, what happens in the various types of seizures (particularly GTCS, which are the most severe and may harm the unborn baby) and syndromes is largely unknown. Seizure frequency and severity may even vary between different pregnancies in the same patient. I have seen extreme cases of tremendous deterioration or improvement during pregnancy, as well as some exceptional cases in which GTCS occurred only during pregnancy.

Some studies indicate that changes are more likely to occur during the first and the third trimesters, and that seizure frequency tends to revert to pre-pregnancy levels after delivery. Using the first trimester as a reference, seizure control remains unchanged throughout pregnancy in 64% of women, 93% of whom are seizure-free during the entire pregnancy. For those with a change in seizure frequency, 17% have an increase and 16% a decrease in seizure frequency.[208] According to unconfirmed reports, seizure deterioration is higher in focal epilepsies than in generalised epilepsies.[209]

Status epilepticus. There is insufficient evidence to support or refute an increased risk of status epilepticus in pregnancy.[159] However, its prevalence is probably very low, ranging from 0–0.6%, which approximates to an annual prevalence of 0.5-1.6% for convulsive and non-convulsive status epilepticus in patients with various types of epilepsy.[210,211]

Seizure deterioration in pregnancy due to changes in plasma AED concentrations

Seizure deterioration in pregnancy can often be attributed to poor compliance, an inappropriate reduction in AED therapy either by the patient or her physician, a pregnancy-related fall in plasma drug concentrations, sleep deprivation, fatigue, hormonal changes or psychological factors. Patients often decide themselves to reduce or stop AED medication as a result of media concerns.

An important factor in seizure deterioration is inadequate plasma levels of AEDs either because of non-compliance (often compounded by vomiting) or, primarily, because of the multiple physiological changes occurring during pregnancy that influence drug disposition, including increased volume of distribution, increased renal elimination, altered hepatic enzyme activity, and a decline in plasma protein concentrations.[170,183] A decrease in plasma albumin and protein binding, and the displacement of AEDs

by endogenous compounds, lead to an alteration in the ratio of total to free drug, which is particularly important for highly protein-bound drugs.[183]

For many AEDs, significant increases in clearance and therefore decreases in plasma levels are characteristic during pregnancy.[157,170,209] There is documented evidence of significant increases in the clearance of lamotrigine and phenytoin during pregnancy. The clearance of phenobarbital, the active monohydroxy derivative of oxcarbazepine and levetiracetam also increases during pregnancy.[157,170,183,206]

Women taking lamotrigine have been best studied in this regard. The pronounced decline in plasma concentrations of lamotrigine during pregnancy has been shown to be associated with a deterioration in seizure frequency in more than 50% of patients, such that patients often require dose adjustments[172,212] or additional AEDs.[208] In the Australian pregnancy registry, the control of convulsive seizures was significantly worse with lamotrigine than with valproate (during the entire pregnancy) or carbamazepine (during the second and the third trimester).[212] Oxcarbazepine is the only other AED associated with poorer seizure control.[206,208] Focal epilepsy, polytherapy and oxcarbazepine monotherapy were independently associated with an increase in seizure frequency in the second and third trimester compared with the first trimester.[208] In the most recent report, 8 of 11 women experienced seizure deterioration during the pregnancy, five of whom had previously been seizure free. In seven women (about 50%), seizure frequency at least doubled during pregnancy, and there was a trend towards a correlation between seizure deterioration and the decrease in the plasma concentration of the monohydroxy derivative (MHD).[206]

The AAN/AES[157] has assessed the changes that occur during pregnancy for each AED, as follows:

Lamotrigine. Pregnancy probably increases the clearance and decreases plasma levels of lamotrigine during pregnancy. The decrease in plasma level is associated with an increase in seizure frequency (one class I and two class II studies).

Carbamazepine. Pregnancy probably causes a small decrease in plasma levels of carbamazepine: 9% in the second trimester and 12% in the third trimester (one class I study).

Phenytoin. Pregnancy probably causes an increase in the clearance and a decrease in plasma levels of phenytoin during pregnancy (one class I study).

Oxcarbazepine. Pregnancy possibly causes a decrease in the level of the active monohydroxy derivative of oxcarbazepine (two class III studies).

Levetiracetam. Pregnancy possibly causes a decrease in plasma levels of levetiracetam (one Class II study).

Phenobarbital, valproate, primidone and ethosuximide. Evidence of a change in clearance or plasma levels of phenobarbital, valproate, primidone or ethosuximide during pregnancy is insufficient to reach a conclusion.

Therapeutic drug monitoring *in pregnancy has* been formally recommended as invaluable in pregnant women with epilepsy because of the significant AEDs changes during pregnancy and the puerperium.[78,157,184,213]

This is particularly recommended for:

- lamotrigine, carbamazepine and phenytoin (level B evidence)[157]
- levetiracetam and oxcarbazepine (as monohydroxy derivative) (level C evidence)[157]
- highly protein-bound drugs; free drug concentrations should be measured for phenobarbital, phenytoin, carbamazepine, valproate and primidone.[157, 184,213]

Current published guidelines recommend that the ideal AED concentration should be established for each patient before conception and that monitoring of AED concentrations should be performed during each trimester and in the last month of pregnancy.[78] Some authors recommend at least monthly monitoring of AED concentrations, especially for lamotrigine.[172]

Clinical context of TDM: There is significant evidence to support active monitoring of AED levels during pregnancy. This is especially true for lamotrigine and oxcarbazepine, as changes in levels were associated with an increase in seizure frequency.[206,212] In pueprerium, there is an increase risk of toxicity if levels of certain AEDs had been adjusted during pregnancy but not

after delivery (see page 181).Unfortunately, there are no clear data on the timing of the return to the pre-pregnancy pharmacokinetic state post-partum. One study[214] demonstrated that an empiric post-partum taper schedule of lamotrigine reduced the occurrence of post-partum toxicity, but more systematic information is needed for all AEDs regarding their pharmacokinetic alterations in order to determine the management of AED dosing in the post-partum period.[157]

TDM should be individualised for each patient with the aim of maintaining a level at which seizure control was good. It is expected that such TDM in pregnancy and purperium will improve seizure control but this is not tested.[157]

Excesses or undue reliance on TDM outside their clinical context is discouraged. (See the section on TDM on page 193.)

Effect of seizures on mother and the unborn baby

GTCS may cause severe harm to both mother and her unborn baby, but may be preventable with appropriate management.

The harmful effects of seizures, and particularly GTCS, are multiple, and may be severe or even fatal, and may be accidental (falls, drowning) or non-accidental (aspiration, pulmonary oedema, cardiac arrhythmias, cardiac asystole). Furthermore, the risk of sudden unexplained death in epilepsy (SUDEP) is significantly higher in patients with GTCS than in patients with other types of seizure. Pregnancy is a particularly vulnerable period, both for the woman and her unborn baby. In pregnancy, a GTCS imposes an increased risk of damage or death to the mother and her unborn baby. Other types of seizure that may be harmful are those associated with autonomic disturbances and cardiac asystole. The consequences of convulsive status epilepticus are much worse than those of brief seizures. A study in the UK found that the odds for maternal death were approximately 10 times higher for women with epilepsy than for the general population.[215] Case histories have suggested that these extra deaths were due to GTCS that occurred mainly after stopping AEDs or poor compliance (but this is not certain as the case histories were often incomplete).[215]

The harmful effects of seizures on the unborn baby also arise from accidental injury, or the hypoxic and other effects of the seizure on the mother or directly on the fetus (e.g. lactic acidosis, bradycardia). Foetal fatalities may rarely occur during status epilepticus; only one foetus died in 12 pregnancies of women with convulsive status epilepticus, but fortunately with no maternal mortality.[208] The number of stillbirths is not increased among women who are adequately treated for epilepsy during pregnancy.

Seizures during pregnancy are not linked to an increased risk for anatomical malformations in the infant, though one report found a 12.3% malformation rate in women experiencing seizures during the first trimester compared with 4% in women who did not (details and other citations in reference 216). However, maternal GTCS during pregnancy are associated with cognitive deficits,[182] which is another important reason for providing adequate AED treatment.

Labour and delivery. The risk of seizures is particularly high during labour and delivery, and the risk is higher in those who had seizures earlier in pregnancy;[209] 1–2% of women will have a GTCS during labour and a further 1–2% will have a GTCS within the next 24 hours. Women at risk of seizures should be managed in specialised obstetric units with facilities for maternal and neonatal resuscitation.

Obstetric and other pregnancy-related complications

Obstetric and other pregnancy-related complications in women with epilepsy are few and probably not significantly different from those in a control population.[159] For women taking AEDs, there is probably no substantially increased risk (>2 times expected) of caesarean delivery or late pregnancy bleeding, and probably no moderately increased risk (>1.5 times expected) of premature contractions or premature labour and delivery. There is possibly a substantially increased risk of premature contractions and premature labour and delivery during pregnancy for women who smoke. There is insufficient evidence to support or refute an increase

in the risk for pre-eclampsia, pregnancy-related hypertension or spontaneous abortion.[159]

Adverse perinatal outcomes

According to the AAN/AES evidence-based review,[159] neonates of women taking AEDs:

- probably have an increased risk of being small for gestational age (defined as birth weight below the tenth percentile for the study population when adjusted for gestational age and gender) of about twice the expected rate
- possibly have an increased risk of 1-minute Apgar scores below of about twice the expected rate.

There is probably no substantially increased risk of perinatal death in neonates born to women with epilepsy. For other perinatal outcomes, such as respiratory distress, intrauterine growth retardation and admission to a neonatal intensive care unit, data were inadequate to draw conclusions.

The infants of women taking enzyme-inducing AEDs are at potential but probably small risk for haemorrhagic disease.[159] It has therefore been recommended that the mother takes oral phytomenadione (vitamin K1) 10–20 mg/day for at least 1 month before delivery and/or that the infant receives vitamin K1 0.5–1 mg intramuscularly at birth. However, there is no consensus amongst guidelines and recommendations on these matters and the risks involved.

Folic acid supplementation for the prevention of major congenital malformations

Low folate levels are associated with an increased risk of spontaneous abortion and MCMs, including neural tube defects, which is why official health guidelines recommend folic acid supplementation for all women in the general population who might become pregnant. This may prevent neural tube defects in the 72% of women at high risk of giving birth to children with such abnormalities. Whether folic acid supplementation would also reduce AED-related MCM in children of women who are taking AEDs, some of which may have folic acid-antagonist properties, is debatable.[157,217] The AAN/AES assessed that the risk of AED-related MCMs in the offspring of women with epilepsy is possibly reduced by folic acid supplementation and recommended that, although there are still insufficient data, "there is no evidence of harm and no reason to suspect that it would not be effective in this group".[157]

> The current recommendation is that all women of childbearing potential, with or without epilepsy, should take a folic acid supplement of at least 0.4 mg/day (higher doses have also been recommended) before conception (usually starting from when they stop contraception) and during at least the first trimester of pregnancy (until the end of the 12th week of pregnancy).

Foods with high folic acid content include green leafy vegetables (e.g. spinach and spring greens), broccoli, fortified breakfast cereals and brown rice.

For women on AEDs, some authorities recommend bigger doses of folic acid. However, a recent class 1 study of the UK Epilepsy and Pregnancy register found no statistical differences in either MCM or neural tube defects between women with epilepsy who received folic acid before conception and those who did not.[217] The authors concluded that the increased risk of MCM in women taking AEDs probably occurs through mechanisms other than folic acid metabolism.[217]

Breastfeeding and AEDs

> Breastfeeding is the ideal way of providing young infants with the nutrients they need for healthy growth and development. Virtually all mothers can breastfeed, provided they have accurate information, and the support of their family and the healthcare system. Colostrum, the yellowish, sticky breast milk produced at the end of pregnancy, is recommended as the perfect food for the newborn, and feeding should be initiated within the first hour after birth. Exclusive breastfeeding is recommended up to 6 months of age.
>
> World Health Organization (WHO)

These WHO recommendations also apply to women with epilepsy who are not taking AEDs. However, for women taking AEDs, the usual advice is that "the benefits of breastfeeding must be weighed against the potential risks of exposing the infant to medications". So how can this balance between benefit and risk

be assessed, and how can a physician be certain about the advice to give the mother with so many unknowns? There is no way to determine whether indirect exposure to maternally ingested AEDs has symptomatic effects on the newborn, as there are no controlled studies comparing the newborns of women taking AEDs with those of women not taking AEDs. A drug that is safe for use during pregnancy may not be safe for the nursing infant.[157]

Most AEDs pass into breast milk and some do so in significant quantities (Table 7.17). Medications that are highly protein bound, that have large molecular weights or that are poorly lipid-soluble do not tend to enter the breast milk in clinically important quantities. However, it is clinically important to appreciate that, in the early post-partum period, large gaps between the mammary alveolar cells allow many medications to pass through this milk that may not be able to enter mature milk; these gaps close by the second week of lactation.

The nursing infant's drug exposure depends on the concentration of the drug in the breast milk and the amount of breast milk consumed by the infant. The pharmacological activity of the medication depends on its absorption, distribution, metabolism and elimination, which may differ in the newborn from that in children and adults, and can also vary with different drugs.[218] It is for these reasons that the amount of AED in the breast milk is not always proportional to the *infant/maternal plasma concentration* (Table 7.17). For example, though the concentration of phenobarbital in the maternal milk is 30–50% of that in the maternal plasma, plasma levels in the infant are high (Table 7.17); the converse is true for levetiracetam. A single dose of phenobarbital may persist for days in an infant, because of the slow rate of barbiturate metabolism in this age group, and may cause lethargy, sleepiness or irritability and agitation. On the other hand, an infant who is not breast fed, but whose mother was taking phenobarbital during pregnancy, may experience withdrawal symptoms. Furthermore, repeated administration of a drug such as lamotrigine via breast milk may lead to accumulation in the infant.[219] Probably any drug whose concentration in breast milk is close to 100% that in the maternal plasma can be problematic; however, further data are needed to confirm this.

There is no threshold level of passive exposure to AEDs that has been established to impart a clinically important risk to the fetus or neonate. The panel of the AAN/AES stipulated that an AED transfer rate of 0.6 (neonatal:maternal plasma concentration ratio or a milk:maternal concentration ratio) was potentially clinically important, together with any trend of increasing plasma concentrations in the neonate by 25% over the evaluation period (generally 3 days up to 1 month).[157]

Table 7.18 lists AEDs according to whether or not they are considered appropriate for breastfeeding by the WHO and the American Academy of Paediatrics. However, even these recommendations may be debated. For example, many authorities warn of the potential for fatal hepatotoxicity with valproate in children under 2 years of age.

Breastfeeding may be particularly problematic in

- premature or otherwise compromised infants that may require altered dosing to avoid drug accumulation and toxicity[220]
- infants of women receiving AED polytherapy.

Useful note

- The infant's AED exposure can be limited by avoiding breastfeeding during periods of peak maternal plasma drug concentration.
- A breastfeeding mother should never stop her medication abruptly, as she may have seizures and the baby may experience drug withdrawal.
- Signs of AED withdrawal in the baby include increased irritability, insomnia, sweating and seizures.

Principles of AED therapy in women of childbearing age in clinical practice

Finding the balance between optimal therapy to control seizures and the avoidance of adverse effects or other harm to the woman and her offspring is the crux of proper management. Women should be made fully aware of all aspects of AED treatment and be able to make informed

AED placental transfer, and amounts in the maternal milk and the infant

AED	
Placental transfer[157]	
Probably potentially clinically important amounts	Carbamazepine, levetiracetam, phenobarbital, phenytoin, primidone, and valproate
Possibly potentially clinically important amounts	Gabapentin, lamotrigine, oxcarbazepine and topiramate
Amounts in maternal milk in relation to plasma levels[218]	
Levels higher or approaching maternal plasma level	Ethosuximide, gabapentin, levetiracetam, topiramate, and zonisamide
Levels 50–80% of maternal plasma level	Lamotrigine, primidone and oxcarbazepine
Levels < 50% of maternal plasma level	Carbamazepine, phenobarbital, phenytoin and valproate
Plasma levels in breastfed infant[218]	
< 20% of maternal levels	Carbamazepine, gabapentin, levetiracetam, oxcarbazepine, phenytoin, topiramate and valproate
> 50% of maternal levels	Ethosuximide and phenobarbital
20–50% of maternal levels	Lamotrigine

Table 7.17

Recommendations on AEDs for breastfeeding women*

Recommendation	AED
Yes	Carbamazepine, ethosuximide, phenytoin and valproate
Yes with caution	Clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin
No	Felbamate
No consensus	Phenobarbital

Table 7.18 *Based on information from Johannessen and Tomson (2008)[218]

decisions. Ultimately, the patient is the decision-maker and the physician the provider of information.

The basic principles of AED treatment in all patients, as described on pages 173–184, also apply to women, but priority should be given to AEDs that are most likely to control seizures and less likely to adversely interfere with the particular needs of women of childbearing age. Efforts should be made to avoid AEDs that may be harmful to women and their offspring. All aspects of the management of epilepsy and the implications for contraception and pregnancy should be thoroughly discussed with the patient, who should also preferably be provided with written information.

Commencing AED therapy in women of childbearing age with newly diagnosed focal epilepsy

AEDs for monotherapy in focal epilepsies are listed in Table 15.3, which also indicates those drugs that do not interact with hormonal contraception. Additional

information regarding teratogenic potential is given in Tables 7.14 and 7.15. It may be easier to first exclude AEDs that score worse than others in the list in Table 15.3. These are:

Valproate is first in the list of unwanted AEDs in women with focal epilepsies for two reasons. Firstly, it poses significant risks in pregnancy, leads to weight gain and has hormonal effects. Secondly, valproate is not as effective as other AEDs in focal seizures of any type. European epileptologists, including myself, were using valproate effectively as the superior AED for generalised epilepsies; we were not recommending it as a first line option in focal epilepsies, for which carbamazepine was preferred. Unfortunately, this clinical practice was spoiled by subsequent 'evidence-based' reports and meta-analyses that found valproate to be "as effective as carbamazepine" particularly in the UK. This resulted in the widespread use of valproate with detrimental effects at least in those women with focal epilepsy that were treated with the drug (see page 484).

Phenytoin has numerous ADRs and mainly aesthetic changes, such as gingival hyperplasia, hirsutism and dysmorphia. It is an enzyme inducer and it has been implicated in the so-called 'foetal phenytoin syndrome' (though this is now under examination).

Phenobarbital is scarcely used today in industrialised countries, mainly because of its sedative effects. It is less teratogenic than valproate and it is still a useful AED in countries with poor resources.

Gabapentin is of very low efficacy, is associated with weight gain and has still unexplored effects in pregnancy.

Topiramate has high efficacy, but is seriously hindered by numerous ADRs that may also affect the foetus and the newborn of women with epilepsy.

Therefore, the first choice in the treatment of women with focal seizures is between carbamazepine, lamotrigine, levetiracetam and oxcarbazepine.

Carbamazepine still remains one of the most effective AEDs and appears to be relatively safe for women. It is an enzyme inducer, but its reputation as a pregnancy category D drug has been partly restored in recent evidence-based studies (Table 7.15).

Oxcarbazepine is still difficult to assess precisely and to ascertain whether it is better than carbamazepine as initially promoted. Its decrease plasma concentration during pregnancy has been associated with seizure deterioration (see page 212).

Lamotrigine has been extensively promoted as the most women-friendly AED and the number of prescriptions for women is rising (see page 208). However, recent evidence indicates that its use is associated with significant problems, including interactions with hormonal contraception and pregnancy that may cause an increase of seizures or toxicity, and its teratogenic potential has not been yet elucidated, with some class 1 and 2 studies reporting a dose-related effect on MCM (for further details see page 205).[176] Adjunctive treatment with lamotrigine and valproate is one of the most teratogenic combinations.

Levetiracetam is more effective than lamotrigine and class 1 studies indicate that it has very low teratogenic potential (Table 7.15), but this needs to be replicated when a larger number of women are recruited in the pregnancy registries. It is unknown whether its reduced plasma concentration during pregnancy is of clinical significance (i.e. whether levetiracetam, like lamotrigine and oxcarbazepine, may be associated with seizure deterioration in women during pregnancy).

Commencing AED therapy in women of childbearing age with newly diagnosed generalised epilepsy

Valproate is unequivocally the most effective AED in generalised epilepsies, so what is the best option for women of childbearing age for whom valproate is now practically impossible to prescribe? In the past, and before the introduction of newer broad-spectrum AEDs, when valproate was the only option for the treatment of generalised epilepsies, we used to inform the patient thoroughly about the pros (best option for protection against generalised seizures) and cons (worse option with regard to teratogenicity and spina bifida) of this drug. We now have the advantage of having lamotrigine and levetiracetam as other options, but we have to detail the pros and cons of each. Lamotrigine is not as innocuous in women as we initially thought; GTCS may

worsen during pregnancy in women on this drug and it often aggravates myoclonic jerks (see Pharmacopoeia, page 582). Currently, levetiracetam appears to be the best substitute for valproate in the treatment of women with generalised epilepsies, though the verdict is still open.

Preconception

The preconception period is important to establish optimal seizure control with the most appropriate pregnancy-friendly AED.

Optimisation of AED therapy involves:

(a) re-evaluation of the diagnosis using the same steps listed on pages 5–10: are the paroxysmal events epileptic; what type of seizures are they; what causes them; and which epileptic syndrome is it?

(b) assessment of the frequency and severity of seizures before and after AED therapy, as well as possible precipitating factors and circadian distribution

(c) recording the course and outcome of previous pregnancies if there were any

(d) consideration of whether current AED therapy is optimal for the patient and the infant, or whether changes are needed, which is probably the case in the women taking valproate and/or polytherapy.

Some women are determined to avoid any AED-induced risks to their babies and stop taking their medication from the time that they prepare to conceive. Withdrawal of AED before pregnancy might be considered if the woman:

- is free of seizures for more than 2 years, though relapse is possible particularly in syndromes such as JME, which often relapse on AED withdrawal
- does not have GTCS or seizures that may result in injury, though these may appear in well-controlled syndromes after AED withdrawal
- the potential consequences of seizure recurrence is thoroughly informed of.

For women in whom seizures are controlled by monotherapy with any AED other than valproate, there is probably no need for any change. The worse possible scenario for the physician is having to make appropriate decisions for women with generalised epilepsies who are controlled on valproate. This is because of the uncertainties with regard to possible relapses that may occur when another AED is substituted, which may not be a problem for women with focal epilepsies as explained above. In generalised epilepsies, the attempt to switch to levetiracetam (or as a second option to lamotrigine) should be made with caution, because of the possibility of seizure recurrence, particularly with lamotrigine. Women with JME should be informed that lamotrigine is not as effective as valproate and levetiracetam and also carries an increased risk of aggravating myoclonic seizures. If valproate is to be maintained, attempts should be made to reduce it to a minimal dosage, possibly divided into 3–4 daily doses.

Women who are controlled on AED polytherapy should, if possible, be converted to monotherapy or to two AEDs by slowly withdrawing the AEDs that are undesirable in women. Again the patient should be warned of the possibility of relapse.

For women who are not controlled on AEDs, the situation is exactly the same as for any other patient who seeks control of seizures, but women-friendly AEDs should be given priority.

Folic acid should be prescribed before and throughout the first trimester (see page 214).

It is common for women to become pregnant while taking AEDs without preconception advice.

The role of the physician is to assess the situation regarding seizures and ADRs, inform the patient and request appropriate tests for the mother and foetus. The possible teratogenic effect of AEDs has been exerted by the end of the first trimester, but cognitive or other effects on the fetus may occur throughout the pregnancy.

Any changes to AED treatment should be made before conception.

Follow-up of women with epilepsy during pregnancy and after delivery should be meticulous and requires good communication between the treating physician, the obstetrician and midwife in

addition to expert prenatal screening and TDM of AEDs that are affected by pregnancy and carry the possibility of seizure relapse, such as lamotrigine and oxcarbazepine. Almost all neural tube defects can be detected by week 20 using high resolution ultrasonography. Routine screening for α-fetoprotein in amniotic fluid probably provides little additional value.[221] Most of the other MCM can also be diagnosed by ultrasonography, but their severity is difficult to assess prenatally.

Women with epileptic seizures should be reassured that they can have happy families with healthy children like any other woman. Their pregnancies may carry some definite risks, but these are small and can be minimised through proper management before, during and after pregnancy.

Principles of management in the elderly with epileptic seizures

In the last decade, increasing attention has been paid to improving the management of the elderly with epileptic seizures,who have many unmet needs. [222–226]

(a) The global elderly population is constantly increasing and the average life expectancy is 78–82 years in the USA, European Union, Japan and Australia (with women living 2–3 years longer than men); one-tenth of the world population is over the age of 60 years.
(b) The prevalence and incidence of epilepsy increases sharply in this population (Figure 1.4)[225] and epilepsy is the third most common neurological condition after cerebrovascular disease and dementia.
(c) Diagnosis is challenging, because co-morbid disorders may imitate epilepsy.
(d) When choosing an AED, it is important to consider the significant pharmacokinetic changes that occur in the elderly as well as co-medications for other co-morbidities.
(e) The elderly are particularly vulnerable to ADRs of AEDs, which are often poorly communicated and assessed.

The proceedings of an expert International Geriatric Epilepsy Symposium were recently published in a supplement of *Epilepsy Research* (2006).[227]

The increase in the incidence and prevalence of epileptic seizures in the elderly is due to co-morbid disorders. Cerebrovasular disease prevails, (30–40%) followed by metabolic disturbances, trauma, central nervous system infections, space-occupying lesions and others.[225] Acute (provoked, occasional) symptomatic seizures are common (see pages 40–41). Conversely, elderly patients with pre-existing epilepsy often experience an improvement in or remission of seizures, as for example with many IGEs such as JME.

Focal seizures are the predominant or exclusive seizure type with or without secondarily GTCS in the elderly. Extratemporal focal seizures are more common than in younger patients. GTCS are also predominantly of focal onset.

Difficulties in diagnosing epileptic seizures in the elderly

Epileptic seizures are often unrecognised or mistaken for non-epileptic paroxysmal events in the elderly.[226] Their manifestations commonly mimic the symptoms of cerebrovascular disease or are considered 'natural' phenomena associated with the ageing process. An epileptic fall, for example, is more likely to be attributed to cerebral ischaemia, loss of balance or be accidental. An epileptic complex focal seizure with impairment

of consciousness is more likely to be considered cerebrovascular or an event of an age-related memory deficit. The diagnostic difficulties are even greater when the patient also has symptoms of cerebrovacular disease, dementia or cardiac problems.

Social isolation, lack of witnesses and the difficulty or inability of the elderly to describe their symptoms are factors that are compounded in the misdiagnosis of epileptic seizures in the elderly.

Frequency of seizures and their severity in the elderly

It is generally accepted that seizures in the elderly are usually infrequent and easily controlled with AEDs, which is also my experience. This view has been validated in a recent study of newly diagnosed elderly patients with epilepsy, which showed that 84% of patients achieved seizure freedom with proper management and that this was statistically significant when compared with newly diagnosed younger populations ($p < 0.001$).[228] Further, in RCTs a patient with a "minimum of one seizure (>60% with two or more seizures) during the 3 months preceding enrolment is considered representative of patients with new-onset geriatric epilepsy".[44]

The majority of focal seizures may not be severe, but the effect of convulsive seizures when they occur in an already vulnerable and sometimes disabled elderly individual may be devastating. Post-ictal confusion may be particularly severe and lengthy (lasting for days) compared with that in younger individuals. The prevalence of status epilepticus is almost twice that in the general population and the mortality (38–50%) is the highest of any age group.[223] Convulsive status epilepticus commonly manifests in the acute state of a cerebral insult (see acute symptomatic seizures). Focal symptomatic non-convulsive status epilepticus and less commonly absence status epilepticus are widely misdiagnosed in any age group, but probably more so in the elderly even if it is protracted for days.[229] Absence status epilepticus in the elderly mainly occurs de novo after benzodiazepine withdrawal.[230]

EEG and other investigative procedures in the elderly

Requests for investigative procedures in the elderly should be limited to those that are absolutely necessary. Otherwise, the patient may suffer unnecessary discomfort. False-positive EEG and brain MRI results are common.

Elderly patients require the same care and diagnostic precision as younger people. Therefore, the diagnostic procedures are universally the same. However, considering that the elderly are often fragile, diagnostic procedures should be limited to those that are absolutely necessary.

Useful clinical advice

The overenthusiastic approach – "Let us do this test as well not to miss that remote possibility" – is discouraged, particularly as 'this test' may be invasive, extremely unpleasant and intolerable to an elderly person in addition to the extra burden of transport from home to the hospital.

Diagnosis should mainly rely on clinical assessment. Blood tests often identify problems such as metabolic or drug-induced toxicity without the need for further tests.

EEG and brain imaging, the two main investigative procedures in the epilepsies, are significantly affected by age and therefore false-positive results are high in the elderly. EEG background abnormalities are common in the elderly and this is the rule rather than exception, particularly in those with cerebrovasular disease and dementia, and those taking psychotropic drugs. Sharp waves and other paroxysmal or focal abnormalities are not of the same diagnostic significance as in younger populations. It is because of all these factors that my EEG reports for an elderly person referred for possible epileptic seizures include the following comment:

"The EEG is abnormal. However, the reason for this and its clinical significance are uncertain. It cannot be taken as evidence for or against epileptic seizures. Such EEG abnormalities in patients of this age are common. Conversely, elderly patients with definite epileptic seizures

may not have the classical spikes or other EEG markers of epileptogenicity that we assess in younger people."

However, rarely EEG may capture ictal events and EEG is of the utmost importance in patients with suspected non-convulsive status epilepticus.

Physiological and other changes in the elderly that may affect AEDs

AED pharmacokinetics may be affected in the elderly, because ageing is associated with significant physiological and other changes.[78,222,231]

(a) Bioavailability may be reduced because of a decline in the ability to absorb the drug; this may particularly affect gabapentin.
(b) Free fractions of protein-bound AEDs may increase significantly (which may not show in TDM) and cause toxicity.
(c) Plasma levels of enzyme-inducing AEDs (Table 7.6) may increase significantly and the elimination half-life may be prolonged because of the declining efficiency of the P450 system, decreasing liver volume and slowing of blood flow. Hepatic glucoronidation is less affected.
(d) For most AEDs that are metabolised and excreted by the kidneys, the clearance of unbound drug is decreased by an average of 20–40% in the elderly.[231]
(e) Plasma levels of AEDs that are primarily excreted in the urine (Table 7.8) may increase significantly because of declining renal function and lower glomerular filtration rate.

The elderly usually have a narrower therapeutic window; that is, the maximum tolerated AED concentration is closer to the lowest therapeutic concentration.[232]

Principles of AED treatment in the elderly

AED treatment of the elderly is significantly different than that of younger adult patients. Elderly patients are more likely to suffer from drug-induced disease than to derive any benefits from ill-advised AED prescribing.

Seizures are predominantly focal with or without secondarily GTCS. Therefore, the choice is between AEDs listed in Tables 7.19 and 15.3 that are licensed for the treatment of focal epilepsies in adults and the elderly. Broad-spectrum AEDs are needed for the few cases of elderly patients with generalised or a mixed type of seizures.

Elderly patients respond well to lower doses and they are particularly sensitive to ADRs. Co-morbidity and co-medication is prominent. Therefore, 'start very low and go very slow' and other procedures of titration detailed in the useful clinical notes (see page 186) are particularly valuable in the AED treatment of the elderly. Small doses, usually half the recommended initial and maintenance dose for adults, may often be therapeutic. ADRs that are common, often severe and underdiagnosed or misdiagnosed may be avoidable by selecting the right AED (Table 7.19) and using very small doses.

Excellent pharmacokinetics, minimal interactions with other drugs and negligible ADRs are the optimal factors in choosing an AED for the elderly (Table 7.19). An ability to achieve a therapeutic effect without titration, parenteral formulations and ease of swallowing are also desirable attributes.[234]

Polypharmacy is discouraged because ADRs and drug–drug interactions are more likely than true seizure benefit. Patients starting treatment two or more years after their first seizure are less likely to achieve seizure control than patients in whom treatment was initiated earlier.[228]

In RCTs in adults (including a variable number of the elderly), all AEDs licensed for monotherapy for focal epilepsy (Table 7.19 and 15.3) have shown approximately equal efficacy (see page 191). In the elderly, there is a paucity of class I and class II RCTs.[44,235] Only gabapentin[236] and lamotrigine[233,236,237] have been adequately tested in face-to-face comparisons with carbamazepine. Although these drugs had similar efficacy, carbamazepine was less well tolerated. Whether the results would be different at different doses, different titration scheme and different methodology is the usual question in these RCTs (see page 190).

Significant clinical note

The key recommendation in the treatment of the elderly is to avoid AEDs with:

- ADRs that may cause more harm (cognitive impairment, confusion, fractures, falls, cardiac abnormalities, ataxia, allergies) than good (seizure improvement is often achieved with small doses of relatively ADR-free AEDs)
- drug–drug interactions (such as with enzyme-inducers) that may adversely affect concomitant medications and vice versa

Small doses, usually half the recommended initial and maintenance dose for adults, may often be therapeutic.

Little information is available on the use and the effect of AEDs in elderly who have co-morbid cardiological disorders (see page 200).

AEDs licensed for monotherapy in focal seizures with and without secondarily GTCSs: comparison of priorities that are important in the treatment of elderly with epilepsy*

	Tolerability	Pharmaco-kinetics (% of perfect score)†	Significant drug–drug interactions	Titration	Need for laboratory tests ‡	Parenteral formulation
Carbamazepine	Medium	Inferior (50)	Yes	Slow	Maximal (1 and 2)	No
Lamotrigine	Excellent	Moderate (73)	Yes	Very slow	Maximal (1 and 2)	No
Levetiracetam	Excellent	Superior (96)	Not clinically significant	Fast	Minimal	Yes
Gabapentin	Excellent	Superior (89)	Not clinically significant	Fast	Minimal	No
Oxcarbazepine	Medium	Moderate (77)	Yes	Slow	Maximal (1 and 2)	No
Phenobarbital	Poor	Inferior (57)	Yes	Slow	Maximal (1 and 2)	Yes
Phenytoin	Poor	Inferior (50)	Yes	Slow	Maximal (1 and 2)	Yes
Topiramate	Poor	Moderate (79)	Yes	Very slow	Maximal (1 and 2)	No
Valproate	Poor	Inferior (52)	Yes	Slow	Maximal (1)	Yes

Table 7.19 Desirable properties are in red. *All AEDs in this table are lisenced for elderly patients in monotherapy of focal seizures. In RCTs, none of the newer AEDs showed better efficacy than carbamazepine but they were better tolerated; gabapentin has shown worse efficacy in clinical practice. For more information, see summary of product characteristics and Table 7.2. For other details and citations see Table 15.3. †The % of perfect score is based on a customised rating system of 16 parameters to evaluate the pharmacokinetic profile of AEDs developed by Patsalos.[233] ‡ (1) Monitoring for adverse drug reactions; (2) therapeutic drug monitoring.

Surgery for epilepsies

The surgical treatment of drug-resistant epilepsy has become increasingly more valuable and often life-saving due to major advances in structural and functional neuroimaging, EEG monitoring and surgical techniques. The outcome from current surgical methods has improved dramatically.[238–240] Paediatric surgical outcomes have become similar to those reported for adults.[241,242]

Early surgical intervention, when successful, might also prevent or reverse the disabling psychosocial consequences of uncontrolled seizures during critical periods of development.

Despite this progress, surgery in epilepsies is underused and referrals are often delayed or not made.[238,243] The reasons for this delay include the fears of the patients and physicians about surgery and undue reliance on newer AEDs and vagus nerve stimulation (VNS) in patients who had failed to respond to appropriate medical treatment for years.

The applications and outcomes of surgical interventions in certain types of intractable seizures and epileptic syndromes are detailed in the relevant chapters of this book. This section refers to general aspects of surgery in epilepsies. This topic has recently been covered in over 300 pages in one of the best books on the treatment of epilepsies – *The Treatment of Epilepsy*.[244]

Surgical treatment for epilepsy need not be a last resort.

Often, successful surgery, particularly in children, is too late to reverse the crippling psychological and social consequences of repeated epileptic seizures during developmental ages that are critical for the acquisition of interpersonal and vocational skills. These patients, even if they remain seizure-free, are permanently disabled.[238]

A new classification of outcome with respect to epileptic seizures following epilepsy surgery has been issued by the ILAE Commission.[245] More recently, the ILAE Subcommission for Paediatric Epilepsy Surgery has published a consensus statement on the unique features of paediatric epilepsy patients that justifies dedicated resources and specialty paediatric surgical centres; guidelines for physicians for when to initiate the referral process for children with refractory epilepsy; and recommendations on presurgical evaluation and post-operative assessments.[242]

Criteria for surgical referral

A candidate for epilepsy surgery must:

- have failed to attain adequate seizure control with adequate trials of antiepileptic drugs (drug-resistant epilepsy) or suffer from surgically remediable syndromes
- have a reasonable chance of benefitting from surgery.

Paediatric referrals differ from that of adults in two important respects.[242] First, seizures in childhood may be associated with developmental arrest or regression, especially in children younger than 2 years. Second, focal epilepsy in childhood is often associated with age-specific aetiologies such as Sturge–Weber or Landau–Kleffner syndrome, hemispheric and other malformations of brain development. Currently, no pre-operative clinical variables predict seizure outcome in the paediatric surgical population.[242] Developmental delay or psychiatric morbidity are not contraindicated for paediatric epilepsy surgery.[242]

Drug-resistant epilepsy for the purposes of surgical referral

Intractable epilepsy is defined in many ways.[240,247] Drug-resistant epilepsy for the purposes of surgical referral is defined by an inadequate response to a minimum of two first-line AEDs, either as monotherapy or in combination, as appropriate to the epileptic syndrome. The recommended duration is at least 2 years of treatment in adults; however, this may be too long for children when considering the consequences of continuing seizures on their development.

The concept of surgically remediable epileptic syndromes

This concept was introduced in order to promote early surgical intervention for certain forms of epilepsy with well-defined pathophysiological substrates that are known to have a poor prognosis after failure of a few AEDs and an excellent surgical prognosis.[248]

The following are the main surgically remediable epileptic syndromes:

- mesial temporal lobe epilepsy with hippocampal sclerosis (hippocampal epilepsy)
- certain temporal or extratemporal neocortical symptomatic focal syndromes with discrete easily resectable structural lesions

- epilepsies of infants and small children that can be treated with hemispherectomy.

Strategy of a surgical work-up

A pre-surgical evaluation and surgery should be carried out in specialised centres for these procedures, which usually differ in children and adults.

A pre-surgical evaluation of candidates for surgery includes:

- an accurate diagnosis based on a meticulous ictal and inter-ictal clinical history
- neuroradiological investigations and particularly high-resolution MRI, often supplemented with functional brain imaging
- neurophysiological identification of the epileptogenic brain region
- neuropsychological evaluation to reveal possible cognitive and linguistic deficits and to predict the effect of cortical resection
- quality of life and psychiatric assessment.

Subsequently, a decision is taken on the most appropriate surgical strategy and the potential outcome is estimated.

Resective surgery is most likely to be successful if the findings from different modalities are concordant with regard to epileptogenic localisation.

Useful warning to patients

Patients referred to specialised surgery centres should be warned of the following:

- waiting lists may be long
- evaluation procedures are often lengthy, lasting for months
- they may not be suitable for surgery.

Types of surgical procedures

Surgery can be one of two types:

1. *Curative (or definitive),* aiming at suppression of the epileptogenic focus through a resective or disconnective surgical procedure.
2. *Palliative (or functional)* with the purpose of reducing the intensity and/or the frequency of a certain seizure type (callosotomy and multiple subpial transections).

Curative (definitive) surgery

Curative surgery physically removes seizure-producing brain tissue and carries a significant chance of producing complete, or at least 90%, improvement in seizures.

Focal resective procedure (lesionectomy)

This is the most common, important and rewarding of all surgical treatments for focal epilepsies. The aim is to resect the total irritative zone to a sufficient extent to lead to the elimination of seizures.

Hippocampal epilepsy benefits most from this procedure (see page 445). A class 1 RCT of surgery for hippocampal epilepsy found that 64% of those who received surgery were free of disabling seizures compared with 8% in the group randomised to continued AED medical therapy. Quality of life and social function significantly improved in the patients who were operated on; morbidity was infrequent and there was no mortality.[238]

Complications are rare, probably less than 1% or 2% overall, and vary with the experience of the surgical team rather than the procedure.

Other temporal and extratemporal epilepsies benefit from resective surgery, which also produces excellent results (see the surgical treatment of relevant focal epilepsies). In these cases the discreteness of the lesion and its relationship to eloquent cortical areas are major determinants of surgical management and outcome.

Often surgical problems may be difficult, needing complex investigative tools such as functional MRI (fMRI), magnetoencephalography (MEG), invasive recording and operating with neuronavigation and possibly intra-operative MRI.[239] The most difficult part is to define exactly the whole area of the irritative brain tissue, because this frequently extends beyond the structural lesion visualised on neuroimaging or the epileptogenic cortical area generating inter-ictal spikes. Where there is no discrete lesion (cryptogenic focal epilepsies), fMRI and both acute and chronic

electrophysiological recordings may be helpful in determining the extent of the resection.

In hypothalamic epilepsy, resective epilepsy has now improved, but it still has high risks. Several different approaches have been used successfully, but their relative efficacy and safety have not yet been established (see page 317).[242]

Cerebral hemispherectomy

Cerebral hemispherectomy for intractable seizures has evolved over the past 50 years and current operations focus less on brain resection and more on disconnection. The main indications are drug-resistant seizures secondary to gross unilateral hemispherical pathology with severe contralateral (to the lesion) neurological deficit, including hemianopia. Common conditions for which hemispherectomy is recommended include Kozhevnikov–Rasmussen syndrome (page 327), hemiconvulsion–hemiplegia syndrome (page 333), hemimegaloencephaly and miscellaneous hemispherical residual atrophic or other lesions, including Sturge–Weber disease.[242] The structural and functional integrity of the other hemisphere should be appropriately verified.

Seizure outcome is excellent with three-quarters (58–78%) of patients becoming seizure free, and it is generally perceived that behaviour and intellectual performance improve in these patients. Outcome is related to the completeness of disconnection and less so to aetiology, although those with malformations of cortical development appear to do worse than others. The surgical mortality rate is low (0–6%).

Palliative (functional) surgery[249]

Palliative surgery is designed to improve seizures by modification of the neuronal pathways responsible for their generation and spreading. Its purpose is to reduce the intensity and frequency of certain seizure types. It rarely (3–5%) results in freedom from seizures.

Corpus callosotomy

Corpus callosotomy, surgical division of the corpus callosum, is the only procedure for devastating atonic seizures with traumatic falls (atonic drop attacks) of epileptic encephalopathies (see Chapter 10). A favourable outcome, from a greater than 50% reduction to occasional complete cessation of these seizures, is obtained in 60–80% of patients. Improvements (40–80%) have also been reported in symptomatic tonic seizures and less often secondary GTCSs according to the extension of the section. These are cases of symptomatic secondarily generalised epilepsy with EEG bifrontal epileptic foci and secondary bilateral synchrony. Global behavioural and intellectual improvement may occur, particularly if surgery is performed early. Other types of seizures are not indicated for callosotomy, even though some improvement may be observed.

Despite improvements and modifications of corpus callosotomy with sequential radiofrequency lesions and stereotactic radiosurgery, morbidity is relatively high and there is a tendency for seizures to return after 2 years. More severe focal seizures may occur postoperatively.

Multiple subpial transections

Multiple subpial transection is an ingenious surgical technique invented by Morrell[250,251] for drug-resistant focal epilepsies involving eloquent motor-, sensory- or language-important cortex and Landau–Kleffner syndrome. This technique eliminates the capacity of cortical tissue to generate seizures while preserving the normal cortical physiological function.

The rationale of the technique is based on the observation that horizontal fibres of the cortex facilitate the propagation of epileptic discharge, whereas the vertical fibres subserve function. Thus, surgical division of the tangential fibres at regular intervals in a cortical epileptogenic area would permanently disrupt side-to-side, intracortical, synchronising, neuronal networks and curtail the epileptic discharges. Function is preserved because these right-angle cuts to the pial surface should not disrupt cortex–subcortical, input–output interactions.

The success of the technique depends on selection of cases with severe epileptogenic abnormality that can be demonstrated to be unilateral in origin despite a bilateral electrographic manifestation.

Vagus nerve stimulation (VNS)

VNS[252–256] is an invasive non-pharmacological treatment licensed for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with focal seizures which are resistant to AEDs. It is also licensed for treatment-resistant depression.

Efficacy

Systematic reviews of the current evidence for the effects of VNS in drug-resistant focal seizures have concluded that this is an effective and well-tolerated treatment.[253] In general, a third of the patients show more than 50% reduction in seizure frequency (but seizure freedom is conspicuously extremely rare), a third show a 30–50% seizure reduction and a third show no response.[257] Concomitant AEDs may be reduced, but I am not aware of any reports of patients where all drugs were withdrawn, thereby using VNS as monotherapy. All patients stay on at least one medication in addition to the VNS. Improvements in various quality-of-life measurements during treatment with VNS have been reported.[258] In practice VNS has been used for a variety of drug-resistant epilepsies, including young children with epileptic encephalopathies, but the results are often conflicting, ranging from good to no effect. In one of the best-controlled studies, 16 children with epileptic encephalopathies were treated with VNS and followed up for 3 years.[259] There were significant fluctuations in effectiveness, but at the end of the study all children were no better than their pre-VNS baselines with regard to seizures and parameters of quality of life.[260] This contradicts the idea based on anecdotal evidence that seizure control and quality-of-life benefits with VNS treatment increase over time, and that improvement may not be immediate but happens over 18–24 months of treatment.

Adverse reactions

Surgery-related complications: infection (3%), which may demand the removal of the device (1%), vocal cord dysfunction (hoarseness and dysphagia) (1%), facial nerve palsy, Horner's syndrome, bradycardia and, exceptionally, asystole (0.1%), wound haematoma and lead breakage (0.1%), and aesthetic complications from the incisions (prevalence unknown).

Perioperative adverse reactions: pain (29%), coughing (14%), voice alteration (13%), chest pain (12%) and nausea (10%).

During treatment: hoarseness (37%), throat pain (11%), coughing (7%), dyspnoea (6%), paraesthesiae (6%), muscle pain (6%) and discomfort in the face or neck when the stimulator is activated. All are related to the intensity of stimulation, can often be reduced by adjusting the generator's programme and may habituate in most individuals.

There are no apparent effects of VNS on vagally medicated visceral functions or AED plasma concentrations. No adverse cognitive or systemic effects are reported with the use of the implanted vagus nerve stimulator.

Technical aspects

The VNS device (manufactured by Cyberonics, Inc.; www.cyberonics.com/) consists of a small, battery-powered, electrical pulse generator implanted under the skin of the left chest. This is linked to the stimulating spring-shaped electrodes that are wrapped around the main trunk of the left vagus nerve via an under-the-skin insulated cable.

The pulse generator is individually programmed to stimulate the left vagus nerve automatically at varying frequencies, typically for 30 s every 5 min, through a computer and a hand-held 'wand'. The frequency is adjusted to the patient's needs.

The treating physician makes readjustments to the programming and stimulus output.

In addition, the patient or carer can activate extra-stimulation at pre-programmed settings through a magnet passed over the generator. This is to shorten or terminate a seizure as soon as possible after its onset. Keeping the magnet over the generator turns off the stimulation.

Surgical procedure and cost

The implantation of the VNS therapeutic device is a surgical procedure requiring general anaesthesia.

It is usually performed by an experienced neurosurgeon and it takes approximately 1 or 2 hours. The generator is inserted in the hollow below the clavicle through an incision in the left axilla. The electrodes are inserted through an incision in the left side of the neck. Patients usually go home the same day that the VNS device is implanted.

The cost is substantial. In addition to the cost of hospitalisation and the operation, the cost of the VNS device is approximately US$15,600. The battery lasts between 3 and 5 years (10 years in the current versions) and is replaced by a small operation under local anaesthesia. A replacement VNS device with new battery is US$11,600.

What is the place of VNS in the treatment of epilepsies?

Reports fulfilling the requirements of evidence-based medicine conclude that VNS is effective in drug-resistant focal epilepsies (when multiple polytherapy has failed) and may improve the quality of life. Similar studies on the effect of VNS in epileptic encephalopathies have been disappointing.

Reports from uncontrolled studies, case reports and their reviews are also in favour of VNS in a number of drug-resistant epileptic disorders including epileptic encephalopathies. Of 129 children from 12 centres in the USA, 72 had a 12-month follow-up or more, with all 129 having follow-up for at least 6 months. Overall, only one child was seizure free and 43% demonstrated greater than 50% improvement, but 43% had no change in seizure frequency.[242] Some data were promising with regard to drop attacks, but the role of VNS versus callosotomy requires further evaluation.[242]

In clinical practice, the opinion of expert paediatric and adult epileptologists that I share is far less enthusiastic:

> A few patients may improve.
>
> Some patients have less hospital admissions.
>
> I would try it in patients who had failed AED therapy and are not suitable for operation but I would not give great hopes to the patients who may also have to meet a significant cost.
>
> An expensive and useless exercise in epileptic encephalopathies.

The truth may be somewhere between these views.

VNS may have a place in drug-resistant epilepsies that are not amicable to surgery.

In a recent study, concurrent (ketogenic or modified Atkins) diet and VNS treatment for medically drug-resistant childhood epilepsy appeared synergistic and yielded rapid 'benefits'.[261]

Useful note

Environmental precautions for those treated with VNS

Strong magnets such as those used in MRI, loudspeakers and hair clippers may interfere with the stimulator or the electrode leads. Body MRI is contraindicated, whereas head MRI should be done with only transmit-and-receive head coils. In general, 'avoid areas where pacemaker warning signs are posted'.

The magnet provided for manual stimulation may damage credit cards, mobile phones, computer disks, televisions and other items affected by strong magnetic fields. Care should be taken to store the magnet away from these types of equipment.

Ketogenic diet

The ketogenic diet[262–272] is undergoing a mini-renaissance in drug-resistant childhood epilepsies and particularly epileptic encephalopathies.

The ketogenic diet and related dietary treatments have been recently reviewed.[273]

Indications and efficacy

Large observational studies, some prospective, and one RCT,[272] are consistent in showing that the ketogenic diet is a relatively safe and effective treatment in infants and children with drug-resistant epilepsies. The diet is particularly effective for epileptic spasms and epilepsies with myoclonic seizures. Overall, estimates indicate that complete cessation of all seizures occurs in 16% of patients, a greater than 90% reduction in seizures occurs in 32%, and a greater than 50% reduction in seizures occurs in 56%.[262] Half the children will continue on the diet for at least 1 year; 40–50% of those starting the diet will have a greater than 50% reduction in seizures after 12 months. Most parents also report improvements in their child's behaviour and function, particularly with respect to attention/alertness, activity level and socialisation.[263] A concomitant reduction in AEDs is often possible. The ketogenic diet is first-line therapy for the treatment of seizures due to glucose transporter protein deficiency.[274]

Rationale and types of ketogenic diet

The ketogenic diet as an effective treatment of drug-resistant epilepsies was introduced in 1921 as a way of duplicating and prolonging the beneficial effects that fasting appeared to have on seizure control. Hence, this diet mimics the changes of starvation. Neurones use ketone bodies rather than glucose as a metabolic substrate. The mechanism of action of the diet remains unknown, and it is difficult to assess which biochemical parameters should be monitored as adjustments are made to the diet. It has been suggested that chronic ketosis may control seizures by increasing the cerebral energy reserves in the brain, thus promoting neuronal stability.

The ketogenic diet is a high-fat, low-carbohydrate, low-protein regimen. The ketogenic ratio (fat :carbohydrate plus protein) ranges from 2:1 to a maximum of 5:1. The constituents are customised to meet the patient's needs and preferences. The diet is a radical medical therapy and nutritional well-being is a constant concern. The diet is usually started as an inpatient. It should be initiated, supervised and monitored by a nutrition support team who also instruct family members on the maintenance of the diet at home. Traditionally, children starting on the ketogenic diet were made to fast for 1 or 2 days until ketosis was seen. They were then started on a third of the calories for 24 hours, then two-thirds of the calories for the next 24 hours, and finally were advanced to a full diet. This fasting period is often a difficult time for young children and their families, and is probably not needed.[275]

The Atkins diet

The popular Atkins diet has recently been used in the treatment of epileptic encephalopathies as a less restrictive alternative therapy to the ketogenic diet.[276–278]

Adverse effects of the ketogenic diet

The ketogenic diet is generally well tolerated and over 94% of patients have maintained appropriate growth parameters.[8] Nephrolithiasis has been reported in 5–8% of children. Other adverse events have included a reduced quantity of bone mass (requiring vitamin D supplementation), gastritis, ulcerative colitis, alteration of mentation and hyperlipidaemia. Altered concentrations of AEDs may cause toxicity. Carbonic anhydrase inhibitors (Table 7.7) should be avoided. When possible, valproate should also be avoided. The diet may be lethal for patients with rare disorders of cerebral energy metabolisms such as pyruvate carboxylase deficiency.

Corticosteroids in the treatment of childhood epilepsies

Corticosteroids are sometimes used to treat severe forms of childhood epilepsies in an attempt to reduce seizures and improve behaviour, cognitive function, motor function or any combination of these.[279–281] Their mechanism of action is unknown, the evidence base for their use is weak (except for epileptic spasms) and their potential ADRs are considerable. Corticosteroid treatment is clinically beneficial only in the treatment of West syndrome, epileptic encephalopathy with continuous spike-and-wave during sleep (which includes Landau–Kleffner syndrome) and possibly Kozhevnikov–Rasmussen syndrome (see relevant chapters). For all other drug-resistant epilepsies, corticosteroid treatment is usually a somewhat desperate move when other therapies have failed, and it is usually administered during periods when control of seizures is particularly problematic. Corticosteroids are also sometimes used for children with protracted and frequent episodes of status epilepticus, mainly in epileptic encephalopathies. It is important to clearly define the purpose of such treatment before its start.

Preparation, doses and regimens of corticosteroids

A variety of preparations are available. Oral prednisone or intramuscular adrenocorticotrophic hormone (ACTH) are the most commonly used.

With ACTH, dose regimens vary from 20 IU/day to 150 IU/m^2 per day. Efficacy and tolerability of natural ACTH is considered to be better than its synthetic analogue tetracosactide (tetracosactrin).

Prednisone is usually given at 1, 2 or 3 mg/kg per day. Other corticosteroids include oral hydrocortisone, betamethasone and dexamethasone (sometimes also intravenously).

Corticosteroids have been given in short courses of a few weeks or longer courses lasting many months. Both non-tapered and tapered regimens have been advocated.

Adverse effects and monitoring of corticosteroid treatment

Corticosteroid treatment is associated with significant adverse effects, particularly when used at high doses and over prolonged periods. Some of these may be fatal. Of more concern are electrolyte disturbances, glucose intolerance, hypertension, increased susceptibility to infections, particularly to certain viral infections such as varicella, and osteoporosis, myopathy and cardiomyopathy. Treatment is also associated with an increase in the ventricular and extra-axial cerebrospinal fluid spaces, which is apparent on brain imaging and usually reversible.

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Neonatal epileptic seizures and neonatal epileptic syndromes

Neonatal epileptic seizures

Neonatal epileptic seizures occur from birth to the end of the neonatal period.[1–9] This is the most vulnerable of all the other periods of life for the development of epileptic seizures, particularly in the first 1 or 2 days from birth. Neonatal seizures differ from those of older children and adults. They may be short-lived events lasting for just a few days, but they often signify serious malfunction or damage of the immature brain, and constitute a neurological emergency that demands urgent diagnosis and management. Most neonatal seizures are acute (provoked, occasional, reactive) symptomatic seizures caused by an acute illness such as hypoxic–ischaemic encephalopathy, stroke or infection. Seizures are the most common and important sign of acute neonatal encephalopathy; they are a major risk for death or subsequent neurological disability and, by themselves, may contribute to an adverse neurodevelopmental outcome.

Clarifications on classification and terminology

The ILAE Commission (1989)[10] broadly classifies the neonatal seizures among 'epilepsies and syndromes undetermined as to whether they are focal or generalised' under the subheading 'with both generalised and focal seizures'. The new ILAE report states the following:

Although the components of neonatal seizures can be described in terms of the seizure types itemized in the list of epileptic seizures [Table 2.3], they often display unique organizational features. Therefore, a study group will be created to more completely define and characterize the various types of neonatal seizures.[11]

Useful definitions

- The neonatal period is defined as the first 28 days of life of a full-term infant.
- Neonatal seizures are those that occur from birth to the end of the neonatal period.
- Gestational age is defined as the duration of pregnancy.
- Chronological age is the actual 'legal' age of the infant from the time of birth.
- Conceptional age is the combined gestational and chronological ages.
- Full-term infants are those with 40 weeks' gestational age.

Demographic data

The prevalence of neonatal seizures is approximately 1.5% and overall incidence approximately 3/1000 live births. The incidence in pre-term infants is very high (57–132/1000 live births). Of neonatal seizures 80% occur in the first 1 or 2 days during the first week of life.

Clinical manifestations

Neonatal seizures are paroxysmal, repetitive and stereotypical events. They are usually clinically subtle, inconspicuous and difficult to recognise from the normal behaviours of the inter-ictal periods or physiological phenomena. There is no recognisable post-ictal state. Generalised tonic–clonic seizures (GTCSs) are exceptional or may not occur.[12]

The most widely used scheme is by Volpe[13] and constitutes five main types of neonatal seizure:

1. subtle seizures (50%)
2. tonic seizures (5%)
3. clonic seizures (25%)
4. myoclonic seizures (20%)
5. non-paroxysmal repetitive behaviours.

In another scheme by Mizrahi,[2,5] neonatal seizures are classified as follows:

- focal clonic
- focal tonic
- generalised tonic
- myoclonic
- spasms
- motor automatisms (which include ocular signs, and oral–buccal–lingual, progression and complex purposeless movements).

Almost a quarter of infants experience several seizure types and the same seizure may manifest with subtle, clonic, myoclonic, autonomic or other symptoms (Figure 8.1).

Recently, Scher[9] has proposed a multi-dimensional classification scheme for neonatal seizures that will help strategise specific therapeutic interventions in order to optimise neurological outcome and anticipate later neurological morbidities, including epilepsy risk. This scheme combines epileptic and non-epileptic seizure descriptions that capture time-specific and brain region-specific mechanisms for seizures.

Subtle seizures

Subtle seizures are far more common than other types of neonatal seizures. They are described as subtle because the clinical manifestations are frequently overlooked. They imitate normal behaviours and reactions. Subtle seizures manifest with the following:

- ocular movements, which range from random and roving eye movements to sustained conjugate tonic deviation with or without jerking. Eyelid blinking or fluttering, eyes rolling up, eye opening, fixation of a gaze or nystagmus may occur alone or with other ictal manifestations
- oral–buccal–lingual movements (sucking, chewing, smacking and tongue protrusions)
- progression movements (rowing, swimming, pedalling, bicycling, thrashing or struggling movements)
- complex purposeless movements (sudden arousal with episodic limb hyperactivity and crying).[14]

Motor seizures

Clonic seizures are rhythmic jerks that may localise in a small part of the face or limbs, axial muscles and the diaphragm, or be multifocal or hemiconvulsive. Multifocal clonic seizures may migrate to other body parts or other limbs. Todd's paresis follows prolonged hemiconvulsions.

Tonic seizures manifest with sustained contraction of facial, limb, axial and other muscles. They may be focal, multifocal or generalised, symmetrical or asymmetrical. Truncal or limb tonic extensions imitate decerebrate or decorticate posturing. These occur particularly in pre-term infants and have a poor prognosis because they frequently accompany intraventricular haemorrhage.

Myoclonic seizures are rapid, single or arrhythmic repetitive jerks. They may affect a finger, a limb or the whole body. They may mimic Moro reflex and startling responses. They are more frequently in pre-term than in full-term infants indicating, if massive, major brain injury and poor prognosis.[15] However, healthy pre-term and, although rarely, full-term neonates may have abundant myoclonic movements during sleep. Neonates have cortical, reticular and segmental types of myoclonus, similar to adult forms.[16]

Spasms producing flexion or extension similar to those of West syndrome are rare. They are slower than myoclonic and clonic seizures and faster than tonic seizures (Figures 2.8 and 8.2).

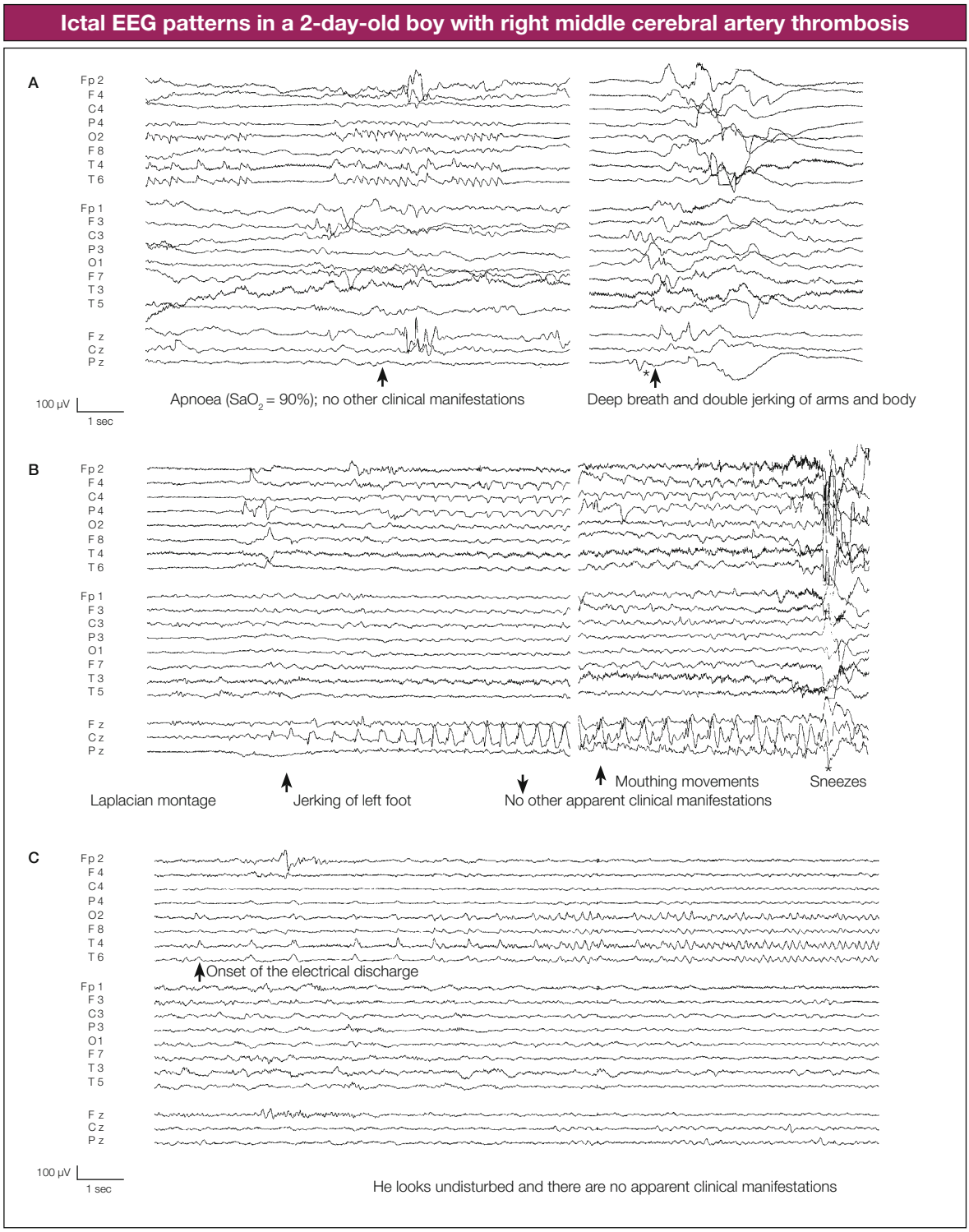

Figure 8.1 (**A**,**B**) Apnoeic, myoclonic, clonic and subtle seizure of motor automatisms associated with various ictal EEG patterns and locations. (**C**) 'Electroclinical dissociation': the electrical discharge is not associated with apparent clinical manifestations.

Tonic seizure with generalised flattening of the EEG

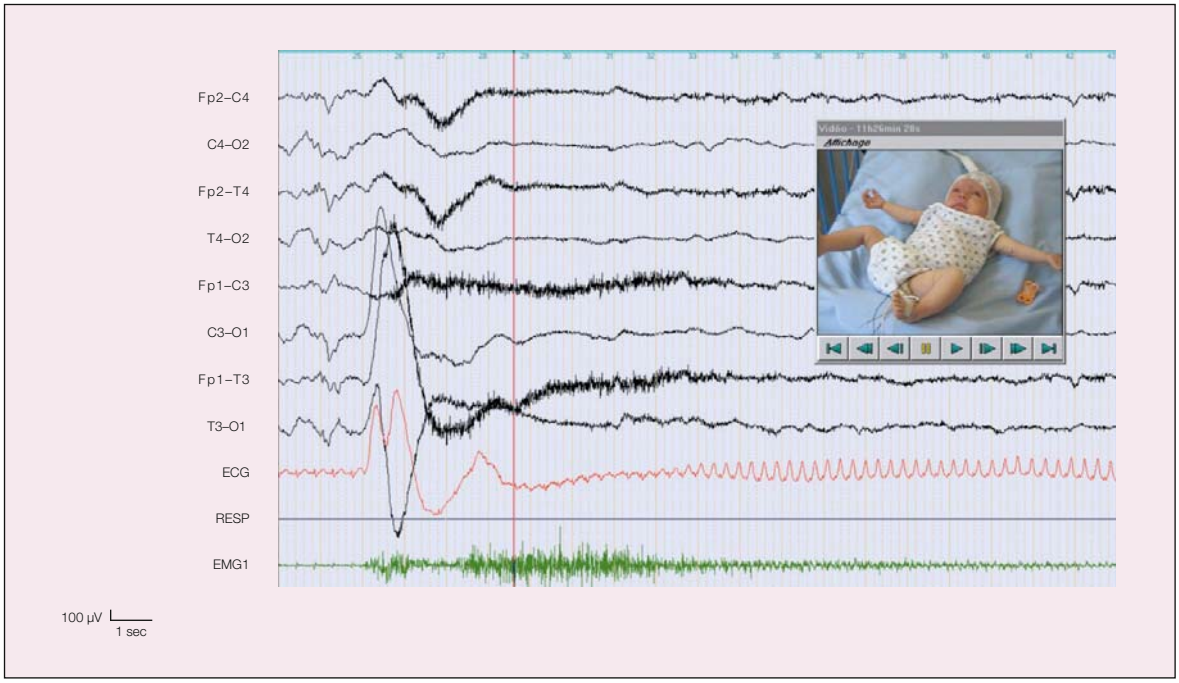

Figure 8.2 *Reproduced with permission from Plouin (2006).*[8]

Autonomic ictal manifestations

Autonomic ictal manifestations commonly occur with motor manifestations in 37% of subtle seizures. These are paroxysmal changes of heart rate, respiration and systemic blood pressure. Apnoea, as an isolated seizure phenomenon unaccompanied by other clinical epileptic features, is probably exceptional.[17] Salivation and pupillary changes are common.

Duration of neonatal seizures

The duration of neonatal seizures is usually brief (10 s to 1–2 min) and repetitive with a median of 8 min in between each seizure. Longer seizures and status epilepticus develop more readily at this age, but convulsive neonatal status epilepticus is not as severe as that of older infants and children.

Non-epileptic neonatal seizures

Kellaway and Mizrahi[2,5] proposed that many of the subtle seizures, generalised tonic posturing and some myoclonic symptoms may be non-epileptic seizures. These show clinical similarities to reflex behaviours of the neonates, but are not associated with ictal EEG discharges and commonly correlate with diffuse abnormal brain processes such as hypoxic–ischaemic encephalopathy and a poor short-term outcome. They are considered as exaggerated reflex behaviours due to abnormal release of brain-stem tonic mechanisms from cortical control – hence, the term 'brain-stem release phenomena':

> They most typically occur in neonates with clinical and EEG evidence of forebrain depression that may release brain stem facilitatory centres for generating reflex behaviours without cortical inhibition.[2,5]

Aetiology

The aetiology of neonatal epileptic seizures is extensive and diverse (Table 8.1). Severe causes predominate. The prevalence and significance of

Main causes of neonatal seizures

	Frequency
Hypoxia–ischaemia • Prenatal (toxaemia, foetal distress, abruption placentae, cord compression) • Perinatal (iatrogenic, maternal haemorrhage, foetal distress) • Postnatal (cardiorespiratory causes such as hyaline membrane disease, congenital heart disease, pulmonary hypertension)	+++++++
Haemorrhage and intracerebral infarction • Intraventricular and periventricular (mainly preterm neonates) • Intracerebral (spontaneous, traumatic) • Subarachnoid • Subdural haematoma • Cerebral artery and vein infarction	++++
Trauma • Intracranial haemorrhage • Cortical vein thrombosis	++++
Infections • Encephalitis, meningitis, brain abscess • Intra-uterine (rubella, toxoplasmosis, syphilis, viral – such as cytomegalovirus, herpes simplex virus, human immunodeficiency virus, coxsackie virus B) • Postnatal (beta-haemolytic streptococci, ***Escherichia coli*** infection, herpes simplex virus,)	++++
Metabolic • Hypoglycaemia (glucose levels <20 mg/day in preterm and <30 mg/day in full-term babies indicating hypoglycaemia; mainly associated with prenatal or perinatal insults) • Neonates of diabetic and toxaemic mothers • Pancreatic disease • Glucogen storage disease (idiopatic) • Hypocalcaemia (early, in first 2 or 3 days, mainly in preterm neonates with prenatal or perinatal insults; late, at 5–14 days, is mainly nutritional; maternal hyperparathyroidism; DiGeorge's syndrome) • Hypomagnesaemia (may accompany or occur independently of hypocalcaemia) • Hyponatraemia (mainly nutritional or iatrogenic) • Inborn errors of metabolism (amino acid and organic acid disorders, hyperammonaemias; they usually manifest with peculiar odours, protein intolerance, acidosis, alkalosis, lethargy or stupor) • Pyridoxine dependency	++
Malformations of cerebral development • All disorders of neuronal induction, segmentation, migration, myelination and synaptogenesis such as polymicrogyria, neuronal heterotopias, lissencephaly, holoprosencephaly and hydranencephaly	+++
Neurocutaneous syndromes • Tuberous sclerosis, incontinentia pigmenti	++++
Drug withdrawal and toxic • Withdrawal from narcotic analgesics, sedative hypnotics and alcohol; heroin- and methadone-addicted mothers; barbiturates	+++
Inadvertent injections of local anaesthetics during delivery	+
Idiopathic benign neonatal seizures (familial and non-familial)	+

Table 8.1

aetiological factors are continually changing and are uneven between developed and resource-poor countries, depending on available improved neonatal and obstetric care. In most cases, the neonate may present with a combination of different neurological disturbances, each of which can cause seizures.

Hypoxic–ischaemic encephalopathy is by far the most common cause – probably 80% of neonatal seizures.

Brain damage due to prenatal distress and malformations of cortical development is being recognised more frequently.

Intracranial haemorrhage and infarction, stroke and prenatal and neonatal infections are common.

Acute metabolic disturbances such as electrolyte and glucose abnormalities have been minimised because of improved neonatal intensive care and awareness of nutritional hazards. Late hypocalcaemia is virtually eliminated, whereas electrolytic derangement and hypoglycaemia are now rare.

Inborn errors of metabolism such as urea cycle disorders are rare.

Pyridoxine dependency, with seizures in the first days of life (reversible with treatment), is exceptional.

Exogenous causes of neonatal convulsions may be iatrogenic or due to drug withdrawal in babies born to mothers on drugs.

Pathophysiology

The increased risk to seizures of neonates may be due to a combination of factors specific to the developing brain that enhance excitation and diminish inhibition. There is an unequal distribution of anticonvulsant and proconvulsant neurotransmitters and networks[18,19] (see also individual neonatal epileptic syndromes).

Diagnostic procedures

Neonatal seizures represent one of the very few emergencies in the newborn. Abnormal, repetitive and stereotypical behaviours of neonates should be suspected and evaluated as possible seizures. Polygraphic video-EEG recording of suspected events is probably mandatory for an incontrovertible seizure diagnosis. Confirmation of neonatal seizures should initiate urgent and appropriate clinical and laboratory evaluation for the aetiological cause (Table 8.1) and treatment. Family and prenatal history is important. A thorough physical examination of the neonate should be coupled with urgent and comprehensive biochemical tests for correctable metabolic disturbances. Although rare, more severe inborn errors of metabolism should be considered for diagnosis and treatment.

Brain imaging

Cranial ultrasonography and brain imaging with CT and preferably MRI[20] should be used for the detection of structural abnormalities, such as malformations of cortical development, intracranial haemorrhage, hydrocephalus and cerebral infarction.

Cranial ultrasonography is the main imaging modality of mainly pre-term neonates. It is limited in resolution and the type of lesions that it can identify.

CT brain scans are now of high resolution and can be generated within seconds. They can accurately detect haemorrhage, infarction, gross malformations, and ventricular and other pathological conditions. Sensitivity is low in malformations of cortical development.

MRI is the superior modality. MRI interpretation should take into consideration the normal developmental and maturational states of neonates and infants. In infants younger than 6 months, cortical abnormalities are detected with T2-weighted images, whereas T1-weighted ones are needed for the evaluation of brain maturation.[20]

Electroencephalography

The neonatal EEG is the most useful EEG application.[2,5,21–23] Well-trained technologists and physicians are required. Polygraphic studies with simultaneous video-EEG recording are essential.[24–26]

Only 10% of neonates suspected of having seizures have EEG confirmation: clonic movements have the highest yield of 44%, but only 17% for 'subtle' movements.

Inter-ictal EEG

Inter-ictal EEG epileptogenic spikes or sharp–slow-wave foci are not reliable markers in this age but

certain inter-ictal EEG patterns may have diagnostic significance (Figures 8.3 and 8.4). These are:[2,5]

- electrocerebral inactivity of a flat or almost-flat EEG of severe brain damage
- the burst-suppression pattern of neonatal epileptic encephalopathies (Figure 8.5)
- theta pointu alternant of benign neonatal convulsions (Figure 8.4)
- persistently focal sharp or slow waves in localised lesions
- quasi-periodic focal or multifocal pattern in neonatal herpes simplex encephalitis[27]
- periodic complexes in glycine encephalopathy[6]
- inter-hemispheric or intra-hemispheric abnormalities.

Background EEG activity, mainly in serial EEGs, often provides objective evidence of the degree and severity of the underlying cause.

Important note

Burst-suppression pattern

The burst-suppression pattern is relatively frequent in the neonatal period. It is associated with heterogeneous seizures and can be induced by drugs.[28,29] It is common in neonatal ischaemic encephalopathy, where it is usually transient and short-lived ('tracé paroxystique' for French neonatologists).[28] Conversely, it is relatively stable, lasting for more than 2 weeks in Ohtahara syndrome and early myoclonic encephalopathy.[30]

Ictal EEG

Ictal EEG patterns vary significantly even in the same neonate and the same EEG recording (Figure 8.1). Ictal EEG paroxysms consist of repetitive waves with a predominant beta, alpha, theta and delta range, or a mixture of all, which may accelerate or decelerate in speed or both (Figures 8.1 and 8.3). They consist of spikes, and sharp, saw-tooth or sinusoidal waves (monomorphic or polymorphic), ranging in amplitude from very low to very high. The patterns may be synchronous or asynchronous, focal or multifocal and, less frequently, generalised. They may appear and disappear suddenly or build up from accelerating localised repetitive waves. Ictal discharges may gradually or abruptly change in frequency, amplitude and morphology in the course of the same or subsequent seizures. Conversely, they may remain virtually unchanged from onset to termination. The background EEG may be normal or abnormal.

Focal EEG ictal discharges usually associate with subtle, clonic or tonic seizures. The most common locations in order of prevalence are centrotemporal, occipital, midline (Cz) and temporal regions. Frontal localisations are exceptional. The same infant may have unifocal or multifocal ictal discharges, which may be simultaneous, develop one from another or occur independently in different brain sites. Clinical or EEG jacksonian march is not seen. Consistently focal EEG paroxysms are highly correlated with focal brain lesions. Seizures that lack or have an inconstant relationship with EEG discharges correlate with diffuse pathological conditions.

'Zips' is a descriptive term that I coined for a common ictal EEG pattern in neonates, which consists of localised episodic rapid spikes of accelerating and decelerating speed that look like zips (Figure 8.3). Zips may be associated with subtle and focal clonic and tonic seizures or remain clinically silent. Zips of subtle seizures are often multifocal and of shifting localisation.

Generalised ictal discharges are more likely to occur with myoclonic jerks and neonatal spasms.

Electroclinical dissociation or decoupling response

Only a fifth (21%) of electrical ictal EEG patterns associate with distinctive clinical manifestations (electroclinical seizures). All others are occult, i.e. they are clinically silent or subclinical (electrical or electrographic seizures).[31]

Electrographic or electrical seizures, namely EEG electrical seizure activity without apparent clinical manifestations, are more common after initiation of anti-epileptic drugs (AEDs). This is because AEDs may suppress the clinical manifestations of seizures but not the EEG ictal discharge. This phenomenon is named the 'decoupling response'[2,5] or 'electroclinical dissociation'.[32] Electroclinical dissociation may arise from foci not consistently reflected in surface electrodes. Neonates with electrographic seizures do

not differ from those with exclusively electroclinical seizures with regard to aetiology or outcome, although the background EEG is more abnormal in the electrographic group.[33] Movements of the limbs occur at a statistically significant higher rate during electroclinical seizures. Electrographic seizures,

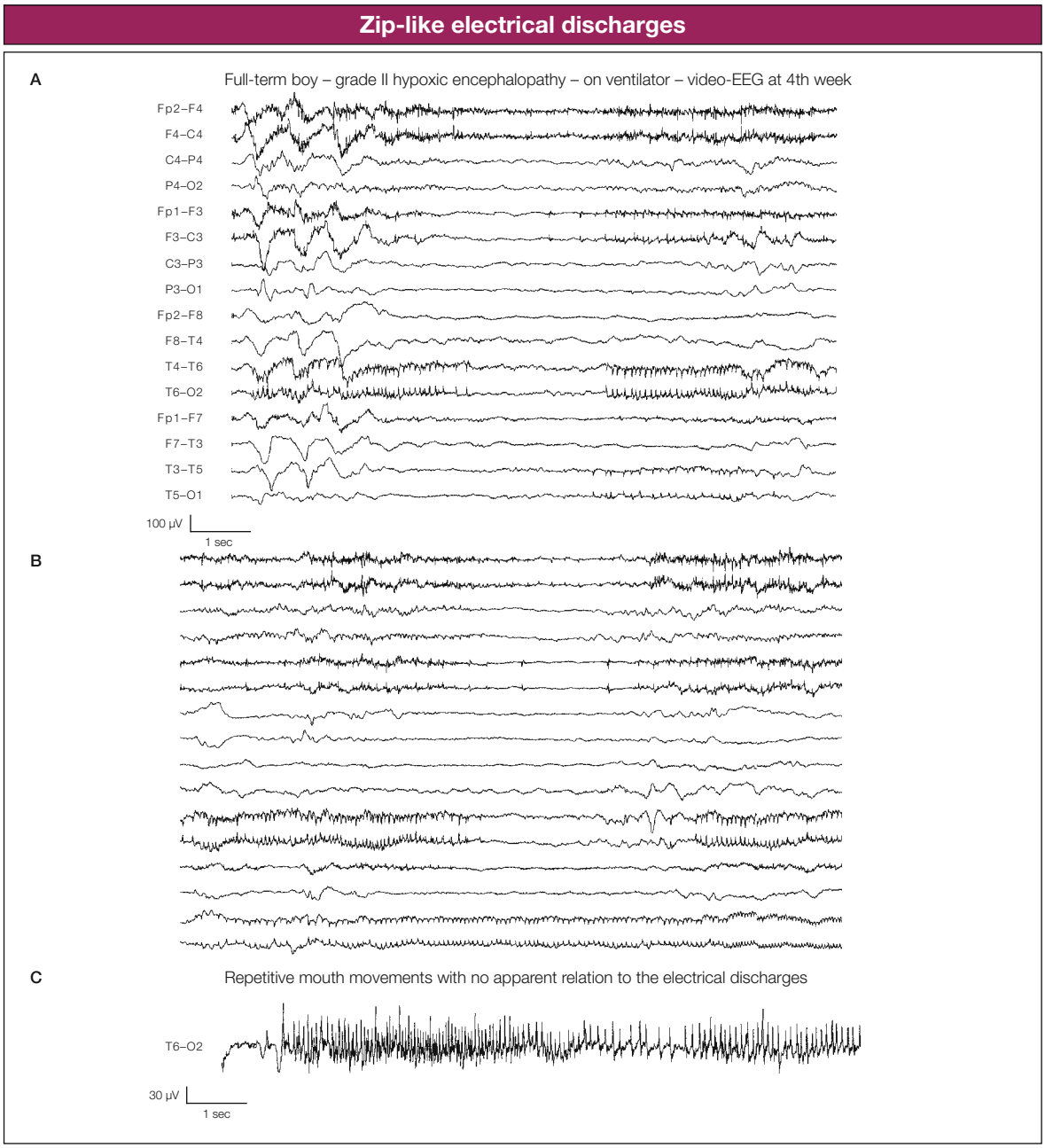

Figure 8.3 (A,B) Continuous recording in a neonate with severe brain hypoxia. Zip-like discharges consist of high-frequency rapid spikes of accelerating and decelerating speed. They start from various locations, terminating in one while continuing in another EEG derivation. (C) Amplification of zips with high sensitivity in T6–O2 derivation. Note that the zips look like, but are not, muscle artefacts, which may also occur when zips are associated with motor seizure manifestations.

similar to electroclinical seizures, are also associated with disturbed cerebral metabolism.[34]

Electrical seizure patterns of usually poor prognosis[2,5]

Alpha seizure discharges are characterised by sustained and rhythmic activity of 12 Hz and 20–70 μV in the centrotemporal regions.

Electrical seizure activity of the depressed brain is of low voltage, long duration, highly localised on one side and with little tendency to spread.

Stimulus-evoked electrographic or electroclinical patterns elicited by tactile or painful stimulation, usually occur in pre-term neonates or neonates with significant diffuse or multifocal brain damage.[35] Most cases die or have significant neurological handicaps.

Post-ictal EEG

Post-ictal EEG usually returns to the pre-ictal state immediately (Figure 8.1). Transient slowing or depression of EEG activity may occur after frequent or prolonged seizures.

Differential diagnosis

Neonatal seizures often impose significant difficulties in their recognition and differentiation from normal or abnormal behaviours of the pre-term and full-term neonate.[24,37] These have been detailed in Chapter 4, and numerous video examples of non-epileptic paroxysmal events (NEPEs) can be seen in the CD companion of reference[37].

As a rule, any suspicious repetitive and stereotypical events should be considered as possible seizures requiring confirmation by video-EEG recording.

Normal behaviours: Among normal behaviours neonates may stretch, exhibit spontaneous sucking movements and have random and non-specific movements of the limbs. Intense physiological myoclonus may occur during rapid eye movement (REM) sleep. Jitteriness or tremulousness of the extremities or facial muscles are frequent in normal or abnormal neonates.

Tremor has a symmetrical 'to and fro' motion, is faster than clonic seizures, mainly affects all four limbs and will stop when the limb is restrained or repositioned. Conversely, clonic seizures are mainly focal, usually have a rate of 3 or 4 Hz or slower, decelerate in the progress of the attack and are not interrupted by passive movements.

Abnormal behaviours: Among abnormal behaviours of neonates with CNS disorders are episodic and repetitive oral–buccal–lingual movements. These are often reproducible with tactile or other stimuli and are interrupted by restraint. Conversely, neonatal seizures persist despite restraint and they are rarely stimulus sensitive.

Non-epileptic movement disorders: Neonatal seizures should be differentiated from benign neonatal sleep myoclonus, hyperekplexia and other non-epileptic movement disorders (see Chapter 4).

Significant impairment of vital signs, which may be periodic, is mainly due to non-neurological causes. Changes in respiration, the heart rate and blood pressure rarely occur as sole manifestations of neonatal seizures.

Inborn errors of metabolism manifest with neonatal subtle seizures or abnormal movements that may not be genuine epileptic seizures. Their identity is often revealed by other associated significant symptoms, such as peculiar odours, protein intolerance, acidosis, alkalosis, lethargy or stupor. In most cases, pregnancy, labour and delivery are normal. Food intolerance may be the earliest indication of a systemic abnormality. If untreated, metabolic disorders commonly lead to lethargy, coma and death. In surviving infants weight loss, poor growth and failure to thrive are common.

Prognosis

This is cause-dependent because the main factor that determines outcome is the underlying cause and not the seizures themselves. Despite high mortality (about 15% in developed and 40% in resource-poor countries) and morbidity rates (about 30% in developed countries), half the neonates with seizures achieve a normal or near-normal state. A third of the survivors develop epilepsy.[36] Table 8.2 provides indicators of good, bad or intermediate prognosis.

Indicators of prognosis
Indicators of bad prognosis
• Severe hypoxia–ischaemia
• Severe congenital malformations of cortical development and meningoencephalitis
• Subtle and generalised tonic seizures
• EEG with electrical ictal activity of the depressed brain, stimulus-evoked electrographic patterns, inter-ictal flat or almost-flat EEG, and burst-suppression patterns
Indicators of good prognosis
• Hypocalcaemia (alimentary type) and other transient metabolic changes
• Extracranial infections with seizures (e.g. otitis, pneumonia, gastroenteritis)
• Benign familial and non-familial convulsions
• Clonic seizures that are short and infrequent
• Normal inter-ictal EEG
Indicators of intermediate or guarded prognosis
• Moderately severe CNS infections or malformations
• Most of the intracranial haemorrhages or infarctions
• More serious metabolic CNS disturbances
• EEG persistence of immature patterns
• Frequent or prolonged clonic seizures and clonic status epilepticus

Table 8.2

Management[4,5,7,38]

Management demands accurate aetiological diagnosis and treatment of the cause of the seizures. The principles of general medical management and cardiovascular and respiratory stabilisation should be early and appropriately applied. Cardiorespiratory symptoms may result from the underlying disease, seizures and anti-epileptic medication.

Neonatal seizures of metabolic disturbances need correction of the underlying cause and not anti-epileptic medication. A trial of pyridoxine may be justifiable.

The drug treatment of neonatal seizures is *empirical* with significant practice variations among physicians. First phenobarbital and then phenytoin are the most commonly used AEDs. Large loading doses are followed by a maintenance scheme for a variable period.

The severity of the seizures appears to be a stronger predictor of the success of treatment than the assigned AED. Mild seizures or seizures decreasing in severity before treatment are more likely to respond regardless of the treatment assignment.

Clinical note

Facts and requirements for the treatment of neonatal epileptic seizures

Neonatal seizures have a high prevalence and their response to AEDs is likely to be different to that of other specified groups of patients. Yet, current treatment of neonatal seizures is entirely empirical. Neonatologists rely on their medical judgement and 'trials by success and error' with off-label uses of both the newer and older AEDs.

The necessity for authorities, including formal regulatory agents, is self-evident.

Phenobarbital and phenytoin are equally effective. If either drug is given alone, the seizures are controlled in less than half of neonates. An RCT of phenobarbital versus placebo in a homogeneous group of newborns at high risk of developing early, subclinical, EEG-detected, neonatal seizures has been designed.[7] This study is intended to 'affirm or refute the common practice of phenobarbital as the first-line treatment of neonatal seizures'.[7]
Fosphenytoin is an attractive alternative to phenytoin because of its lesser potential for adverse reactions at the infusion site and the facility for intramuscular administration.
Intravenous benzodiazepines such as diazepam, lorazepam, clonazepam and midazolam are used, particularly in Europe, for acute neonatal seizures, although in a recent controlled study the results with benzodiazepines as second-line treatment were not encouraging.[39]
Primidone, valproate, lidocaine, carbamazepine, and paraldehyde are also used mainly as adjunctive AEDs if others fail (paraldehyde is now no longer available in the USA).

Newer AEDs are not licensed in the treatment of neonatal seizures. However, a recent survey in the USA showed that 73% of paediatric neurologists recommended one or both of levetiracetam (47%) and topiramate (55%) and made different dosing recommendations. Respondents considered both agents to be efficacious in the majority of cases; adverse effects were recognized more frequently with topiramate.[40] Lamotrigine is also used.[41]

Maintenance treatment: This may not be needed or may be brief because the active seizure period in neonates is usually short. Less than 15% of infants with neonatal seizures will have recurrent seizures after the newborn period.[42] A normal EEG and other predictors of good outcome may encourage early discontinuation of treatment. The current trend is to withdraw the AED 2 weeks after the last seizure.

Do electrographic (electrical) seizures need treatment?

There is a significant difference of opinion as to whether EEG electrical seizure activity that may persist despite drug control of clinical seizures needs more vigorous treatment. Electrical seizures may be highly resistant to drug treatment and attempts to eliminate them may require high doses of usually multiple drugs, with significant adverse reactions such as CNS or respiratory depression and systemic hypotension. The risks should be weighed against the benefits while also remembering that these will eventually subside.

Neonatal epileptic syndromes

Despite the high prevalence of neonatal seizures, epileptic syndromes in neonates are rare. The following four syndromes have been recognised by the currently valid 1989 ILAE classification (Table 5.1):[10]

1. benign neonatal familial convulsions
2. benign neonatal convulsions
3. early myoclonic encephalopathy
4. early infantile epileptic encephalopathy with suppression burst.

These four neonatal syndromes were retained (with some modifications in their names) in the ILAE Task Force diagnostic scheme (Table 5.2).[42] In the most recent ILAE report of 2006, the recognised epileptic symdromes in the neonatal period are (Table 5.2):[11]

- benign familial neonatal seizures: this may be a disease and not a syndrome (level 3 recommendation of confidence).
- early myoclonic encephalopathy: although this may be different from Ohtahara syndrome, the clinical distinction can be difficult (level 3 recommendation of confidence).
- Ohtahara syndrome: (level 3 recommendation of confidence).

- Benign neonatal seizures (non-familial) are categorised among 'conditions with epileptic seizures that do not require a diagnosis of epilepsy' as proposed in the first edition of this book.

Clarifications on classification

The 1989 ILAE classification considers:

- 'benign familial neonatal convulsions' and 'benign neonatal convulsions (non-familial)' as 'idiopathic generalised epilepsies (age related)';[10] the new ILAE reports abandon the name convulsions, using instead seizures[11,43]
- 'early myoclonic encephalopathy' and 'Ohtahara syndrome' as 'generalised symptomatic epilepsies of non-specific aetiology (age related)';[10] the new ILAE reports classify them as 'epileptic encephalopathies (in which the epileptiform abnormalities may contribute to progressive dysfunction)' (see Chapter 10).[11,43]

Benign familial neonatal seizures

Benign familial neonatal seizures are a rare autosomal dominant channelopathy characterised by frequent brief seizures within the first days of life.[44–49]

Demographic data

Onset is commonly in the first week of life, mainly on the second or third day. Affected pre-term babies develop seizures later.[50] A third of patients have seizure onset as late as age 3 months.[51] Boys and girls are equally affected. The syndrome appears to be rare but may be under-recognised or not reported. The incidence is 14.4/100,000 live births.[50]

Clinical manifestations

Seizures mainly occur in otherwise normal neonates after a normal pregnancy and delivery, and with no precipitating factors. Seizures are brief, of 1 or 2 min duration, and may be as frequent as 20–30 per day.

Most seizures start with tonic motor activity and posturing with apnoea, followed by vocalisations, ocular symptoms, other autonomic features, motor automatisms, chewing and focal or generalised clonic movements.[45,52] The clonic components of the later phase are usually asymmetrical and unilateral. The post-ictal state is brief and inter-ictally the neonates are normal.

Pure clonic or focal seizures are considered to be rare.

Aetiology

These seizures are, as mentioned earlier, an autosomal dominant channelopathy with a high degree (about 85%) of penetrance. Most affected families have mutations (conventional, deletions or duplications) in the voltage-gated potassium channel subunit gene *KCNQ2* on chromosome 20q 13.3.[53] A small proportion of families have mutations in the associated gene *KCNQ3* on chromosome 8q.24.[54–56] *KCNQ2* and *KCNQ3* form a heteromeric potassium channel that determines the M-current, which influences the resting membrane potential. Mutations in either *KCNQ2* or *KCNQ3* can produce the same phenotype. Genetic mutations are unknown in some families with benign familial neonatal seizures.

Mutations in the sodium channel subunit gene *SCN2A* appear specific to 'benign familial neonatal–infantile seizures', which is a newly described, clinically intermediate variant between benign familial neonatal seizures and benign familial infantile seizures (see page 268).[57]

Diagnostic procedures

All relevant biochemical, haematological and metabolic screening and brain imaging are normal.

Genetic testing

Identification of a *KCNQ2*, *KCNQ3*, or *SCN2A* mutation can prevent unnecessary investigations and diagnostic uncertainties in these patients. However, currently, testing for these genes is not routinely available in clinical practice and is expensive because of their size and the distributions of mutations.

Electroencephalography

The inter-ictal EEG may be normal or discontinuous, have focal or multifocal abnormalities or have a theta pointu alternant pattern (Figure 8.4). The inter-ictal EEG is of limited value, although it may exclude other causes of serious neonatal seizures.

The ictal EEG commonly starts with a synchronous and bilateral flattening of 5–19 s coinciding with apnoea and tonic motor activity. This is followed by bilateral and often asymmetrical discharges of spikes and sharp waves with a duration of 1 or 2 min, which coincide with vocalisations, chewing and focal or generalised clonic activity.[45,48]

Differential diagnosis

A family history of similar convulsions, a prerequisite for the diagnosis of benign familial neonatal seizures, eliminates the possibility of other diseases. However, other causes of neonatal seizures should be excluded.

Despite artificially similar names,[3,43] benign familial neonatal seizures are entirely different from benign neonatal seizures (non-familial) (Table 8.3).

Prognosis

Seizures remit between 1 and 6 months from onset and in 68% during the first 6 weeks. However, 10–14% may later develop other types of febrile (5%) or afebrile seizures. Afebrile seizures are probably heterogeneous. Idiopathic generalised seizures are more common and there have also been accounts of rolandic seizures. The subsequent risk of afebrile seizures depends on whether other affected relatives developed a seizure disorder later in life.[58,59] Learning disabilities (around 2.5%) are not significantly different from the expected rate for the general population.[60]

A recent study found that in four (40%) of ten families at least one affected individual showed delayed psychomotor development or mental retardation.[49] Three of the four mutations were familial,

Benign (non-familial) neonatal seizures versus benign familial neonatal seizures

	Benign (non-familial) neonatal seizures	Benign familial neonatal seizures
Main seizures	Mostly clonic	Tonic–clonic
Onset	Fifth day of life	Second or third day of life
Duration of seizures	Status epilepticus (median 20 hours)	Repetitive isolated seizures
Main causes	Unknown, probably environmental	Autosomal dominant
Subsequent seizures	Practically nil (0.5%)	Relatively high (11%)
Psychomotor deficits	Minor	Practically non-existent
Ictal EEG	Usually localised spikes	Usually generalised flattening
Inter-ictal EEG	Usually theta pointu alternant	Normal or focal abnormalities

Table 8.3

while the fourth mutation was *de novo*. Mutations associated with an unfavourable outcome tended to be located within the functionally critical S5/S6 regions of the *KCNQ2* gene.[49]

Deaths during neonatal seizures are exceptional but have been reported.[61]

Management

There is no consensus over treatment. Convulsions usually remit spontaneously without medication. The use of AEDs does not influence the eventual outcome. Prolonged seizures may be shortened or terminated with benzodiazepines and phenytoin.

The family's reaction to and their fears about this inherited disease, as well as means of appropriate consultations in order to reduce the magnitude of their fears, should be appropriately considered.[62]

Benign neonatal seizures (non-familial)

Benign neonatal seizures (non-familial)[48,63–65] constitute a short-lived and self-limited benign epileptic syndrome. They manifest with a single lengthy episode of repetitive clonic seizures, which constitute clonic status epilepticus.

Clarifications on classification

In the 1989 ILAE classification, benign neonatal seizures (non-familial) were classified as idiopathic generalised epilepsies (age related).[10] However, many authors have emphasised that this is a predominantly focal (and not generalised) seizure syndrome.[66] This syndrome belongs to the category of 'conditions with epileptic seizures that do not require a diagnosis of epilepsy'.[11,43]

Recently, this syndrome has been renamed 'benign idiopathic neonatal seizures'.[44]

Demographic data

The age at onset is characteristically between days 1 and 7 of life. It is far more common (90%) between days 4 and 6, for which the syndrome's synonym 'fifth day fits' was coined.[63] Boys (62%) are affected slightly more than girls. The prevalence is 7% of neonatal seizures, but this has declined significantly in recent years.[48]

Clinical manifestations

There is a one-off event of a repetitive lengthy seizure that constitutes clonic status epilepticus, which occurs in otherwise normal full-term neonates. This event consists of successive unilateral clonic convulsions affecting the face and limbs. Convulsions may change sides and also may less often be bilateral. Apnoea is a common concomitant, occurring in a third of these clonic fits. Each seizure lasts for 1–3 min, repeating at frequent intervals and cumulating in discontinuous or continuous clonic status epilepticus. The whole seizure–status event lasts from between 2 hours and 3 days, with a median of about 20 hours. It does not recur. Tonic seizures are incompatible with this syndrome.

Aetiology

This is probably environmental, which would explain its significant periodic variations in prevalence. Benign neonatal seizures (non-familial) have been attributed to:

- acute zinc deficiency detected in the cerebrospinal fluid of affected neonates

Inter-ictal EEG in a neonate with benign neonatal seizures (non-familial)

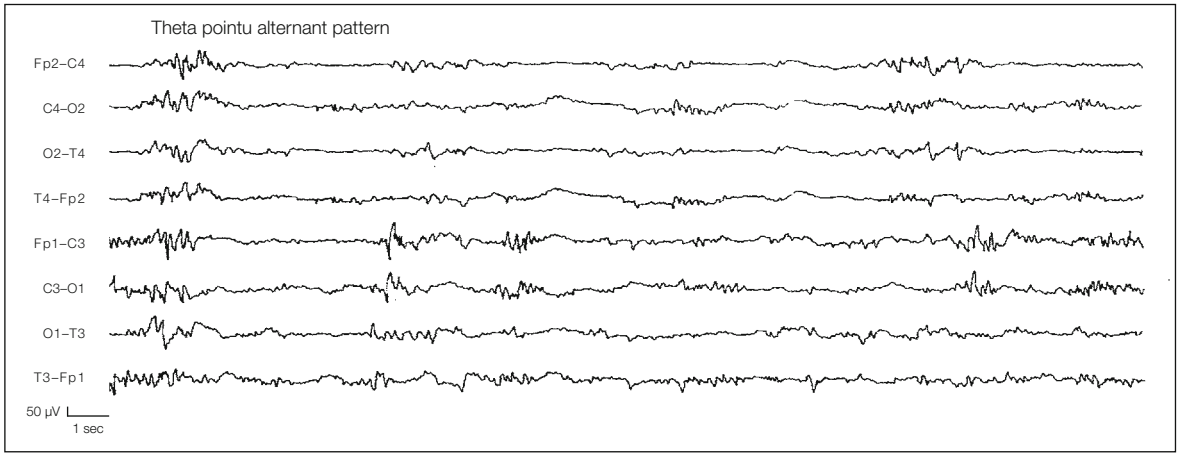

Figure 8.4 The theta pointu alternant pattern is usually associated with a good prognosis. It consists of runs of a dominant theta-wave activity of 4–7 Hz mixed with sharp waves, often of alternating sides. It is not reactive to various stimuli. It may occur on awake and sleep EEGs, and may persist for 12 days after the cessation of convulsions. However, the theta pointu alternant pattern is not specific because it may be recorded in other conditions such as hypocalcaemia, meningitis and subarachnoid haemorrhage, and in neonatal encephalopathies including hypoxic–ischaemic encephalopathy and benign familial neonatal seizures. *Reproduced with permission from Plouin (1992).*[68]

- viral illness, mainly rotavirus
- type of feeding.

There is no genetic background.

This syndrome provides firm evidence that even prolonged seizures in early life may not produce hippocampal damage in the absence of other complicating factors.[67]

Diagnostic procedures

By definition all tests other than the EEG are normal.[48]

Electroencephalography[48]

The inter-ictal EEG shows a 'theta pointu alternant pattern' in half the cases (Figure 8.4). The other half show focal or multifocal, non-specific abnormalities or a discontinuous pattern, or it may be normal in about 10%.

In follow-up studies, centrotemporal spikes are found at a later age in otherwise asymptomatic cases.

The ictal EEG consists of rhythmic spikes or slow waves mainly in the rolandic regions, although they can also localise anywhere else.[48,68] The EEG ictal paroxysms may be unilateral, generalised or at first localised and then generalised. The duration of the ictal discharges is 1–3 min and this may be followed by subclinical discharges for many hours.

Differential diagnosis

The diagnosis can be made only after other causes of neonatal seizures have been excluded. The aetiologies of neonatal seizures with favourable outcomes include late hypocalcaemia, subarachnoid haemorrhage and certain meningitides (Table 8.2).[48,68] There are significant differences between benign neonatal seizures (non-familial) and benign familial neonatal seizures despite the artificially similar names[3,43] and the fact that they have a similar age at onset (Table 8.3).

Diagnostic tips

- A single episode of repetitive clonic seizures that are mainly unilateral, often of alternating sides and lasting for around 20 hours in a full-term neonate, which was normal up to that stage.
- All relevant investigations, except the EEG, are normal.

Prognosis

The prognosis is commonly excellent with normal development and no recurrence of seizures. Minor psychomotor deficits and occasional febrile or afebrile seizures (0.5%) have been reported. In only one study did afebrile seizures or developmental delay occur in half the patients and there was a single case of sudden infant death.[69]

Management

Convulsions usually remit spontaneously without medication. Prolonged seizures may be shortened or terminated with intravenous administration of benzodiazepines and phenytoin. These AEDs should be discontinued soon after the seizures subside.

Early myoclonic encephalopathy

Early myoclonic encephalopathy is a dreadful but fortunately rare epileptic encephalopathy of the first days and weeks of life.[28,70–74]

Clarifications on classification

Early myoclonic encephalopathy is classified among other epileptic encephalopathies (see Chapter 10).[43]

Demographic data

Early myoclonic encephalopathy usually starts in the first days of life, sometimes immediately after birth. More than 60% start before 10 days of age and rarely after the second month. Boys and girls are affected equally. The prevalence and incidence are unknown. There are about 80 reported cases, but this may be an underestimation because neonates with such a severe disease and early death may escape clinico-EEG diagnosis.

Clinical manifestations

The syndrome manifests with a triad of intractable seizures. Erratic myoclonus appears first, followed by simple focal seizures and later by tonic epileptic (infantile) spasms.

Erratic or fragmentary myoclonus is the defining seizure type that may sometimes appear immediately after birth. The term 'erratic' is because the myoclonias shift typically from one part of the body to another in a random and asynchronous fashion. Erratic myoclonus affects the face or limbs. It is often restricted in a finger, a toe, the eyebrows, eyelids or lips, occurring in the same muscle group and often migrating elsewhere, usually in an asynchronous and asymmetrical fashion. Myoclonias are brief, single or repetitive, very frequent and almost continuous. It is exceptional for a baby with early myoclonic encephalopathy to have mild and infrequent jerks.

Massive, usually bisynchronous axial, myoclonic jerks may start from the onset of the disease or occur later, often interspersed with erratic myoclonias.

For definitions of myoclonus, myoclonic and other seizures, see Chapter 2.

Simple focal seizures, often clinically inconspicuous, manifest with eye deviation or autonomic symptoms such as flushing of the face or apnoea. Focal clonic seizures affect any part of the body. Asymmetrical tonic posturing also occurs.

Tonic seizures occur frequently and usually appear in the first month of life. They manifest with truncal tonic contraction, which usually also involves the limbs. They occur during wakefulness and sleep.

Genuine tonic epileptic spasms are rare and generally appear later. They usually develop within 2–4 months of the onset of myoclonias, they are solitary or occur in clusters, and are more frequent during alert stages than sleep stages.

Psychomotor development may be abnormal from the onset of seizures or arrests and deteriorates rapidly afterwards. There may be marked truncal hypotonia, limb hypertonia, disconjugate eye movements, dyspnoea, or opisthotonic or decerebrate posturing. All patients have bilateral pyramidal signs. Practically, there is no trace of intelligent activity. Patients are unable to follow moving objects with their eyes.

Aetiology

Early myoclonic encephalopathy is a multi-factorial disease with a high incidence of familial cases.[30,73] In some families there is an autosomal recessive inheritance. Inborn errors of metabolism are the most common causes, which also explains the high incidence of siblings with this disorder. These inborn errors of metabolism include non-ketotic hyperglycinaemia, propionic aciduria, methylmalonic acidaemia, D-glyceric acidaemia, sulphite and xanthine oxidase deficiency, Menkes' disease and Zellweger syndrome, and molybdenum co-factor deficiency.[73]

A case with a clinical picture of early myoclonic encephalopathy and an atypical burst-suppression pattern had full recovery after administration of pyridoxine.[75] Lesional brain abnormalities are rare.

Pathophysiology

Most probably, early myoclonic encephalopathy and Ohtahara syndrome are the earliest forms of epileptic encephalopathies as detailed in Chapter 10. Spreafico, *et al*[76] proposed a common neuropathological basis irrespective of aetiology. Numerous large spiny neurones, scattered in the white matter along the axons of the cortical gyri, represent interstitial cells of neocortical histogenesis that failed to follow their natural programming to die at the end of gestation or soon after birth.[76]

Diagnostic procedures

These are the same as those for neonatal seizures, attempting to find an aetiological cause. Brain imaging is usually normal at the onset of the disease but progressive cortical and periventricular atrophy often develop. Malformations of cortical development are very rare.

When considering the relatively high rate of inborn errors of metabolism and mainly non-ketotic hyperglycinaemia, a thorough metabolic screening

The burst-suppression pattern in a neonate with severe hypoxic encephalopathy

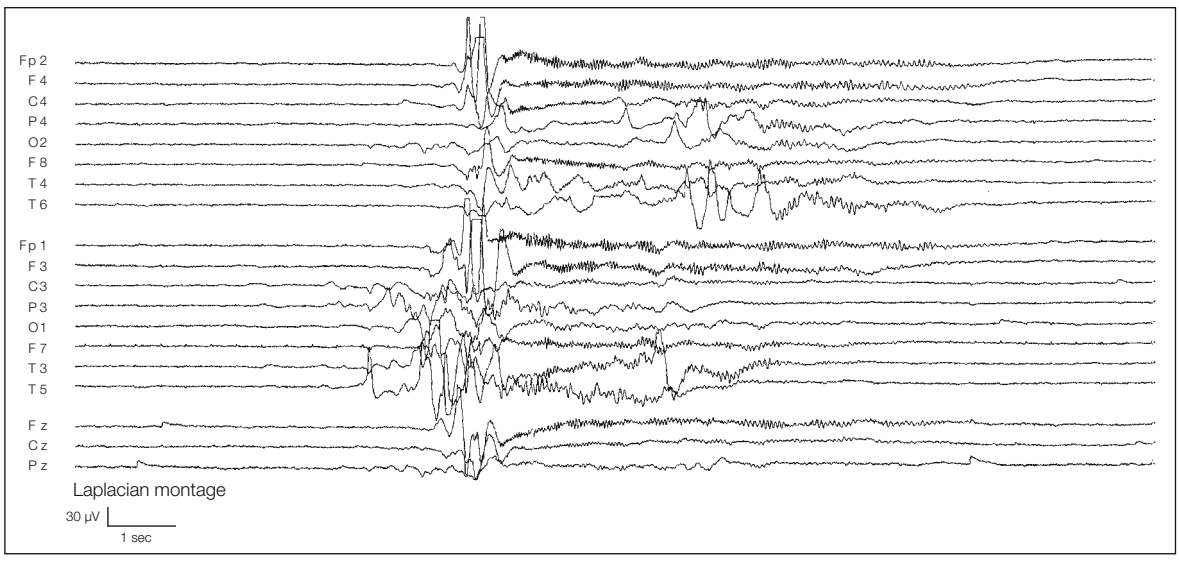

Figure 8.5

is mandatory. This should include serum levels of amino acids and particularly glycine and glycerol metabolites, organic acids and amino acids in the cerebrospinal fluid.

Electroencephalography

Inter-ictal EEG consists of a repetitive burst-suppression pattern without physiological rhythms (Figure 8.5). The bursts of high-amplitude spikes and sharp-and-slow waves last for 1–5 s and alternate with periods of a flat or almost flat EEG, lasting 3–10 s. In most cases the burst-suppression pattern becomes more apparent during deep sleep and may not occur in the EEG of wakefulness.[73] The burst-suppression pattern may appear late at 1–5 months of age in some cases and characteristically persists for a prolonged period.[77]

Erratic myoclonias usually do not have an ictal EEG expression and may follow the bursts.

The burst-suppression pattern evolves to atypical hypsarrhythmia or multifocal spikes and sharp waves 3 or 4 months from onset of the disease. However, this EEG state of atypical hypsarrhythmia is transient and returns to the burst-suppression pattern, which persists for a long time.

Differential diagnosis

The main differential diagnosis of early myoclonic encephalopathy is from Ohtahara syndrome (see Table 8.4).[30,78–80]

Prognosis

Early myoclonic encephalopathy is one of the most dreadful diseases. More than half the patients die within weeks or months of onset and the others develop permanent severe mental and neurological deficits.

Management

There is no effective treatment. Adrenocorticotrophic hormone (ACTH) therapy and AEDs (clonazepam, nitrazepam, valproate, phenobarbital and others) are of no benefit. Patients with non-ketotic hyperglycinaemia may benefit from a reduction in dietary protein and administration of sodium benzoate 120 mg/kg daily, although the outcome is commonly very poor.[81]

A trial with pyridoxine is justifiable.[75]

Diagnostic tips

The diagnosis of early myoclonic encephalopathy should be suspected with:

- segmental and erratic myoclonias affecting the face and limbs, usually restricted in a finger, the eyebrows and perioral muscles, that are almost continuous and often shift from place to place
- a persistent EEG burst-suppression pattern.

Ohtahara syndrome

Synonym: early infantile epileptic encephalopathy with suppression burst.

Ohtahara syndrome is a rare and devastating form of severe epileptic encephalopathy of very early life.[72,73,79,80,82–84]

Clarifications on classification

Ohtahara syndrome is classified among other epileptic encephalopathies (see Chapter 10).[43]

Demographic data

Onset is mainly around the first 10 days of life, sometimes within the uterus or up to 3 months after birth. There may be a slight male predominance. There are about 100 reported cases but this may be an underestimation because many newborn babies with such a severe disease and early death may escape clinico-EEG diagnosis. According to one report 'attacks of cerebral spasms occur in 1.5–5 per 1000 newborn post-partum'.[85]

Clinical manifestations

Ohtahara syndrome manifests with clinico-EEG features of mainly tonic spasms and burst-suppression EEG patterns that consistently occur in the sleeping and waking states.

Tonic spasms usually consist of a forward tonic flexion lasting 1–10 s, which is singular or in long clusters 10–300 times every 24 h. They may be generalised and symmetrical or lateralised. They occur in both the awake and sleep stages. Less often, a third of the neonates may have erratic focal motor clonic seizures or hemiconvulsions. Alternating hemiconvulsions or GTCSs are exceptional. Myoclonic seizures are rare. Erratic myoclonias are not featured.

Aetiology

The most common cause is malformations of cerebral development such as hemimegaloencephaly, porencephaly, Aicardi syndrome, olivary–dentate dysplasia, agenesis of mamillary bodies, linear sebaceous nevus syndrome, cerebral dysgenesis and focal cortical dysplasia.[73] Mutations within the aristaless-related homeobox gene have been recently identified in two cases of Ohtahara syndrome. Rarely, other lesional brain or metabolic disorders may also be responsible.[30,73] There are no familial cases.

In neuropathological studies, patients with Ohtahara syndrome had the most severe lesions in comparison with early myoclonic encephalopathy and West syndrome.[86]

Pathophysiology

Ohtahara syndrome is likely to be the earliest age-related specific epileptic reaction of the developing brain to heterogeneous insults, similar to those of other epileptic encephalopathies that occur at a later brain maturity age (see Chapter 10). This is supported by the fact that between 2 and 6 months of age, the clinico-EEG features often change to those of West syndrome and later to those of Lennox–Gastaut syndrome.

There may be a dysfunction of the catecholaminergic and serotoninergic systems, which could be responsible for this type of neonatal epileptic encephalopathy.[86]

Diagnostic procedures

These are the same as for neonatal seizures, involving attempts at detecting an aetiological cause and possible treatment. Brain imaging usually shows severe abnormalities and malformations of cortical development. Metabolic screening is mandatory if brain imaging is normal.

Electroencephalography

The EEG burst-suppression pattern has a pseudo-rhythmic periodicity, is continuous during wakefulness and sleep, appears at the onset of the disease and disappears within the first 6 months of life. The bursts consist of high-amplitude slow waves mixed with spikes lasting for 2–6 s. The suppression period of a flat or almost-flat EEG lasts for 3–5 s. The interval between the onsets of two successive bursts is in the range of 5–10 s.

Tonic spasms of variable duration are concomitant with the burst phase.[82] Tonic spasms may also occur with the following EEG features:

- diffuse desynchronisation with disappearance of burst-suppression activity when tonic spasms cluster at intervals of 5–10 s
- a pattern in which the burst-suppression pattern becomes more frequent and diffuse, and of higher amplitude compared with the inter-ictal pattern.

There is an age-related evolution of clinical and EEG patterns from Ohtahara syndrome, first to West syndrome and then to Lennox–Gastaut syndrome. On the EEG, a characteristic development is the gradual disap-

Ohtahara syndrome versus early myoclonic encephalopathy

	Ohtahara syndrome	Early myoclonic encephalopathy
Main seizures	Tonic spasms	Erratic myoclonias, focal seizures, clusters of spasms
Main aetiology	Malformations of cerebral development	Genetic and metabolic
Burst-suppression pattern	Pseudo-rhythmic and continuous in sleep and awake – starts earlier and is of shorter duration	Probably accentuated by sleep and may not occur in wakefulness – starts later and lasts longer
Paroxysmal bursts	Longer	Shorter
Suppression	Shorter	Longer
Transformation to West syndrome	As a rule	Common but transient

Table 8.4

pearance of the burst-suppression pattern and the emergence of hypsarrhythmia within 3–6 months of onset. This may again progress later to the slow spike–wave EEG patterns of Lennox–Gastaut syndrome.[87]

Some survivors may show highly localised or entirely unilateral spikes and these patients may frequently have severe focal seizures. Multifocal spikes are frequent, whereas an EEG void of spikes is rather exceptional. Asymmetrical burst-suppression patterns are more likely to develop spike foci and less likely to progress to hypsarrhythmia.

Differential diagnosis

The main differential diagnosis is from early myoclonic encephalopathy (Table 8.4).[30,78–80]

Prognosis

This is a devastating syndrome associated with high mortality and morbidity. Half the patients die within weeks or months of onset and the others soon develop permanent severe mental and neurological deficits. In survivors, the clinical and EEG patterns change to those of West syndrome within a few months of onset and may also change to those of Lennox–Gastaut syndrome if patients reach the age of 2 or 3 years.

Diagnostic tips

- Tonic seizures during the awake and sleep stages in the early days or weeks of life are almost pathognomonic of Ohtahara syndrome.
- An EEG burst-suppression pattern with a pseudo-rhythmic appearance occurring during the awake and sleep stages.

According to Ohtahara, *et al*[87] patients with burst-suppression patterns that evolve to hypsarrhythmia and then to slow spike–wave EEGs have the worst prognosis and a high mortality rate. Conversely, patients who develop spike foci have fewer seizures and less mortality despite severe psychomotor handicaps.

Management

There is no effective treatment. ACTH therapy and any type of AEDs are of no benefit. Newer drugs have not been properly tested. Zonisamide and vigabatrin had some beneficial effect in single case reports. Neurosurgery in focal cerebral dysplasia is sometimes beneficial.[89]

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nine

Idiopathic epileptic seizures and syndromes in infancy

Idiopathic epileptic seizures and syndromes in infancy are important to recognise because they are age related and age limited. They do not occur in adults, are of excellent prognosis and anti-epileptic drug (AED) treatment is often unnecessary.

The infantile (in-fans = unable to speak) period is arbitrarily defined from 4 weeks (end of neonatal period) to 1.5 years (start of early childhood period) of life.

Febrile seizures are categorised among 'conditions with epileptic seizures that do not require a diagnosis of epilepsy'.[1–3]

The following are idiopathic epileptic syndromes with onset in infancy (Table 5.2):[1–3]

- epilepsy with febrile seizures plus (EFS+; see page 213)
- benign (familial and non-familial) infantile seizures (see page 215)
- myoclonic epilepsy in infancy (MEI; see page 217) (the word 'benign' was recently removed from the previous name 'benign myoclonic epilepsy in infancy' because, according to the ILAE report, 'this is not benign in some infants').[3]

Febrile seizures

Febrile seizures[4–11] (a term preferred to febrile convulsions) are due to an age-related (6 months to 5 years) and predominantly genetic benign susceptibility to epileptic fits, precipitated by fever without evidence of intracranial infection or other cause. Children who have suffered a previous non-febrile seizure are excluded.

Clarifications on classification

The 1989 classification of the ILAE categorised febrile seizures among the 'situation-related seizures',[1] which is synonymous with 'conditions with epileptic seizures that do not require a diagnosis of epilepsy' of the ILAE Task Force.[2] According to the new ILAE report, and with which I fully agree:

> *Febrile seizures:* Classically, the seizures that constitute this condition consist of two forms: simple and complex; however, many different types undoubtedly exist. This condition may eventually be understood to encompass many different entities.[3]

Seizures with fever in children who have suffered a previous non-febrile seizure are excluded[12] and the term 'febrile seizures' should be limited to an epileptic seizure precipitated by fever arising from

infection outside the nervous system in a child, aged from 6 months to 5 years, who is otherwise neurologically normal[13] (although the latter is not applicable in complex febrile seizures).

Febrile status epilepticus of longer than 30 min is either one long-lasting seizure or a series of shorter seizures where the infant fails to regain consciousness inter-ictally.[14–17]

Demographic data

By definition, onset is strictly between 6 months and 5 years of age (peak at 18–22 months).[4,5,13] Boys slightly (60%) predominate. Prevalence is about 3% of children, but this is higher in certain ethnic groups (e.g. 7% for Japanese). The annual incidence rate is 460/100,000 children in the age group 0–4 years.[18]

Clinical manifestations

> One minute he was a little boy with a cold and slight fever, lying on the sofa feeling miserable and the next his body was madly convulsing… It was very scary.
>
> *From an internet description by a father*

A rectal temperature level of at least 38°C (others propose 38.5°C) may be more important than a rapid rise of fever.[19] The majority (78%) of febrile seizures occur within the first day of the onset of fever;[7] they may occur before the fever is noticed or late in the course of a febrile illness.

The causes of fever vary and include upper respiratory tract infection or pharyngitis (38%), otitis media (23%), pneumonia (15%), gastroenteritis (7%), roseola infantum (5%) and non-infectious illness (12%). Viral diseases are more common, probably reflecting their higher prevalence in children. A particular association with influenza A has been emphasised.[20]

Seizures occurring soon after immunisation with diphtheria/pertussis/measles and tetanus vaccines are due to fever and not to an adverse effect of the vaccine. Furthermore, recent findings strongly support the view that cases of alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose *de novo*; *SCN1A* mutations were identified in 11 of 14 patients with alleged vaccine encephalopathy.[21]

Seizures

Generalised tonic–clonic seizures (GTCSs) are by far the most common seizure type (80%). Tonic (13%), atonic (3%), unilateral or focal onset tonic–clonic seizures (4%) may occur in the remaining 20%. Rarely there may be only staring accompanied by stiffness or floppiness, rhythmic jerking movements without prior stiffening, focal stiffness or jerking. Febrile seizures with myoclonic jerks only (febrile myoclonic seizures) have a similar age of onset to other febrile seizures.[22–24]

Repetitive seizures in the same febrile illness occur in 16% of patients.

As a result of different prognostic implications, febrile seizures are categorised into simple and complex febrile seizures (Table 9.1).

Simple febrile seizures (70% of all) have strict inclusion criteria:

- they occur in neurologically healthy children aged between 6 months and 5 years
- the seizures are brief (<15 min) and generalised
- they happen only once during a 24-hour period of a febrile illness.[4,5]

Complex febrile seizures (also known as 'complicated' or 'atypical') are:

- prolonged (8%), lasting >15 min
- repetitive (11–16%) in clusters of two or more within 24 hours
- focal at onset or occur in children with perinatal psychomotor deficits (3.5–7%). These also include those with the exceptional Todd's post-ictal paresis (0.4%).

> A third of all febrile seizures may have one, two or all three of these complicating factors.[14,25–27]

Post-ictal symptoms other than drowsiness are rare and should raise the suspicion of another diagnosis.

Simple febrile seizures versus complex febrile seizures

	Simple febrile seizures	Complex febrile seizures
Prevalence among febrile seizures	70%	30%
Neurologically normal	Inclusion criterion	Included but not necessary
With neurodevelopmental abnormalities	Exclusion criterion	3.5–7% of all febrile seizures*
Age range	6 months to 5 years	6 months to 5 years
Duration <15 min	<15 min	Included but not necessary*
Duration >15 min or febrile status epilepticus	Exclusion criterion	8% of all febrile seizures*
Once in a 24-hour period of a febrile illness	Inclusion criterion	Included but not necessary
Repetitive in clusters of two or more in a 24-hour period of a febrile illness	Exclusion criterion	11–16% of all febrile seizures*
Generalised-onset tonic–clonic seizures (80% of all febrile seizures)	Inclusion criterion	Included but not necessary
Focal onset or focal epileptic seizures	Exclusion criterion	4% of all focal seizures*
Post-ictal hemiparesis	Exclusion criterion	0.4% of all febrile seizures*
Risk of subsequent epilepsy	Low (1%)	High (6–49%)

Table 9.1 *A third of all febrile seizures may have one or all of these complicating factors.

Risk factors of a first febrile seizure

The risk of a first febrile seizure is approximately 30% if a child has two or more of the following independent factors:[28,29]

- a first- or second-degree relative with febrile seizures
- a delayed neonatal discharge of >28 days of age
- parental reports of slow development
- day-care attendance.

Risk factors for recurrence

Half the children will have one (32%), two (15%) or more (7%) recurrent seizures after a first febrile seizure. Half of those with a second febrile seizure will suffer at least one additional recurrence.

Recurrences are more likely when:

- the first febrile seizure occurs in the first year of life, during a short and low-grade febrile illness, or is complex
- there is a family history of febrile seizures in first-degree relatives
- there are persistent neurological abnormalities.

Aetiology

Febrile seizures are often familial with a genetic predisposition.[30–32] Children with siblings or parents who have a history of febrile seizures are at a four- to fivefold higher risk than the general population. Boys are more susceptible than girls. Concordance rate is as high as 70% in monozygotic and 20% in dizygotic twins. The mode of inheritance is unknown, although this is probably polygenic. Autosomal recessive inheritance is unlikely because an excess of parents is affected and the risk to siblings is less than 25%.[14] Autosomal dominant inheritance is rare but well documented.

No definitive gene or locus for common febrile seizures has yet been established. In rare autosomal dominant kindreds of febrile seizures at least five different genetic loci were identified: 8q13-21,[33] 19p13.3 and 19q13.1,[34,35] 5q14-q15,[36] 6q22-q24[37] and 21q22.[38] Furthermore, genetic defects have been identified in the syndrome of epilepsy with febrile seizures plus (EFS+), which is characterised by

heterogeneous phenotypes of focal and generalised epileptic seizures (see page 213).

Pathophysiology

The pathophysiology of febrile seizures is unknown. They constitute a specific response to fever irrespective of cause.

Evidence suggests the involvement of various sodium channels, $GABA_A$ receptors and additional auxiliary proteins in the pathogenesis of FS+ and even in simple febrile seizures.[30,32,39,40] A rare inherited cause – a mutation in the $GABA_A$ receptor subunit *GABRG2* gene – has been recently shown to cause a temperature-dependent intracellular trafficking defect.[41]

Circulating toxins and immune reaction products and viral or bacterial invasion of the CNS have been implicated, together with a relative lack of myelination in the immature brain and increased oxygen consumption during the febrile episode. Immaturity of thermoregulatory mechanisms and a limited capacity to increase cellular energy metabolism at elevated temperatures have been suggested as contributory factors.

The central histaminergic neuronal system may be involved in the inhibition of the seizures associated with febrile illnesses in childhood. Children in whom the histamine levels in cerebrospinal fluid do not rise during febrile illnesses may be susceptible to febrile seizures.[42]

A specific association between acute human herpesvirus 6 infection (roseola infantum) and febrile seizures has been postulated.[43]

Diagnostic procedures

The main concern is to correctly diagnose 'febrile seizures' as opposed to 'seizures with fever', such as acute symptomatic febrile seizures and those occurring in the context of pre-existing epilepsy.

Febrile seizures do not require any investigations if the diagnosis is certain. The EEG and brain imaging are unhelpful and should therefore be discouraged.

Electroencephalography

An EEG is not needed.[47] It is more likely to be normal or show non-specific abnormalities that may be overemphasised by inexperienced neurophysiologists. An EEG also does not have any predictive value for either the risk of recurrence of febrile seizures or the development of epilepsy.[47]

Important clinical note

The investigations done on a child with a simple or complex seizure during a febrile illness should be directed by the degree of illness and the suspected underlying infection.[11] Meningitis should be thoroughly considered and appropriately diagnosed or ruled out on clinical grounds and probably with a lumbar puncture, particularly in children under 2 years of age with or without meningism that show features of being unwell for a few days, vomiting, drowsiness, petechiae, decreased feeding, complex febrile seizures and, in particular, febrile status epilepticus.[11,44–46] Lumbar puncture may be mandatory in children who have a convulsion with fever in their first year of life (although this is still debatable).

Differential diagnosis

Of immense clinical importance is the distinction of febrile seizures from 'convulsions with fever' such as in meningoencephalitis, and metabolic or neurodegenerative diseases.

A high index of suspicion for acute bacterial meningitis in the child with febrile convulsive status epilepticus is paramount. The classical symptoms and signs of acute bacterial meningitis may be absent in febrile convulsive status epilepticus.[46]

'Febrile seizures' should be clearly distinguished from 'seizures with fever', which are acute symptomatic febrile seizures caused by pyogenic or viral meningitis, herpes simplex encephalitis, other acute encephalitides, cerebral palsy with intercurrent infection and metabolic or neurodegenerative disease with a seizure precipitated by fever. Children who have a prolonged seizure or who have not

completely recovered within 1 hour should be suspected of having one of these conditions and investigated accordingly.[13]

Another main diagnostic issue is whether a first febrile seizure is a genuine febrile seizure or FS+ or the first manifestation of another genetically determined epileptic syndrome (see prognosis below). 'Atypical febrile seizures' is a common misdiagnosis of Panayiotopoulos syndrome (see Chapter 12).

The occurrence of non-febrile generalised convulsive seizures in association with viral gastroenteritis, without dehydration or electrolyte imbalance, have recently attracted interest both within[48,49] and outside of Asia.[50] This constitutes a benign condition; investigations may not be necessary and prognosis is excellent.

Prognosis

Overall, children with febrile seizures have a sixfold excess (3%) of subsequent non-febrile seizures and epilepsy compared with controls.[25,26,51] Simple febrile seizures (70%) have only a twofold excess (1%). Significant risk factors for later epilepsy are shown in Table 9.2.

Non-febrile seizures start a few months to 30 years after the first one, but 85% start within 4 years. The risk is 2% by age 5, 4.5% by age 10, 5.5% by age 15 and 7% by age 25.[51] Conversely, children with no risk factors have a 2.4% chance of developing non-febrile seizures by the age of 25 years compared with 1.4% for the general population.[51] The rates are similar irrespective of the type of treatment for febrile seizures.[52]

Non-febrile seizures, if these occur, are of any type but generalised are more common than focal.[51]

Generalised non-febrile seizures tend to occur in children with frequent, brief, generalised febrile seizures and when there is a positive family history of non-febrile seizures.

Focal non-febrile seizures are likely in children with prolonged lateralised febrile seizures (20%), earlier onset and persisting neurological abnormalities.[51] The estimated risk of developing temporal lobe epilepsy (TLE) subsequent to prolonged febrile seizures is negligible, probably 1/75,000 children per year.[53,54] Conversely, a third of patients with hippocampal epilepsy have a previous history of prolonged febrile seizures (see mesial TLE with hippocampal sclerosis, page 385).[55]

Predisposition to both febrile seizures and other non-febrile epileptic syndromes is well documented. Febrile seizures precede the onset of various forms of epilepsies in 10–15% of children[54,56] (see individual syndromes of idiopathic generalised epilepsy [IGE] such as myoclonic epilepsy in infancy, benign childhood focal seizures such as rolandic and Panayiotopoulos syndrome, and other more severe forms of epilepsies such as Dravet syndrome). Also, pre-existing developmental hippocampal abnormality may predispose individuals to having prolonged febrile seizures.[57]

Significant risk factors for later epilepsy

Significant risk factors for later epilepsy are:

- Abnormal neurological or developmental status before the first febrile seizure
- Family history of non-febrile seizures
- Complex febrile seizures

The risk after complex febrile seizures is:

- 6–8% when a single complex feature is present
- 49% when all three complex features (prolonged, repetitive and focal febrile seizures) are present

Table 9.2

Intellectual and behavioural outcome

Children with febrile seizures perform as well as other children in terms of their academic progress, intellect and behaviour.[58] The subsequent psychomotor development of children who were normal before the onset of febrile seizures remains normal.[58,59] If psychomotor deficits, learning difficulties and behavioural problems are found in children with febrile seizures, these are not related to the seizures, but probably reflect the overall developmental status of the child.[60]

Management

This is based mainly on the recent recommendations of the American Academy of Pediatrics.[4,5]

Acute management of a child with a febrile seizure

Control of the seizures is paramount. Long-lasting febrile convulsive seizures (>10 min) or status epilepticus (>30 min) is a genuine paediatric emergency that demands appropriate and vigorous treatment, similar to non-febrile convulsive status epilepticus (Chapter 3).[17,52] Early, usually parental, treatment is more effective than late emergency treatment.[52] The parents of children with recurrent seizures should be advised to place the child on his or her side or stomach on a protected surface and administer a preparation of rectal benzodiazepine. In an emergency facility, the child's airway should be kept clear, oxygenation maintained, and intravenous or rectal benzodiazepines given to halt the seizure (Table 3.3).

Diazepam intravenously at a dose of 0.25–0.5 mg/kg, or in rectal preparations at a dose of 0.5 mg/kg, is probably the first choice (page 79). Rectal absorption of liquid diazepam is very rapid; it reaches the brain within minutes and has an almost intravenous efficacy. A disadvantage of diazepam is its short duration of action.

Lorazepam administered intravenously (0.1 mg/kg), which is less likely to cause respiratory depression and probably has a longer duration of action than diazepam, is often preferred in medical facilities (page 80).

Midazolam administered by buccal (0.4–0.5 mg/kg) or intranasal (0.2 mg/kg) application has superior efficacy to diazepam[61,62] and is becoming the drug of choice for terminating prolonged seizures in the home (page 80).[63,64]

Treatment of the fever and, mainly, the underlying illness is also important. Antipyretic treatment during febrile illnesses does not reduce the recurrence rate and cannot be recommended other than to make the child more comfortable and avoid dehydration. Paracetamol is more widely used than ibuprofen, whereas aspirin is avoided because it has been associated with the development of Reye syndrome.

Physical methods of reducing the fever such as sponging with tepid water, fanning and cold bathing have a quicker but shorter effect than antipyretics. However, they are likely to cause discomfort and are not usually recommended in the UK.[13]

Prophylactic management

The best treatment for children with a first febrile seizure is education and reassurance for the parents.[65]

Simple febrile seizures do not need prophylactic treatment. The risks are small and the potential side effects of drugs appear to outweigh the benefits.

Prophylactic treatment may be desired if a child has one or, mainly, a combination of the following features:

- complex febrile seizures
- neurological abnormalities
- age <1 year
- frequent recurrences.

Prophylactic treatment may be continuous or intermittent at the time of a febrile illness. Neither of these may be needed for most children with febrile seizures, who almost invariably do well.

Continuous treatment consists of daily administration of, mainly, phenobarbital (which at a blood level of 15 µg/ml can effectively reduce the risk of recurrences) and, less often, valproate (fatal hepatitis in this age group or pancreatitis make valproate probably unacceptable). Carbamazepine and pheny-

toin are ineffective in the prevention of febrile seizures.[4,5]

Intermittent treatment at the time of a febrile illness, mainly with rectal or oral diazepam, is an alternative to continuous medication (again a debatable issue). There is a small reduction in the recurrence risk with a dose of diazepam 0.3 mg/kg, although a third of children will have significant side effects of somnolence or ataxia.

These recommendations need updating with regard to the AEDs used; for example, many physicians are, rightly, reluctant to prescribe phenobarbital.

Supportive family management

A total of 47% of parents thought that their child was dying during the initial febrile seizure.[66]

The parents of young children should have general information provided by the family doctor about fever and febrile seizures. Parents who have watched their child during a fit need specific information in order to avoid long-term reactions.[67,68]

Supportive family management includes education about febrile seizures and providing specific instructions about antipyretic and anti-epileptic prophylaxis and emergency procedures for possible subsequent seizures.

Epilepsy with febrile seizures plus

Synonyms: generalised epilepsy with FS+ or autosomal dominant epilepsy with FS+.

'Febrile seizures plus' is a term to denote childhood-onset febrile seizures, which (unlike the typical febrile seizures) start earlier (from less than 6 months with a mean of 1 year) than the classical febrile seizures. They are often multiple and continue beyond the age of 5 years, usually remitting by mid-childhood (median 11 years). Individuals with FS+ may also have additional non-febrile seizures. In some children with FS+, seizures with fever occur beyond age 5 years, whereas in others, all seizures beyond age 5 years are non-febrile.[69–75]

Epilepsy with febrile seizures plus (EFS+)[39,40,69–75] is the most important familial epileptic syndrome because it links febrile seizures with various other epileptic seizures and syndromes, and documents genetic relationships between the benign and severe and the focal and generalised epileptic disorders.

Clarifications on classification

EFS+, described by Berkovic and his associates,[69–75] was initially recognised by the ILAE as a syndrome in development.[2] Now, the new ILAE report recognises 'febrile seizures plus as an epileptic condition that is part of the familial syndrome known as EFS+. The latter is broader than a single generalised syndrome and may be a useful category for future classifications.'[3]

The name EFS+ is preferred to the other synonyms because (1) the spectrum of the syndrome includes diverse types of focal and generalised seizures[77] and (2) autosomal dominant inheritance in EFS+ might be rare, and most of EFS+ display a complex pattern of inheritance.[74]

Demographic data

The age at onset, from the first months of life to childhood, varies considerably between individuals, even individuals of the same family. As a rule, FS+ usually start 6 months earlier than the classical febrile seizures. Both sexes are equally affected. The prevalence is unknown, but may be high considering the increasing numbers of publications and the very broad spectrum of EFS+.

Clinical manifestations

The syndrome of EFS+ is characterised by heterogeneous clinical phenotypes. By definition, in all

families some patients have FS+, which are often preceded by classical febrile seizures.

Typical febrile seizures and FS+ are the most common clinical phenotypes that may occur alone (75% of affected patients) or in combination with other types of seizures, including:

- brief non-febrile generalised convulsions
- other generalised seizures, such as absences, myoclonic jerks, tonic seizures and, more frequently, myoclonic–atonic seizures
- focal seizures of mainly frontal or temporal lobe origin may occur[78] in approximately 13% of affected individuals,[79] and these focal seizures may dominate in some members of affected families.[77]

EFS+ shows marked genetic and phenotypic heterogeneity. There are extreme intra- and inter-familial clinical variations with regard to seizure type, seizure frequency, severity and prognosis. Within the EFS+ spectrum, more severe syndrome phenotypes can occur including Dravet syndrome, epilepsy with myoclonic–astatic seizures (EM-ASs) and TLE.[80,81]

Aetiology

EFS+ is a purely genetic disorder with profound heterogeneity. Inheritance was considered generally autosomal dominant with incomplete penetrance,[76] but this may not be the only situation.[82] In fact more recent studies indicate that autosomal dominant inheritance is rare. A more complex pattern of inheritance is emerging.[74]

EFS+ is genetically heterogeneous with two loci described on chromosome 19q (*GEFS+*) and chromosome 2q (*GEFS2*). Mutations were found in the *SCN1A*, *SCN1B* and *SCN2A* genes (encoding the α_1, α_2 and β_1 voltage-gated sodium channel subunits) and the *GABRG2* gene ($GABA_A$-receptor γ_2-subunit).[83] More recent studies have indicated that mutations of *SCN1A*, *SCN2A*, *SCN1B* and *GABRG2* in patients with EFS+ are rare.[79]

There may be many mechanisms by which sodium channel alterations cause the various clinical phenotypes of EFS+. There is a possibility of simultaneous involvement of multiple genes for the seizure phenotypes.[74] To produce the different seizure types observed in families with EFS+, seizure predisposition determined by the EFS+ genes could be modified by other genes and/or environmental factors.[81]

Diagnostic procedures

Brain MRI is normal. The EEG findings are diverse and depend on the clinical phenotype.[73] Half of the patients have normal EEGs. The most common EEG abnormality is sparse and brief generalised polyspike–wave discharges (GPSWD) or generalised spike–slow-wave discharges (GSWD) that might require sleep EEGs for their detection. In patients with focal seizures, the EEG shows focal sharp waves, which are mainly localised in the frontal and temporal regions.[77,79]

In EM-AS and Dravet syndrome the EEG abnormalities are severe, as described in the relevant chapters.

Differential diagnosis

The main diagnostic issue is whether a first febrile seizure is a classical febrile seizure or FS+; however, they are usually impossible to differentiate initially. It is only when at least two febrile seizures occur outside the age range of classical febrile seizures (i.e. earlier than 6 months or later than 5 years) that a diagnosis of FS+ is certain.

Distinguishing features of the EFS+ syndrome are the persistence of febrile seizures beyond the age of 5 years, the occurrence of non-febrile seizures and family history.

Absences, when they are present, are usually brief, mild and easily distinguishable from the severe absences of childhood or juvenile absence epilepsy.

The evolution to severe phenotypes such as EM-AS or Dravet syndrome[84] be comes apparent only with the emergence of non-febrile seizures compatible with these disorders.

Prognosis

Overall, EFS+ was initially considered benign and self-limited.[76,84] Non-febrile seizures occur in about a quarter of patients and these are usually infrequent and often remit by mid-childhood (a median of 11 years). However, this overall good prognosis is now reconsidered, particularly since the inclusion of Dravet syndrome[84] and EM-AS, among EFS+.

Management

Repetitive febrile seizures or FS+ may require prophylactic treatment (see Chapter 7). Treatment of more severe phenotypes has been described in the relevant sections.

Benign infantile seizures

Synonym: Watanabe–Vigevano syndrome.

Benign infantile seizures, familial and non-familial,[85–93] constitute a benign age-related idiopathic syndrome of infancy. The seizures are focal and the infants are otherwise normal. Watanabe described the non-familial forms[85] and Vigevano the familial forms.[86]

Considerations on classification

The ILAE diagnostic scheme initially recognised two types of benign infantile seizures (familial and non-familial) (Table 5.2).[2] However, as I have previously proposed,[94] these are now unified in one syndrome in the new ILAE report:[3]

> The familial and non-familial forms of benign infantile seizures are identical except for the family history. Consequently, the sporadic form cannot be considered a separate syndrome, and both should be combined into a single syndrome, unless subsequent information indicates otherwise.[3]

Demographic data

Age at onset is from 3 to 20 months with a peak at 5 or 6 months. The familial form mostly starts between 4 and 7 months. Boys and girls are equally affected in the sporadic form, but more girls are reported in the familial cases. Only small numbers, about 100 of all types, have been reported so far but this may increase with improved awareness of the condition.

Clinical manifestations

Seizures characteristically occur in clusters of five to ten per day for 1–3 days and may recur after 1–3 months. A third of patients have single isolated seizures 10–15 days before the clusters occur.

The seizures are focal, predominantly diurnal and brief (0.5–3 min). Longer seizures (3–6 min) occur at the beginning of the clusters and in the familial cases.

The seizures manifest with motor arrest, impairment of consciousness with decreased responsiveness, staring, eye and head deviation, and mild unilateral clonic convulsions. Simple automatisms are frequent. Alternating from one side to the other is common. The seizures may progress to hemiconvulsions or generalised convulsions.

Aetiology

The familial form is most probably autosomal dominant with genetic heterogeneity. Linkage has been found to chromosomes 19q12-13.1,[95] 2q24[96] and 16p12-q12.[97]

Benign familial infantile seizures do not appear to have genetic links with benign neonatal seizures, although these may also prove to be channelopathies.

Of significant genetic interest is the description of familial forms with seizure onset in the intermediate age (1–3 months) between benign neonatal and infantile seizures, as well as familial infantile convulsions in families with choreoathetosis[98,99] or hemiplegic migraine.

Benign familial neonatal–infantile seizures[100] is an autosomal dominant disorder starting between the ages of 2 days and 7 months with non-febrile focal seizures of mainly posterior onsets, which remit by 12 months. The disorder is a sodium channelopathy caused by mutations in the sodium channel subunit gene *SCN2A*.[100] No such mutations were found in ten families with benign familial infantile seizures.[100]

Familial infantile convulsions and choreoathetosis are an autosomal dominant disorder with benign infantile seizures together with variably expressed paroxysmal choreoathetosis.[97–99,101,102]

Familial hemiplegic migraine and benign familial infantile seizures[103] partially cosegregate in some rare families with novel missense mutations in the *ATP1A2* Na^+/K^+-ATPase pump gene on chromosome 1q23.[104]

The sporadic cases of benign infantile seizures may be identical to the familial ones, but with reduced expressivity, or they may be due to exogenous factors such as rotavirus infections.[105]

Diagnostic procedures

All relevant tests applied for infantile seizures are normal. However, they are needed, particularly for the sporadic cases, in order to exclude symptomatic infantile seizures.

Electroencephalography

The inter-ictal EEG is normal. The ictal EEG demonstrates focal discharges of fast activity mixed with spikes that usually spread to neighbouring areas or the whole brain (Figure 9.1).[105–107] Onset may be

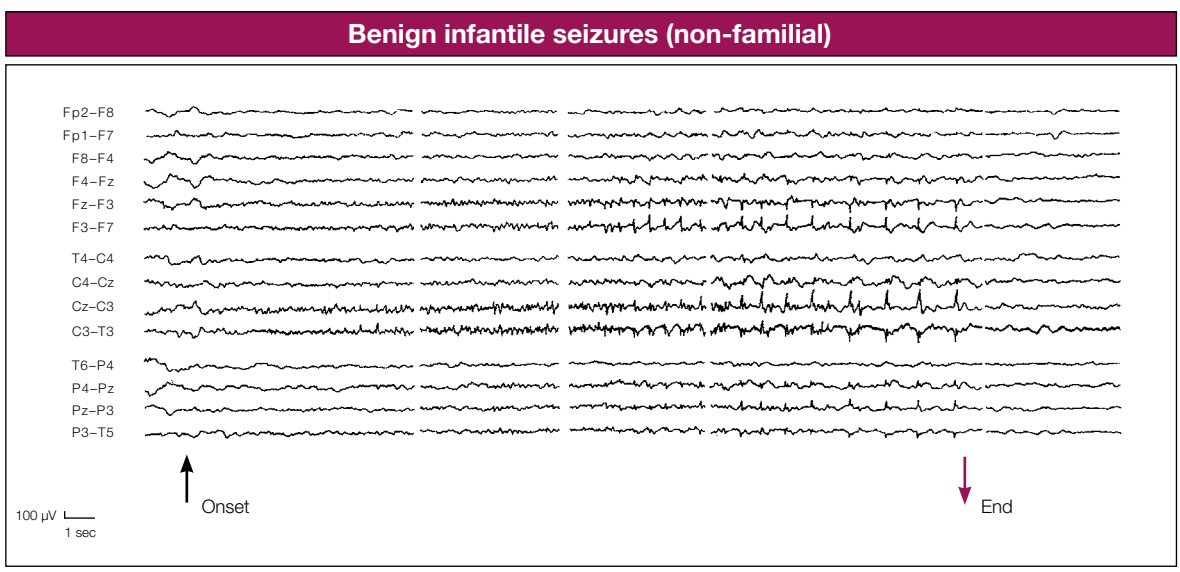

Figure 9.1 An ictal EEG of a seizure in an 8-week-old baby who, at this age, had three focal seizures of right-sided convulsions involving the face and upper limbs (see case 17.2 in Panayiotopoulos[107]). Brain MRI was normal. The inter-ictal EEG was normal. Subsequent EEGs were normal and treatment stopped at age 10 months. He was well until the age of 7 years when he started having typical rolandic seizures. One year later, he developed epilepsy with continuous spikes and waves during slow-wave sleep (Figure 10.12). The arrows mark the onset and termination of the seizure. Note the ictal EEG onset with focal left-sided fast spikes of low amplitude.

frontal, temporal, parietal or occipital, and may vary in location and side between seizures of the same patient.[106]

Differential diagnosis

This may be difficult in the sporadic form, which requires a long follow-up before such a diagnosis can be established. Other syndromes with familial benign infantile seizures should be considered.

Prognosis

Prognosis is usually good.[108,109] Seizures remit within 1 to 2 years of onset. Development is normal. In untreated cases there can be isolated or brief clusters of seizures within this period.

Management

In the active seizure period, AED treatment is usually effective. Complete seizure control is achieved in almost all cases. Recurrences after 1 or 2 months may occur in a third of patients, but these are also easily controlled by drug dose adjustments. AEDs are usually withdrawn after 1–3 years with no relapses. Watanabe mainly used carbamazepine, whereas Vigevano used valproate or phenobarbital. Benzodiazepines or phenobarbital are insufficient for the cessation of clustered seizures.[110]

Myoclonic epilepsy in infancy

Myoclonic epilepsy in infancy (MEI)[111–123] is probably the earliest form of an age-dependent IGE syndrome and is manifested mainly or exclusively by just myoclonic jerks. The jerks may be spontaneous, reflex or both.

Clarifications on classification

The recent report of the ILAE Classification Core Group deleted the word 'benign' from benign MEI 'because this is not benign in some infants'.[3] However, this may be premature without defining exactly what this syndrome is and particularly whether those with reflex myoclonic jerks (reflex MEI) are truly separate from those with spontaneous myoclonic jerks only. Furthermore, it should be the majority rather than a 'few cases' that determine the overall features and prognosis. Even the most benign medical conditions may infrequently develop to an unfavourable prognosis (e.g. seasonal viral flu).

Demographic data

Onset is between 6 months and 3 years, but in a few infants it may start earlier (4 months) or later (4 to 5 years). Boys are twice as likely to be affected as girls. The prevalence may be around 1% or 2% of all epilepsies starting before the age of 3 years.[117] This syndrome is based on retrospective studies and single case reports of approximately 100 patients, sometimes heterogeneous and including those with stimulus-elicited (reflex) myoclonic jerks.[117]

Clinical manifestations

Myoclonic seizures are the predominant and often the only type of fits in MEI. They mainly affect the head, eyeballs, upper extremities and the diaphragm (Figure 9.2). The jerks are brief and singular or clusters that vary in frequency and violence. They manifest clinically with head nodding and, more rarely, flexion or extension of the body. The upper limbs usually fling upwards and outwards, whereas the eyeballs may

A typical patient with MEI with myoclonic jerks only and excellent prognosis

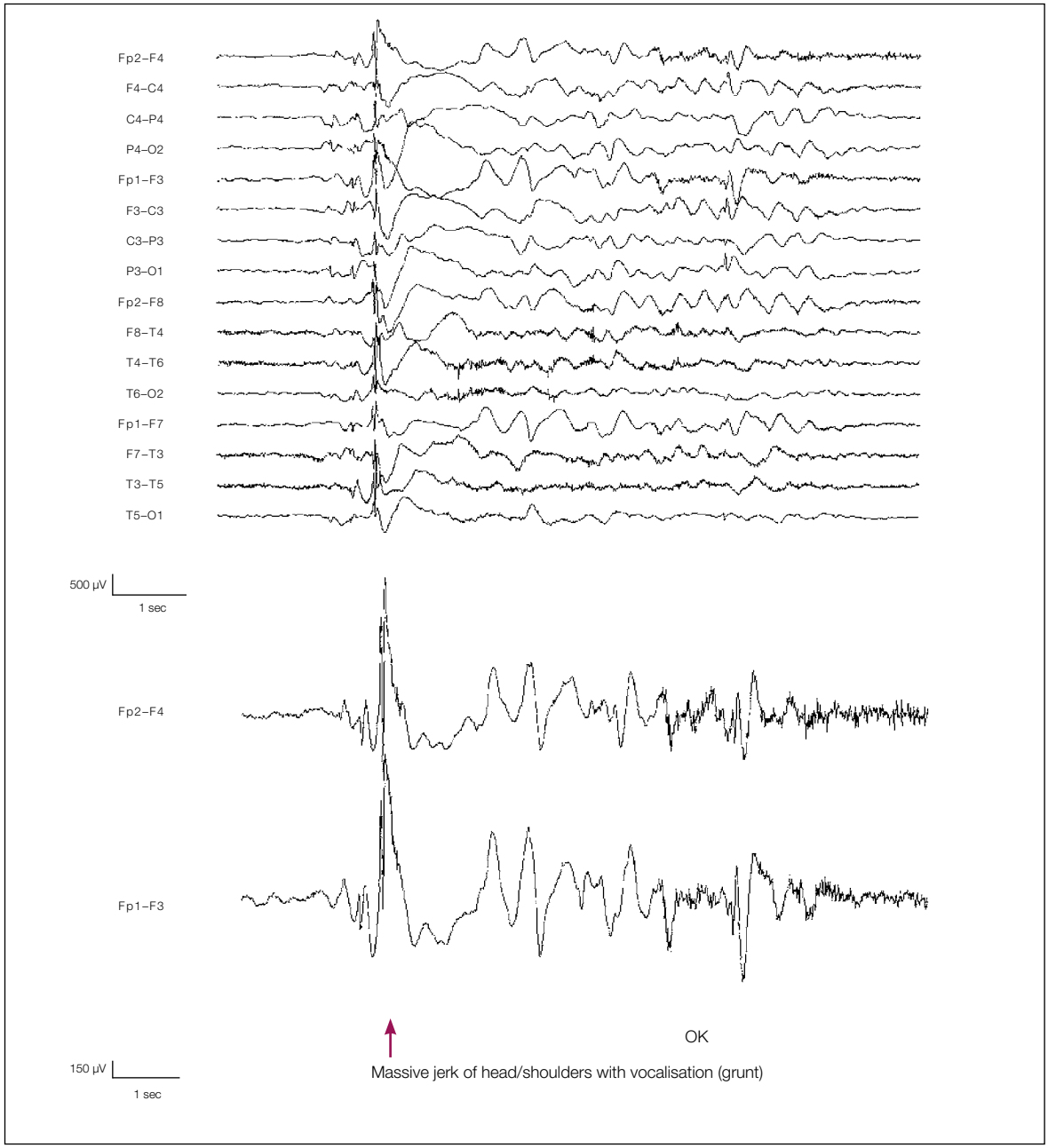

Figure 9.2 At age 3 years, this girl developed frequent and violent myoclonic jerks mainly in the head and shoulders with grunting noises. She was referred for a routine EEG 6 weeks from the onset of the jerks. On the basis of the history, the EEG technician applied video-EEG recording and deliberately extended the recording for clinical events. Two electroclinical seizures were captured, one of which is shown in this figure. Clinically, the first symptom was a sudden jerk of the head and shoulders backwards. This coincided with a giant (approximately 1 mV) spike or multispike–slow-wave followed by rhythmic slow activity at around 3–5 Hz, together with some random spikes and slow waves. The whole discharge lasted for approximately 5–7 s. The seizures stopped only when clonazepam was added to valproate (valproate was probably not needed). Subsequent serial EEGs were normal. At age 6 years she was no longer on medication, had developed well, was free of seizures and had a normal EEG.

roll upwards. A brief yell, probably resulting from the contraction of the diaphragm, sometimes accompanies the jerks. Falls may occur in the rare event that the lower limbs are affected. Myoclonic jerks may sometimes be very mild and inconspicuous.

Consciousness is commonly intact, but clusters of jerks may be associated with mild clouding.

Myoclonic seizures are usually spontaneous, occurring randomly in alert stages and exaggerated by drowsiness and NREM sleep. In some patients they tend to cluster on awakening or during the first hours of sleep. Reflex myoclonic jerks are sometimes prominent. Patients may have spontaneous or reflex-only jerks, or both.

The duration of the jerks is usually brief (1 or 2 s). Some children have marked clusters of generalised clonic seizures, exclusively during sleep or on awakening, which are prolonged by up to 15–20 min and can cause cyanosis without loss of consciousness.[112]

Other types of seizures: A fifth of patients have simple, brief and infrequent febrile seizures, usually preceding the onset of myoclonias.

A fifth of the patients may develop infrequent GTCSs, usually in their early teens.

Non-febrile seizures of uncertain categorisation, before the onset of myoclonic seizures or during the clinical course of the disease, have been reported.[113]

In one report, 6 of 11 children also had non-epileptic myoclonus.[124]

Precipitating factors

A fifth of patients have clinical and EEG photosensitivity.[111,116,122,123,125] In 10% the myoclonic jerks are predominantly or exclusively elicited by unexpected acoustic or tactile stimuli, and these may be of a better prognosis.[111,116,126,127] Single jerks or clusters of two to eight symmetrical limb jerks, mainly of the arms, are elicited by sudden noise or tactile stimuli when either awake or asleep. Startle is important. If expected the stimulus is ineffective.[111]

Aetiology

MEI is probably the earliest form of an IGE. There is no evidence that it is linked with juvenile myoclonic epilepsy or indeed any other type of IGE. A family history of epilepsy or febrile seizures is present in 30% of cases.

Familial MEI with autosomal recessive inheritance and linkage to chromosome 16p13 has been reported in one family, but in this case myoclonic seizures persisted into adulthood and all patients developed GTCSs in their early teens.[128]

Diagnostic procedures

All tests other than EEGs are normal. The inter-ictal EEG is normal. Spontaneous, inter-ictal GPSWD without associated jerks are exceptional.

The ictal EEG during jerks shows GPSWD or GSWD with a duration of 1–3 s (Figure 9.2). Frequently, ictal EEG discharges are limited to the rolandic and vertex regions.[121]

Drowsiness and early stages of sleep exaggerate the EEG discharges that may occur with or without jerks. EEG generalised discharges of mainly multiple spikes with jerks are often stimulus evoked by photic stimulation or unexpected acoustic or tactile stimuli. These occur in the awake or sleep stages.

Differential diagnosis

MEI should be differentiated from non-epileptic conditions such as hypnagogic jerks and Fejerman syndrome (benign non-epileptic myoclonus, page 94). Hypnagogic jerks do not occur in waking states and the EEG is normal. Benign non-epileptic myoclonus resembles epileptic spasms rather than the myoclonic jerks of MEI.

It should not be difficult to differentiate MEI from epileptic encephalopathies such as West, Dravet or Lennox–Gastaut syndrome with multiform seizures, severe EEG abnormalities and often neurodevelopmental deficits.

Prognosis

Remission usually occurs between 6 months and 5 years of onset. Patients with jerks provoked by auditory or tactile stimuli have a better prognosis, and the jerks are easily controlled with AEDs and

avoidance of precipitating factors. Conversely, EEG photosensitivity may persist many years after clinical remission.

In general, 10–20% of patients with MEI develop infrequent GTCSs in their early teens when medication has been withdrawn.

Psychomotor development is often normal, but 10–20% of children may later develop mild (usually) cognitive, behavioural or motor deficits, particularly if untreated.

Management

The response to AED treatment is usually excellent. Patients with photosensitivity are more difficult to control. Patients with auditory and somatosensory evoked myoclonus may not require treatment or withdrawal from AEDs may be initiated after 1 year.

With valproate, 80% of patients become seizure free. However, no other suitable AEDs have been tried in this condition. This should include monotherapy with small doses of:

- clonazepam, which is more effective than valproate in controlling myoclonic jerks
- levetiracetam, which is the most potent new anti-myoclonic drug and which also significantly suppresses photosensitivity).

AED withdrawal should be slow.

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Epileptic encephalopathies in infancy and early childhood

Epileptic encephalopathies are severe brain disorders in which the epileptic electrical discharges may contribute to progressive psychomotor dysfunction.[1–14] They start at an early age and manifest with electrographic EEG paroxysmal activity that is often aggressive; seizures that are commonly multiform and intractable; cognitive, behavioural and neurological deficits that may be relentless; and sometimes early death.

The concept of 'epileptic encephalopathies' is based on the assumption that aggressive ictal (seizure) and electrical (electrographic) epileptogenic activity during brain maturation is the main causative factor of progressive cognitive and neuropsychological deterioration or regression.[15,16] Conversely, this deleterious epileptic activity is a specific age-related brain reaction of excessive neocortical excitability to different pathological conditions, which are focal or diffuse, of symptomatic or idiopathic cause. This age-related epileptogenic reaction is peculiar to the immature brain and varies significantly in accordance with the stage of brain maturity at the time that this occurs. Thus, EEG demonstrates primarily burst-suppression patterns in the neonatal period, hypsarrhythmia in infancy and slow generalised spike–wave discharges (GSWD) in early childhood. With advancing age, the seizure and electrographic epileptogenic features may evolve from one to another age-related stage; i.e. from burst-suppression to hypsarrhythmia and then to slow GSWD. All epileptic encephalopathies have a tendency to abate, discontinue or even stop in adolescence but often with serious neurocognitive residuals.

The aetiopathophysiology of these syndromes has not been fully elucidated. It may be multiple and not necessarily the same for all. The major determinant is the brain functional and structural immaturity, with a 'cause–effect' interaction between abnormal electrical discharges generated by and modifying/acting upon neuronal circuits that are in development.

The following are syndromes of epileptic encephalopathies with onset in the neonatal period, infancy and early childhood:[17]

- early myoclonic encephalopathy (see Chapter 8)
- Ohtahara syndrome (see Chapter 8)
- West syndrome
- Dravet syndrome ('severe myoclonic epilepsy in infancy')[1,17,18]
- Lennox–Gastaut syndrome
- 'epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) including Landau–Kleffner syndrome (LKS)'
- myoclonic encephalopathy in non-progressive disorders.

I have also included hypothalamic epilepsy (page 317) in this section because a number of authorities consider it to be a form of epileptic encephalopathy with progressive severe seizures and cognitive and behavioural decline.[19,20]

In addition, I have also included atypical benign partial epilepsy of childhood (APEC) for reasons detailed on page 315, even though this is not a recognised epileptic syndrome.

Clarifications on classification

There are two changes in the new ILAE report of the Core Group[17] in comparison to the ILAE diagnostic scheme:[1]

1. LKS and 'epilepsy with continuous spike and waves during slow-wave sleep (CSWS)' are now considered as a single entity called 'epileptic encephalopathy with CSWS including LKS' (see page 303).
2. In addition, the new report now considers that there is sufficient evidence to support 'myoclonic status in non-progressive encephalopathies' as a syndrome, which it has called 'myoclonic encephalopathy in non-progressive disorders'.

West syndrome

West syndrome is an age-related specific epileptic encephalopathy resulting from multiple and diverse causes. It is characterised by a unique type of seizure called epileptic (infantile) spasms (Figure 10.1) and gross EEG abnormalities of hypsarrhythmia (Figure 10.2).[13,21–46] An expert consensus on West syndrome was published in November 2004.[46]

Clarifications on classification

The 1989 ILAE Commission[18] categorises West syndrome among the 'generalised cryptogenic or symptomatic epilepsies (age related)'. The 2001 ILAE diagnostic scheme[1] classifies West syndrome among the 'epileptic encephalopathies' and prefers 'epileptic spasms' to 'infantile spasms':

> West syndrome is commonly used synonymously with infantile spasms. However, officially infantile spasms refer to a type of seizures (preferably called 'epileptic spasms'), which are common but not exclusive for West syndrome.[1,47]

Demographic data

Onset is between 3 and 12 months (peak at 5 months) in 90% of cases. Males (60–70%) predominate. Incidence is 3–5 per 10,000 live births.

Clinical manifestations

> These bobbings… they come on whether sitting or lying; just before they come on he is all alive and in motion… and then all of a sudden down goes his head and upwards his knees; he then appears frightened and screams out.
>
> W. J. West (1841)[48]

West syndrome usually starts insidiously with mild epileptic spasms occurring two or three times in succession. The full-blown features develop in a few weeks with spasms typically occurring in clusters of 1–30 per day, with each cluster having 20–150 attacks. Usually the intensity of spasms in a given cluster will peak gradually but, towards the end of a cluster, the interval between spasms lengthens and their severity decreases until they gradually cease, often leaving the child exhausted. Rarely, patients manifest with single rather than clusters of spasms.[46]

The epileptic spasms are clusters of sudden, brief (0.2–2 s), bilateral tonic contractions of the axial and limb muscles. They are slower than myoclonic jerks and faster than tonic seizures (Figure 2.7). They may involve widespread muscle groups or be fragmented, involving flexion of the neck only (bobbing of the head), abdomen (mild bending) or just the shoulders (a shrug-like movement). The force is usually violent, but it may also be mild or intermediate.

Epileptic spasms of a child with Down syndrome who developed West syndrome

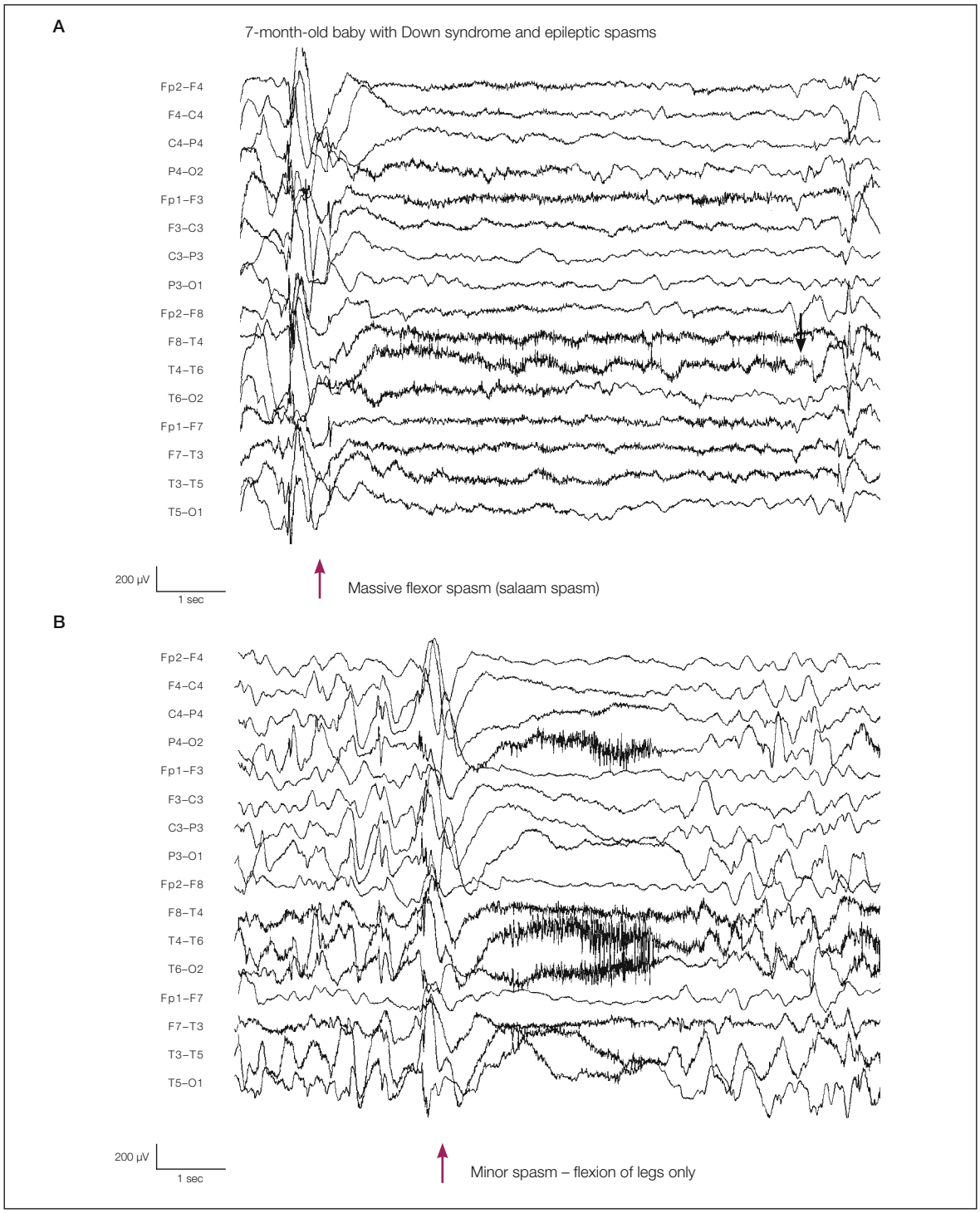

Figure 10.1 From a video-EEG recording of a 7-month-old baby with Down syndrome who developed West syndrome. There were numerous major (**A**) or minor (**B**) epileptic spasms.

The spasm is often followed by motionlessness and diminished responsiveness lasting up to 90 s. On rare occasions this 'arrest' effect constitutes the entire seizure. Alteration and pauses of respiration during the spasms are common (60%), whereas changes in heart rate are rare. A cry or laughter often follows the end of the attacks.

Each infant has more than one type of spasm, which may also be influenced by body positions:

Spasms may be flexor, more often flexor extensor and less frequently extensor.

Flexor spasms are common (40% of all) and are well expressed by the synonyms 'salaam spasms', 'jack-knife spasms', 'spasmes en flexion', 'grusse krampfe' and 'blitz, nick and salaam krampfe' (lightning, nodding and salaam spasms). There is abrupt flexion of the neck and the trunk, the arms raise forwards or sideways sometimes with flexion at the elbows, and the legs are elevated with flexion at the hips and knees.

Extensor spasms are less frequent, constituting approximately a fifth of all epileptic spasms, manifesting with sudden backwards movements of the head, hyperextension of the body, and extension and abduction of the limbs similar to the Moro reflex.

Flexor–extensor spasms are the most common spasms (constituting half of epileptic spasms), and combine sudden contraction of both flexor and extensor muscles with flexion of the neck, trunk and arms, but extension of the legs.

Epileptic spasms are usually symmetrical, although 1–30% may have lateralising features with the head or eyes turned to one side or one limb consistently moving more vigorously.[49–51] Eye deviation or nystagmoid movements occur in 60% of epileptic spasms and may be an isolated ictal symptom.

Subtle epileptic spasms may appear as episodes of yawning, gasping, facial grimacing, isolated eye movements and transient focal motor activity.[46]

There is no aetiological or prognostic significance to the frequency, violence or flexion–extension of epileptic spasms. However, asymmetrical, lateralised or unilateral spasms are highly correlated with contralateral cerebral lesions of symptomatic West syndrome.

The epileptic spasms predominantly occur on arousal and in alert states, less often during non-rapid eye movement (NREM) sleep (3%) and exceptionally during REM sleep.[6,40] The twilight state, just before sleep or just after waking, often acts as a precipitating factor. Sudden loud noises or tactile stimulation, but not photic stimulation, may precipitate epileptic spasms. Feeding may also provoke the spasms.

Other seizure types: In symptomatic cases, focal seizures with lateralised motor behaviours occur frequently. These may generate secondarily epileptic spasms in infants with focal cerebral lesions and a poor response to adrenocorticotrophic hormone (ACTH).

Drop attacks (tonic, atonic or both) may be the first manifestation of West syndrome with late onset.

Developmental delay, mild or severe, predates the onset of spasms in about two-thirds of cases. In the other third, the infants are normal before the onset of epileptic spasms. Deterioration of psychomotor development usually occurs with the onset of epileptic spasms and affects head control, reaching for objects and eye tracking. Axial hypotonia, lack of hand grasping or eye contact may have a negative prognostic significance.

Clinical note

Reversible causes for epileptic spasms

Drugs such as theophylline[57] or anti-allergic agents of histamine H_1-receptor antagonists, particularly ketotifen,[58] may induce epileptic spasms and hypsarrhythmia that are entirely reversible upon drug withdrawal.

Pyridoxine dependency, which is treatable, can in rare instances present with epileptic spasms. This is most likely when other seizure types have occurred before the onset of spasms.[46]

Aetiology

The aetiology is multiple and diverse. Aetiologically, West syndrome is classified, in order of prevalence, as symptomatic (about 80% of all) due to discernible organic insults, and cryptogenic or idiopathic

Main causes of symptomatic West syndrome

- Pre-, peri- and postnatal brain ischaemia are probably the most common causes (responsible for 20–80% of cases) of symptomatic West syndrome
- Brain congenital anomalies are found in a third of cases
- Half of all patients with tuberous sclerosis have epileptic spasms (constituting 7–25% of West syndrome) and this is significant because of a better response to vigabatrin
- Other common causes of epileptic spasms are malformations of cortical development and include Aicardi syndrome, agyria, pachygyria and laminar heterotopia, hemimegaloencephaly and focal cortical dysplasia, bilateral peri-sylvian microgyria, porencephaly and their variations
- Infants with chromosomal abnormalities are found in all series of West syndrome. Of children with Down syndrome, 3% may develop epileptic spasms and these appear to have a much better prognosis with regard to seizures
- Congenital or acquired infections, including viral (cytomegalovirus, rubella, herpes simplex virus, enterovirus, adenovirus and pertussis), bacterial (meningococcus and pneumococcus), protozoan (toxoplasmosis) and others, are a significant cause of epileptic spasms. The outcome of epileptic spasms in these children is very poor, signifying the importance of prevention and early treatment of the causative agent
- Inborn errors of metabolism are rare
- Hypothalamic hamartoma may occasionally present with infantile spasms as an initial or early seizure type

Table 10.1

(5–30%). The prevalence of these broad aetiological groups varies significantly in accordance with the methodological investigations.

Symptomatic West syndrome is by far the most common. Several pre-, peri- and postnatal insults are responsible (Table 10.1), and range widely from hypoxia–ischaemia, infections, trauma and intracranial haemorrhage, to malformations of cortical development, neurocutaneous diseases, genetic and chromosomal abnormalities and, less often, inborn errors of metabolism.

Probably symptomatic (cryptogenic) West syndrome may have a prevalence of 10–15%. With improved technology, their prevalence is declining as their causes are increasingly being documented.

Idiopathic West syndrome, with normal pre-morbid development and possible hereditary predisposition such as a family history of epilepsy, febrile seizures or EEG genetic patterns, constitutes 5–30% of all cases. Idiopathic West syndrome may have a good prognosis with regard to seizures and psychomotor development.

Genetic factors in West syndrome: unless the aetiology is a specific genetic disorder, such as tuberous sclerosis, or a twin pregnancy, familial occurrence is low at 4% or 5% of cases.[52] A familial idiopathic West syndrome has been described.[53] In rare families, West syndrome occurs in an X-linked recessive mode exclusively in male offspring from asymptomatic mothers. X-linked cases are associated with alanine expansion mutations of the aristaless-related gene localised to the chromosomal region Xp21.3-Xp22.[54–56]

Diagnostic procedures

A thorough clinical neurodevelopment assessment and ophthalmological and ultraviolet skin examination may reveal the underlying cause in symptomatic cases, including tuberous sclerosis and Aicardi syndrome. Laboratory screening for electrolyte, metabolic or other disturbances are usually normal. Infectious diseases may be apparent from clinical presentation and infants with suspected infection should have the appropriate investigations, including a cerebrospinal fluid (CSF) examination. Infants with frequent vomiting, lethargy, failure to

thrive, peculiar odours and unexplained neurological findings should have urine and serum amino acid screening and serum ammonia, organic acid, lactate, pyruvate and liver function tests. Most paediatricians rightly recommend these neurometabolic tests in all cases unless an alternative cause is clear. Chromosome analysis may lead to a specific diagnosis in infants with unexplained West syndrome.

Brain CT scan and, more specifically, MRI are indicated. These should be performed before steroid treatment, which may lead to apparent atrophy on the CT or MRI scan. Positron emission tomography (PET) of brain glucose metabolism is highly sensitive in detecting focal cortical abnormalities in patients with West syndrome, even when the CT or MRI scan are normal.[59] Bilateral hypometabolism of the temporal lobes, even in the absence of abnormal CT and MRI scans, has a bad prognostic significance.[36]

Electroencephalography[21,28,38,60,61]

Hypsarrhythmia (*hypsos* = high) is the archetypal inter-ictal EEG pattern and occurs in two-thirds of patients. This EEG pattern is one of anarchy, being a chaotic mixture of giant abnormal, arrhythmic and asynchronous biological brain electrical activity of slow and sharp waves, multi-focal spikes and polyspikes. As a result of their high amplitude, individual components and localisation are impossible to detect at routine sensitivity recordings of 100 μV/cm (Figure 10.2). There are no recognisable normal rhythms.

Asymmetrical and other patterns of modified or atypical hypsarrhythmia occur in a third of cases. Various EEG features have traditionally been labelled as modified or atypical hypsarrhythmia. Their presence depends on the stage of West syndrome at which the EEG is performed. It may depend on treatment and as an aggregate variable, it probably has little practical prognostic significance in randomised studies.[46]

REM sleep shows relative EEG normalisation. In NREM sleep, hypsarrhythmia becomes fragmented and presents with discontinuous, repetitive, high-amplitude discharges of spikes/polyspikes and slow waves, which are more synchronous than in the awake-stage EEG. These discharges are separated by low-amplitude EEG activity that may contain sleep spindles. This sleep EEG pattern may be seen in some infants with a relatively normal awake EEG, mainly at the onset of epileptic spasms.

Certain inter-ictal EEG patterns may contribute to an aetiological diagnosis

Symmetrical hypsarrhythmia is most likely to occur in idiopathic and cryptogenic cases. Asymmetrical and unilateral hypsarrhythmias almost always indicate ipsilateral brain structural lesions. Consistently focal slow waves indicate localised lesions. These become more apparent with intravenous diazepam, which reduces the amount of hypsarrhythmia.

Lissencephaly and Aicardi syndrome may have relative specific EEG patterns with frequent burst-suppression activity. West syndrome of tuberous sclerosis rarely has a typical hypsarrhythmic appearance, whereas spike foci with secondary bilateral synchrony in sleep are frequent.

Progress of hypsarrhythmic EEG patterns with age: The chaotic hypsarrhythmic pattern of West syndrome gradually becomes more organised, fragmented and disappears with age. By age 2 and 4 years, this may be replaced by the slow GSWD pattern of Lennox–Gastaut syndrome. Multi-focal independent spike EEG patterns appear first, followed by generalised spike discharges from where the slow GSWD of Lennox–Gastaut syndrome emerges.[62]

Ictal EEG

Ictal EEG patterns are variable with at least 11 different types, lasting for 0.5 s to 2 min. The most common and more characteristic pattern in 72% of the attacks is a brief duration (1–5 s; Figure 10.1), and it consists of (1) a high-voltage, generalised slow wave, (2) episodic, low-amplitude fast activity and (3) marked diffuse attenuation of EEG electrical activity (electrodecremental ictal EEG pattern). A high-amplitude, biphasic, slow-wave or spike-and-wave activity may occur.

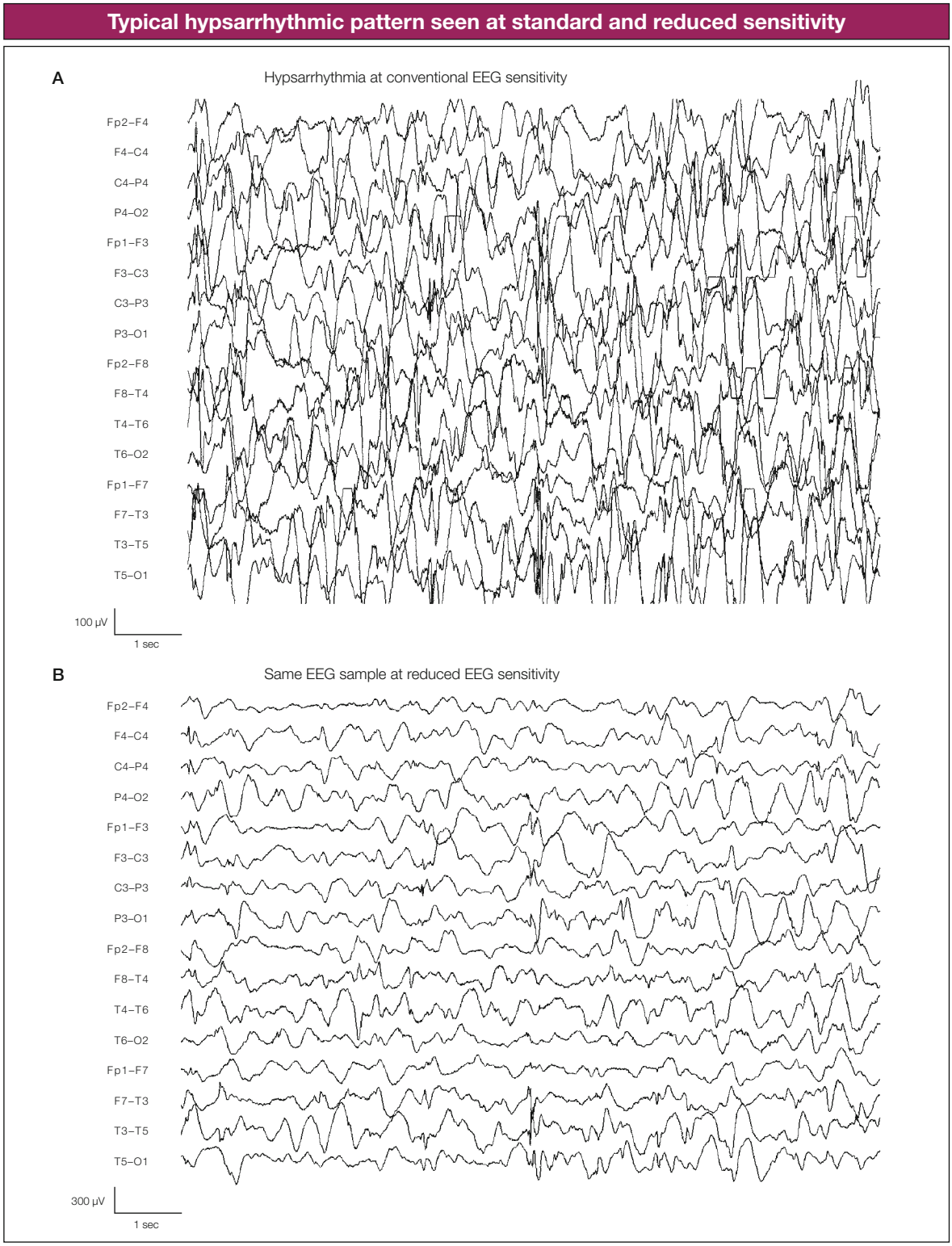

Figure 10.2 Same typical hypsarrhythmic pattern seen at standard (**A**) and reduced (**B**) sensitivity.

Differential diagnosis

West syndrome should be easy to diagnose because of the unique characteristic features of each attack and because of the serial and unprovoked clustering. However, parents and physicians often miss this.[29] Erroneous diagnoses include exaggerated startle responses or 'colic and abdominal pain', non-epileptic episodic disorders and gastro-oesophageal reflux.[29]

Benign myoclonus of early infancy (benign non-epileptic infantile spasms or Fejeman syndrome)[63–65] is not an epileptic condition, but may cause diagnostic problems because of a similar age at onset and similar spasms (see page 112). A normal EEG is of decisive significance in the differential diagnosis.

Benign neonatal sleep myoclonus[66–68] (see page 112) is another non-epileptic condition that may be mistaken as epileptic spasms, although myoclonic jerks and not spasms are the main symptom and they occur only during sleep. The EEG is normal.

Sandifer syndrome of gastro-oesophageal reflux (see page 112) may also be confused with epileptic spasms. Head cocking, torticollis, abnormal dystonic posturing of the body and mainly opisthotonus may imitate epileptic spasms. However, these spells often occur in relation to feeds and the babies usually have a history of vomiting, a failure to thrive and respiratory symptoms. Hiatus hernia is common and the EEG is normal.

West syndrome is also easily differentiated from *other benign or severe forms or epilepsies of this age group* because of the unique presentation of epileptic spasms that differs significantly from myoclonic jerks and tonic seizures.

Prognosis

West syndrome is a serious epileptic encephalopathy. The following conclusions probably give a fair account of the overall prognosis irrespective of cause.[22,43,52,69–77]

Mortality has fallen to about 5% in developed countries because of improved medical care. Deaths may be due to the underlying cause and treatment mainly with ACTH and corticosteroids. It is less often due to seizures.

Of patients with West syndrome, 60% develop other types of seizure that are usually resistant to treatment. Lennox–Gastaut type and complex focal seizures are the most common.

Half of the patients have permanent motor disabilities, and two-thirds have, usually severe, cognitive and psychological impairment.[22,72–75] Autistic behaviour, hyperkinetic syndrome and psychiatric disorders may even be seen in otherwise normal patients with a previous history of epileptic spasms.

Only about 5–12% of patients have normal mental and motor development.

However, prognosis is determined almost exclusively by the causative factors and their severity. The epileptic spasms themselves and their response to treatment may not be of significant prognostic significance.

Diagnostic tips

Recognition of epileptic (infantile) spasms is easy due to the characteristics of the individual attacks and mainly their clustering, often on arousal.

On a practical level it is necessary to ask the parents to demonstrate and imitate the attacks physically rather than merely to describe them. If in doubt, demonstrating or showing a video with typical attacks is often conclusive: the 'that's it' phenomenon (see page 4).

Benign phenomena such as a Moro reflex, attacks of colic or even attempts to sit up may be a cause of confusion that can be avoided by remembering that epileptic spasms occur in clusters. Singular events are rare.

The consensus is that idiopathic and cryptogenic West syndrome have a significantly better prognosis than symptomatic cases, with 15–30% of patients achieving relative normality. More optimistic is the view that the seizures cease and development is normal in all patients who fulfil the following strict inclusion criteria of idiopathic West syndrome:[32,78]

- normal development before, during and after the active seizure period, with preservation of visual function

- normal functional and structural brain imaging or other symptomatic causes
- symmetrical epileptic spasms and EEG hypsarrhythmia.

Additional helpful criteria of the idiopathic West syndrome are:

- a family history of other forms of idiopathic epilepsy or febrile seizures
- EEG genetic traits, such as photoparoxysmal responses or spike–wave discharges or rolandic spikes
- an EEG-identifiable basic activity and sleep spindles despite a hypsarrhythmic pattern
- absence of focal inter-ictal EEG slow-wave abnormalities even after intravenous diazepam
- reappearance of hypsarrhythmia between consecutive spasms of a cluster
- spontaneous remissions in untreated patients, which occur frequently.[79]

Management

An American Academy of Neurology practice parameter report on the drug treatment of West syndrome has recently been published.[44]

ACTH and less often corticosteroids or vigabatrin are the drugs of choice, controlling the epileptic spasms in two-thirds of patients within days of initiating any of these medications.[44,45] However, no treatment has been conclusively shown to improve the long-term intellectual development of these infants.

Lamotrigine, levetiracetam, nitrazepam, pyridoxine, sulthiame, topiramate, valproate and zonisamide are also used as adjunctive medications when ACTH and vigabatrin fail.

There is no firm evidence of a beneficial treatment effect with long-term pyridoxine use in West syndrome. Customarily, children in whom the aetiology of West syndrome cannot be definitely established receive an intravenous infusion of 100–200 mg of pyridoxine during EEG monitoring. Infants with pyridoxine dependency, which is rarely the cause of epileptic spasms, usually improve within minutes.[46] However, intravenous pyridoxine is associated with a risk of apnoea and may not be associated with rapid resolution of the hypsarrhythmia.[46]

Resective neurosurgery may be the desperate solution in intractable cases with localised structural lesions. However, this is still in the provisional stage provided for hopeless cases that may need multi-lobar resection or hemispherectomy.[80,81] Persistent spasms not amenable to focal surgery and patients who suffer from drop attacks may benefit from total callosotomy, whereas anterior callosotomy is ineffective.[82]

Vagus nerve stimulation is not recommended by the ILAE.[83]

Dravet syndrome

Synonym: severe myoclonic epilepsy in infancy.

Dravet syndrome[84–92] is a rare progressive epileptic encephalopathy that is genetically determined.

Clarifications on classification

The 1989 ILAE classification used the descriptive nomenclature 'severe myoclonic epilepsy in infancy' and classified it among 'epilepsies and syndromes undetermined as to whether they are focal or generalised'.[18] 'Dravet syndrome' is the eponymous term introduced by the ILAE Task Force.[1,17]

Demographic data

Onset is always within the first year of life, with a peak age at 5 months, affecting previously normal children. Twice as many boys are affected. The

prevalence is approximately 3–6% of epilepsies starting before the age of 3 years. The incidence is approximately 1 per 30,000 infants.[93]

Clinical manifestations

Dravet syndrome is characterised by a tetrad of seizures, which is seen in more than half of cases:

- early infantile febrile clonic convulsions
- myoclonic jerks
- atypical absences
- complex focal seizures.

Convulsive, myoclonic or absence status epilepticus are frequent.

Not all of the seizures may occur; a fifth of patients may not have myoclonic jerks.[84,93–95] Tonic seizures are exceptional if they do occur.

Diagnostic pitfalls

Note that:

- not all patients develop myoclonic jerks
- not all patients start with febrile convulsions
- not all patients develop absence seizures.

There are three periods of evolution with Dravet syndrome.

The first period is relatively mild (the pre-seismic period), it lasts for 2 weeks to 6 months and manifests mainly with febrile clonic convulsions intermixed with some tonic components. These are mainly unilateral and less often generalised. They are usually long (10 min) progressing to convulsive status epilepticus in about a quarter of cases.

In three-quarters of patients seizures are usually provoked by hyperthermia of around 38°C, minor infections, immunisations or hot baths. The remaining one-quarter of patients have non-febrile convulsive seizures. Isolated episodes of focal myoclonic jerking and, more rarely, focal seizures may predate or appear just before the febrile convulsions.

These seizures recur frequently within 6–8 weeks and later may also be non-febrile.

The second period is relentlessly aggressive (the seismic period) with the emergence of other multiple-seizure types and severe neurocognitive deterioration. Various forms of febrile and non-febrile convulsive seizures, myoclonic jerks, atypical absences and complex focal seizures occur on a daily basis and frequently evolve to status epilepticus.

Myoclonic seizures usually appear 1 or 2 years after onset but may also occur at a much earlier age or even before febrile convulsions. They affect facial muscles, limbs and axial muscles causing flexion or extension and often falls. They often occur several times per day and may cluster in myoclonic status epilepticus. However, other patients may have jerks only hours or days before a convulsive seizure. Myoclonic jerks are usually violent but they may also be mild and inconspicuous. They usually disappear during stages III and IV of sleep.

Atypical absence seizures (in 40–93% of patients) are short (5 or 6 s) with moderate impairment of consciousness and often with myoclonic jerks.

Focal seizures (almost half of patients) present with atonic or adversive components, autonomic phenomena (pallor and peri-oral cyanosis) and automatisms. They occasionally progress to generalised tonic–clonic seizures (GTCSs).

Status epilepticus: Myoclonic, atypical absence, complex focal and convulsive status epilepticus, either alone or in combination, are common and frequent. These various types of status epilepticus may last for hours or days and may be facilitated or precipitated by photic stimulation, eye-closure or fixation on patterns.

Absence status epilepticus of decreased responsiveness often combines with unsteadiness, dribbling, frank ataxia and with erratic small myoclonias, sometimes associated with hypertonia. Complex focal and rarely simple focal status epilepticus occur. Episodes of EEG GSWD interspersed with erratic small myoclonic jerks may persist for hours or days.

Cognitive and neurological deterioration is variable but usually severe. It develops between the second and sixth years and remains stable later. Neurological deficits consist of ataxia, pyramidal symptoms and paroxysmal movements.[96]

The third period is static (the post-seismic period). The seizures may improve, but serious mental and neurological abnormalities are irreversible.

The relentless worsening and progression of the symptoms usually comes to a halt at around the age of 11 or 12 years. This marks the post-seismic period where seizures improve but do not stop.

Convulsive seizures, less dramatic and less frequent, occur mainly at the end of the night and are often precipitated by fever. Some diurnal seizures may manifest with clonic convulsions of a limb or the face, followed by hypotonia and sleep. Febrile status epilepticus may continue in adolescence.

Myoclonic attacks and atypical absence status epilepticus tend to decrease but they are still exacerbated by fever.

Cognitive and neurological deficits and signs persist without worsening.

Seizure-precipitating factors

Hyperthermia (febrile illnesses, warm environment, hot baths) is a frequent precipitating factor, particularly at onset of seizures, but this may continue in adolescence ('febrile seizures plus'). Photic and pattern stimulation, movements and eye closure precipitate GSWD, myoclonic jerks and absence seizures. A quarter of patients have self-induced seizures by hand waving or pattern stimulation.

Aetiology

Dravet syndrome is mostly genetically determined, but the mode of inheritance is unknown. Approximately half of patients have a family history of various epileptic syndromes (including idiopathic generalised epilepsy) and mainly febrile seizures. Rarely, siblings or twins may suffer from this syndrome.

A recent breakthrough discovery is that Dravet syndrome is related and may be the severest phenotype of the 'epilepsy with febrile seizures plus' (EFS+) spectrum (see page 265). Mutations in the voltage-gated sodium channel gene *SCN1A* were found in a high percentage (range 35–100%) of patients with Dravet syndrome.[86,97–101] Most cases of Dravet syndrome arise from *de novo* mutations (missense, frame shift and nonsense) of the *SCN1A* gene.[101–104] Inherited *SCN1A* gene mutations appear to associate with mild phenotypes in most family members.[101,103] Phenotypes with complete (myoclonic seizures and/or atypical absences) or incomplete (only segmental myoclonias) seizure semiology show no difference in the type or rate of *SCN1A* gene mutations. The differences may be attributed to other genetic mechanisms.[104] The mutant channels show remarkably attenuated or barely detectable inward sodium currents.[99]

More recently, the phenotypic spectrum of *SCN1A* gene defects has been broadened to include 'intractable childhood epilepsy with GTCSs'[101] and other borderline cases of Dravet syndrome.[86] Other sodium channel genes or modifying genes may be involved in the pathogenesis of Dravet syndrome,[86] as suggested by the findings of (1) a family with an individual with Dravet syndrome in whom a third $GABA_A$-receptor γ_2-subunit mutation was found;[105] (2) a family in which the proband and the healthy father shared the same mutation of the *SCN1A* gene;[86] and (3) families with definite Dravet syndrome who do not carry the mutant for the *SCN1A* gene.[106] Dravet syndrome is likely to result from the cumulative effects or interaction of a few or several genes, of which the EFS+ gene is merely one player.[103]

Diagnostic procedures

The general consensus is that there is no metabolic abnormality. Tissue biopsies are normal. Other causes of progressive myoclonus should be excluded.

Genetic testing: a severe *SCN1A* gene defect, if present, is strongly supportive but not diagnostic of Dravet syndrome.[86] No mutations are found in a relatively high percentage of typical cases and some patients have copy number variations in SCN1A which are not detectable by conventional sequencing. Their detection requires the application of specific techniques, such as multiplex ligation-dependent probe amplification or equivalent technologies.[107]

Brain CT and MRI scans are either normal or show mild cerebral or cerebellar atrophy. Functioning brain imaging may be normal or show focal hypoperfusion and hypometabolism, even when the MRI is normal.[87,88]

Electroencephalography

The EEG shows a similar progression to that of the clinical state, from normal to severely abnormal.[84,97,108–111]

The inter-ictal EEG may initially be normal, but 20% show generalised photoparoxysmal responses. The 'theta pointu alternant pattern' may be seen (Figure 8.4). Within 1 year the EEG becomes very abnormal in two-thirds of patients. The background progressively deteriorates with diffuse theta and delta waves. Brief asymmetrical paroxysms of polyspike/spike–slow-wave discharges (GPSWD) usually dominate the EEG. These may not be recorded in 10–15% of patients. Focal and mainly multi-focal abnormalities of sharp or slow spike-waves are frequent. EEG paroxysmal abnormalities are facilitated by sleep.

Photoparoxysmal discharges occur in 40% of patients but persist in less than 5%. Eye closure and pattern stimulation may also induce generalised discharges and myoclonic jerks.[5,9,23,24]

The ictal EEG varies according to the type of seizure. Myoclonic jerks are often but not always associated with GPSWD. Atypical absences occur with irregular slow GSWD. Focal seizures show focal ictal discharges, frequently with localised episodic fast activity and rapid spikes.

Differential diagnosis

The sequence of polymorphic seizures, their resistance to treatment and the progression to mental and neurological deterioration are characteristic of Dravet syndrome. An early diagnosis of Dravet syndrome can be reliably made using clinical criteria from the second or third seizure in the first year of life.

At the initial pre-seismic period, febrile seizures are the most apparent diagnosis to differentiate (see diagnostic tips box).

Difficulties may exist in differentiating Dravet syndrome from 'intractable childhood epilepsy with GTCSs'.[101,112] This is an entity recognised primarily in Japanese literature[101] and may be the same disorder as the 'severe IGE of infancy with GTCSs' described by Doose.[112] Patients develop febrile seizures by 1 year of age, often recurring in clusters or status epilepticus, with GTCSs remaining the predominant seizure type. Cognitive decline is usual and neurological deficits may develop.[101] Borderline cases have clinical features similar to those of core Dravet syndrome, but are not necessarily consistent with all the accepted criteria for such a diagnosis.[84,86,109]

Lennox–Gastaut syndrome is easily differentiated because of the predominance of tonic seizures, frequent pre-existing neurological abnormalities and absence of febrile convulsions.

In *'epilepsy with myoclonic–astatic seizures (EM-AS)'* of Doose (see page 378),[3] focal seizures and focal EEG abnormalities do not usually occur.

Myoclonic epilepsy in infancy has only brief myoclonic seizures (see page 269), febrile convulsions are milder and the EEG is markedly different from Dravet syndrome.

Progressive myoclonic epilepsies[33] may have similar features, although at this age they may run a different course (Chapter 17).[87,88,108]

Prognosis

This is a severe epileptic encephalopathy disorder with marked mental and neurological deficits. All but a few exceptional cases have a sinister prognosis.[87,88,108] Early death occurs in 15% of patients. Probably less than 10% of patients preserve some communicative skills.

Diagnostic tips

Febrile seizures in Dravet syndrome

Paediatricians should maintain a high index of suspicion for Dravet syndrome if the febrile seizures are:

- prolonged beyond 15 or 30 min
- unilateral
- mainly clonic
- frequent
- precipitated by low fever, often <38°C
- of early onset (before 1 year of age)
- concurrent with non-febrile seizures.

The diagnosis is nearly certain if intractable myoclonic jerks and mental deterioration appear within 1 or 2 years from onset.

Management

Seizures are intractable. Anti-epileptic drugs (AEDs) may reduce them but do not control them and it is doubtful if they affect the outcome.[87,88,108] Valproate, benzodiazepines, melatonin,[113] phenobarbital (in convulsive seizures), ethosuximide (in absence and myoclonic seizures) and bromides are temporarily beneficial. Carbamazepine and phenytoin are contraindicated. Of the newer AEDs, topiramate,[114] stiripentol,[115] zonisamide and mainly levetiracetam[116] have been found to be useful.[84] Stiripentol has been recently licensed in 2009 to use in conjunction with clobazam and valproate as adjunctive therapy for refractory GTCS in Dravet syndrome. Lamotrigine is contraindicated.[117]

A ketogenic diet is beneficial, starting as early as possible.[118]

Long, generalised or unilateral convulsions should be prevented by early treatment of infectious diseases and hyperthermia and avoidance of precipitating factors.

Status epilepticus is treated as in any other similar condition (see Chapter 3).

Lennox–Gastaut syndrome

Lennox–Gastaut[5,119–124] syndrome is a childhood epileptic encephalopathy characterised by the triad of:

- polymorphic intractable seizures that are mainly tonic, atonic and atypical absence seizures
- cognitive and behavioural abnormalities
- EEG with paroxysms of fast activity and slow (<2.5 Hz) GSWD.

Clarifications on classification

There is no consensus of what Lennox–Gastaut syndrome is (see Table 10.2 for the inclusion criteria). Lennox–Gastaut syndrome was categorised among the generalised cryptogenic or symptomatic epilepsies in the 1989 classification,[18] but the ILAE Task Force now classifies it among the epileptic encephalopathies.[1,17]

Lennox–Gastaut and other syndromes such as EM-AS (see page 378) have undefined boundaries resulting in what appears as 'an overlap of syndromes':[125,126]

> The epilepsies described under the headings of Lennox–Gastaut syndrome and of myoclonic epilepsies raise one of the most controversial problems of childhood epileptology… There is still considerable confusion surrounding the concept of the Lennox–Gastaut syndrome, so the definition of the syndrome and its relationship to other forms of epilepsy, especially those that feature myoclonic seizures, remains a subject of dispute. Only the more typical syndromes are reasonably well defined, but many patients are impossible to include in a definite category.[126,127]
>
> There is hardly another field in paediatric epileptology presenting such terminological uncertainty and confusion as is to be found in the domain of epileptic syndromes with generalised minor seizures of early childhood.[125]

The so-called 'myoclonic variant Lennox–Gastaut syndrome' is probably a mistaken diagnosis of EM-AS.[126] Similarly, other myoclonic epilepsies with brief seizures reported as intermediate cases between EM-AS and Lennox–Gastaut syndrome most likely reflect the undefined boundaries of the current definitions.

Focal epilepsies with secondary bilateral synchrony has been another major cause of confusion. Of Gastaut's original cases, 60%, when re-evaluated, were suffering from epilepsy with secondary bilateral synchrony and did not have paroxysms of fast rhythms during sleep.[128]

To emphasise the diversity of opinion over Lennox–Gastaut syndrome, I take the example of two studies from the same country (USA) published in the same journal (*Epilepsia*).[129,130] In one of them[129] the inclusion criteria were:

- the onset of multiple seizure types before the age of 11 years

Inclusion criteria for Lennox–Gastaut syndrome

These are not well defined but most authorities demand the following triad:

- At least two types among tonic, atonic and atypical absence seizures. Some authors demand that atypical absences are one of the mandatory seizure type. Others prefer tonic seizures. Myoclonic seizures are not a prerequisite criterion for inclusion or exclusion
- Generalised slow spike–wave discharges. Although all agree with this, episodic fast activity is justifiably an additional requested EEG abnormality by others
- Impaired intellectual functioning. There are recent reports that this is no longer a prerequisite of Lennox–Gastaut syndrome

Age at onset, abnormal or normal brain imaging and causative factors are usually not considered important. Accordingly, Lennox–Gastaut syndrome may even start in adult life

Table 10.2

- at least one seizure type resulting in falls
- an EEG demonstrating slow GSWD (<2.5 Hz).

In the other study[130] the criteria were:

- multiple seizures (two or more) with one being tonic seizures
- slow GSWD (at least in one EEG)
- age at onset of any time.

Mental handicap was not used as a diagnostic criterion in either of them.[129,130]

Demographic data

Onset is between 1 and 7 years with a peak at 3–5 years. Boys (60%) present slightly more than girls. The incidence is low at 2.8 per 10,000 live births.[131] However, because of its intractable nature, the prevalence is relatively high at about 5–10% of children with seizures.[124]

Clinical manifestations[124]

Lennox–Gastaut syndrome is characterised by polymorphic seizures and neuropsychological decline. The most characteristic seizures are tonic fits, atypical absences and atonic seizures, in that order. Myoclonic jerks occur in 11–28% of patients alone or in combination with other seizures. However, myoclonic jerks do not predominate in the 'pure' Lennox–Gastaut syndrome.

Onset may be insidious with symptoms appearing anew for no obvious reason in cryptogenic cases. Previous psychomotor deficits are apparent in symptomatic cases. Cognitive and behavioural abnormalities are present before seizure onset in 20–60% of cases.

Half of the cases of West syndrome and other infantile epileptic encephalopathies progress to Lennox–Gastaut syndrome. Conversely, 10–30% of patients with Lennox–Gastaut syndrome developed from West syndrome or other epileptic encephalopathies, although the transition phase is difficult to evaluate. Focal and generalised seizures are also common predecessors.

Tonic seizures are the most common (approximately 80–100%) and probably the most characteristic seizure type in Lennox–Gastaut syndrome (see Figures 10.3–10.5). These are usually symmetrical, commonly brief (2–10 s) and of variable severity from inconspicuous to violent. Descriptively, tonic seizures are axial, axorhizomelic and global tonic seizures (see page 39).[132]

A series of tonic seizures, reminiscent of epileptic spasms but of longer duration, may occur, particularly when Lennox–Gastaut syndrome develops from West syndrome.

Concurrent autonomic manifestations may occasionally be the prominent symptom of the attacks.

Tonic seizures occur in wakefulness and more often during NREM sleep. Some patients may have hundreds

Samples from a video-EEG of a 10-year-old girl with severe symptomatic Lennox–Gastaut syndrome from age 6 months

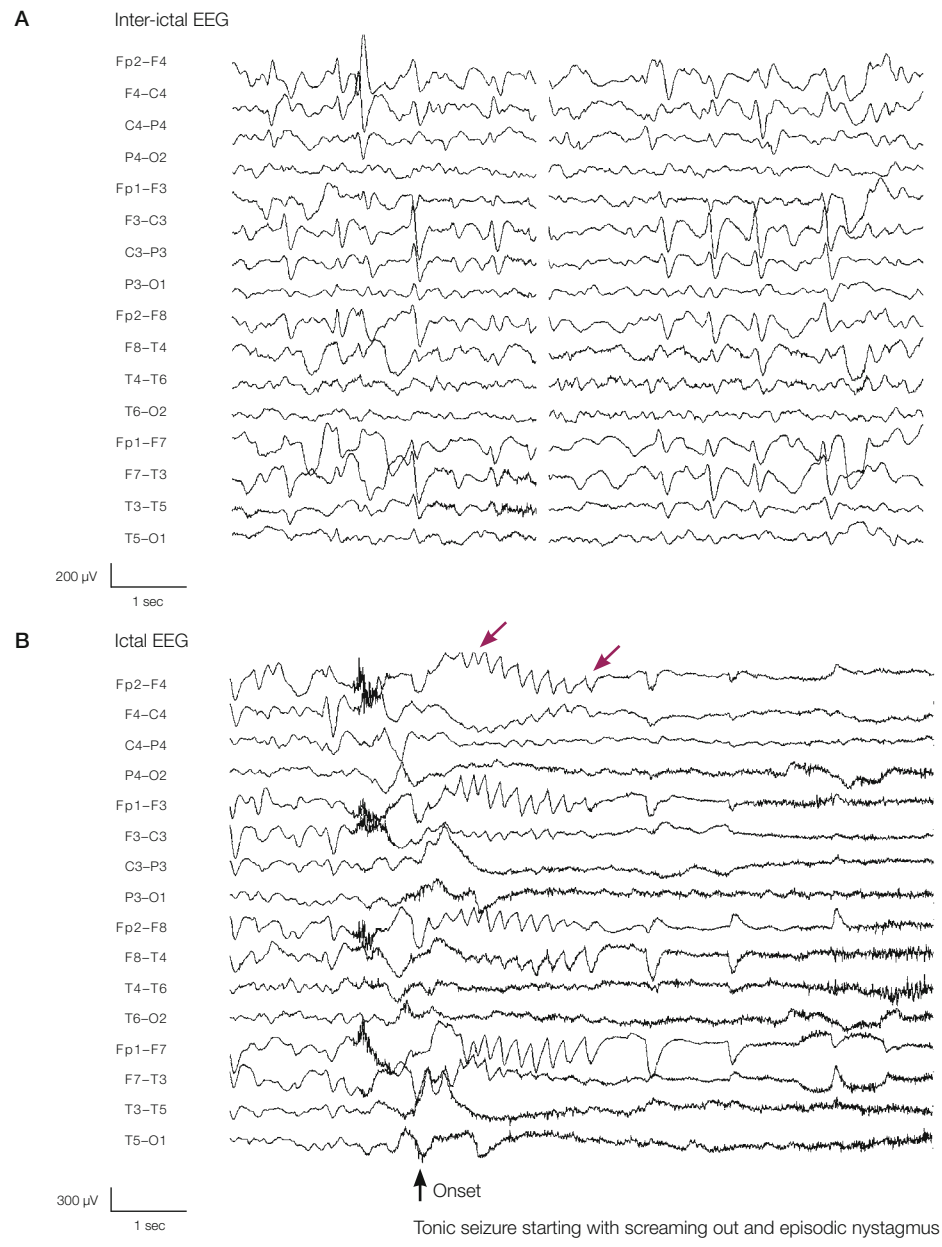

Figure 10.3 This girl had a marked neuronal migration deficit in the right hemisphere and her seizures were multiform and intractable to any medication. (**A**) A grossly abnormal inter-ictal EEG with continuous, high-amplitude, sharp–slow-waves or spike–slow-waves. These were multi-focal right or left, mainly frontal but also midline or posterior. (**B**) A tonic seizure started clinically with a scream (black arrow) and episodic nystagmus (red arrows show the eye movement artefacts of the nystagmus). The ictal EEG consisted of an abrupt onset of flattening, which lasted for 25 s, followed by high-amplitude, generalised, sharp and slow waves at approximately 1 Hz. The EEG returned to its pre-ictal state after about 1 min from the onset of the seizure. Despite unilateral structural abnormalities, the inter-ictal, ictal and post-ictal EEG abnormalities were not consistently lateralised.

From a video-EEG of a child with Lennox–Gastaut syndrome due to malformations of cortical development[133]

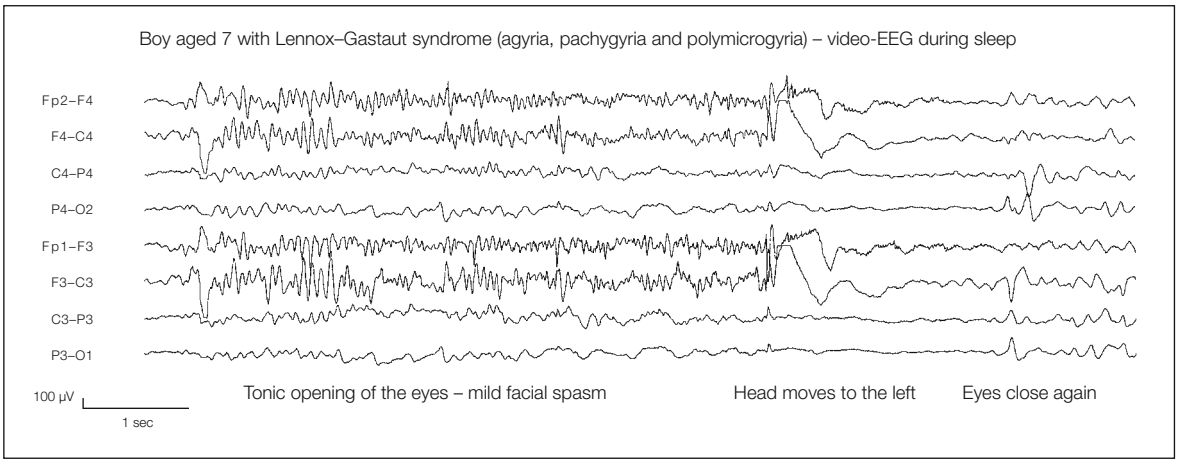

Figure 10.4 A tonic seizure presenting with mild clinical symptoms occurs during marked paroxysmal fast activity. Turning of the head and symmetrical flattening of the EEG follow. His older brother also had the same disease (Figure 6.6).

From a video-EEG of a young man aged 17 years with Lennox–Gastaut syndrome

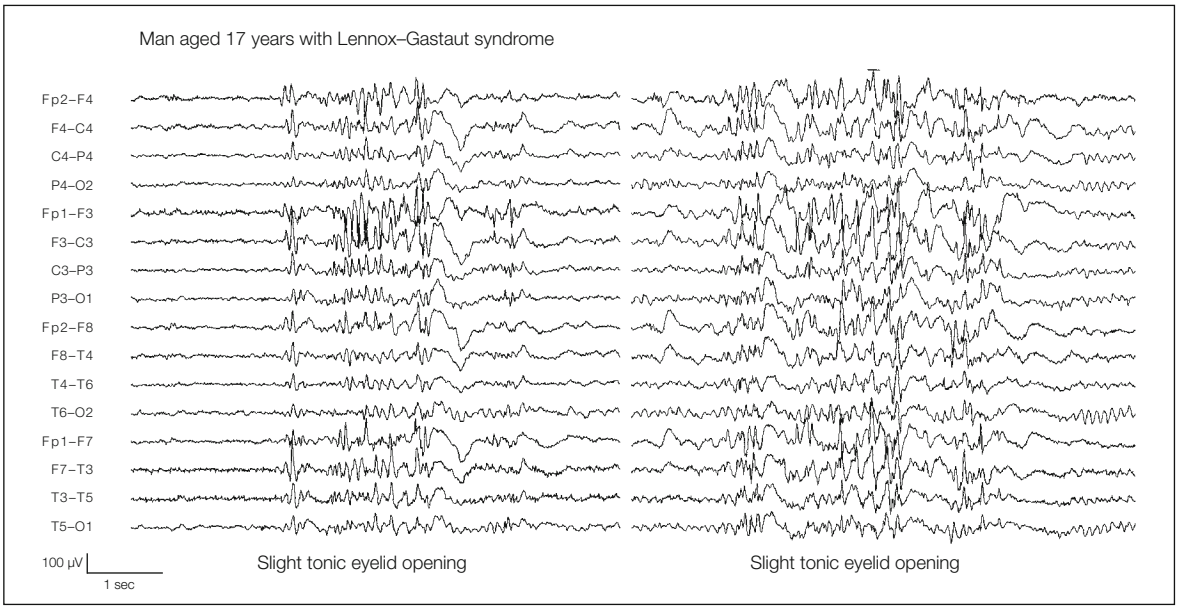

Figure 10.5 EEG fast paroxysms are associated with inconspicuous manifestations of tonic seizures (slight tonic eyelid opening) that would be impossible to detect without video-EEG recording.

of them during sleep. They do not occur during REM sleep. In early onset Lennox–Gastaut syndrome clusters of tonic spasms frequently occur on awakening.

Atypical absence seizures (Figures 10.6 and 10.7) occur in two-thirds of patients. There is 'clouding' rather than loss of consciousness with gradual onset

Video-EEG sample of a classical and lengthy atypical absence seizure

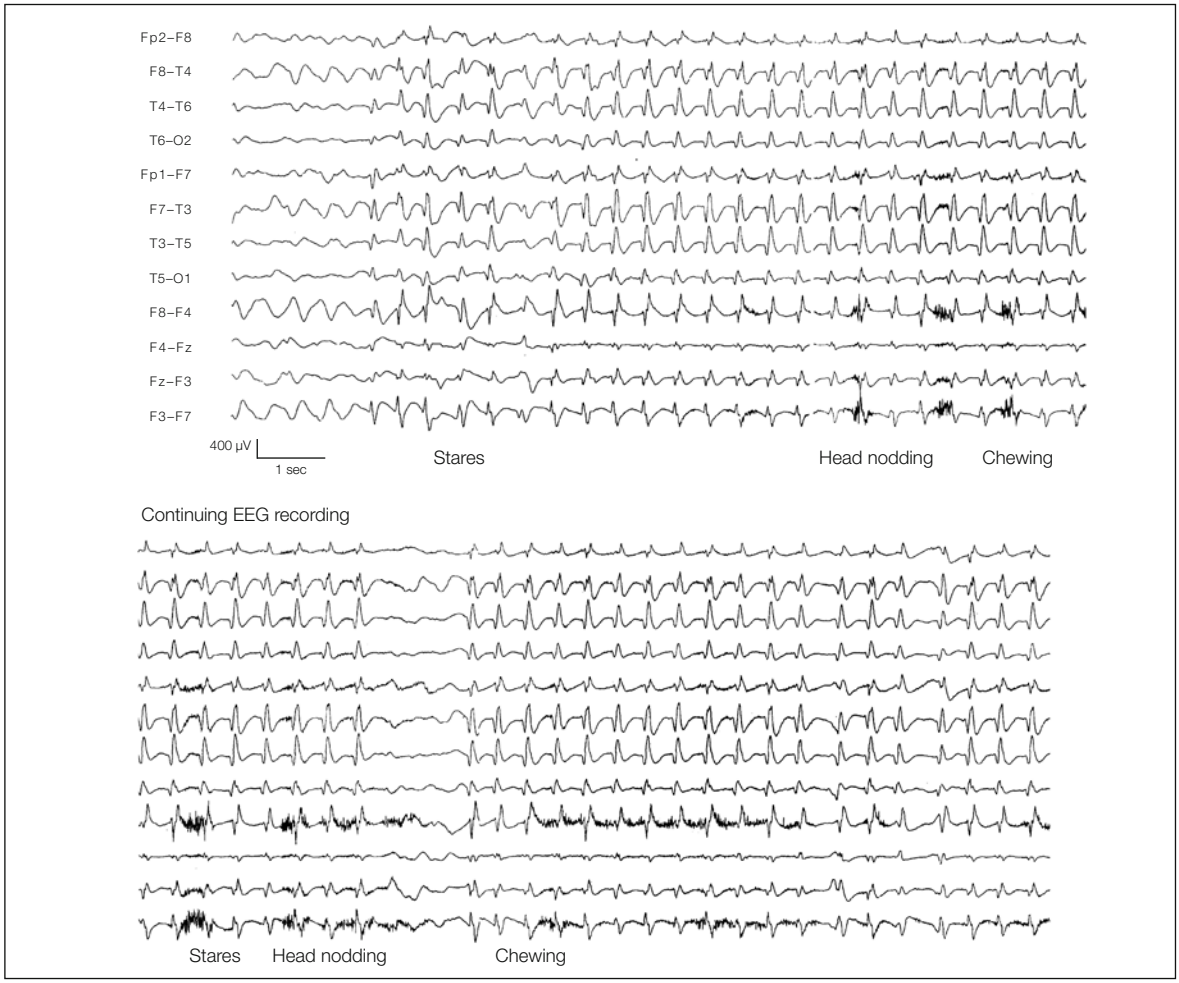

Figure 10.6 Boy, aged 11 years, with severe learning difficulties and frequent multiform seizures of Lennox–Gastaut. The ictal symptoms fluctuated and consisted of staring, head nodding and automatisms. The ictal discharge consisted of slow GSWD at 2–2.5 Hz.

and gradual termination. The patients may continue with their activity, although slower and often with mistakes. Impairment of their cognition may be so mild that it can be clinically undetectable. Selective impairment of higher cortical functions with maintained responsiveness may occur.

Changes in tone and myoclonic jerks may be very pronounced. Often, there is loss of trunk or head postural tone, facial muscle or neck muscle stiffening, eyelid or perioral myoclonus, random jerks of the head or limbs, and head nodding.

The main differences between atypical and typical absence seizures are shown in Table 2.8.

Atonic seizures consist of sudden, brief (1 or 2 s) and severe loss of postural tone. They occur in almost half of patients. They are frequent and involve the whole body or only the head.

> The trunk and head slump forwards and the knees buckle.

Generalised loss of postural tone causes a lightning-like fall. Atonic seizures are the most frequent cause

A video-EEG sample from a lengthy recording to assess whether this 9-year-old girl with severe symptomatic Lennox–Gastaut syndrome was in atypical status epilepticus

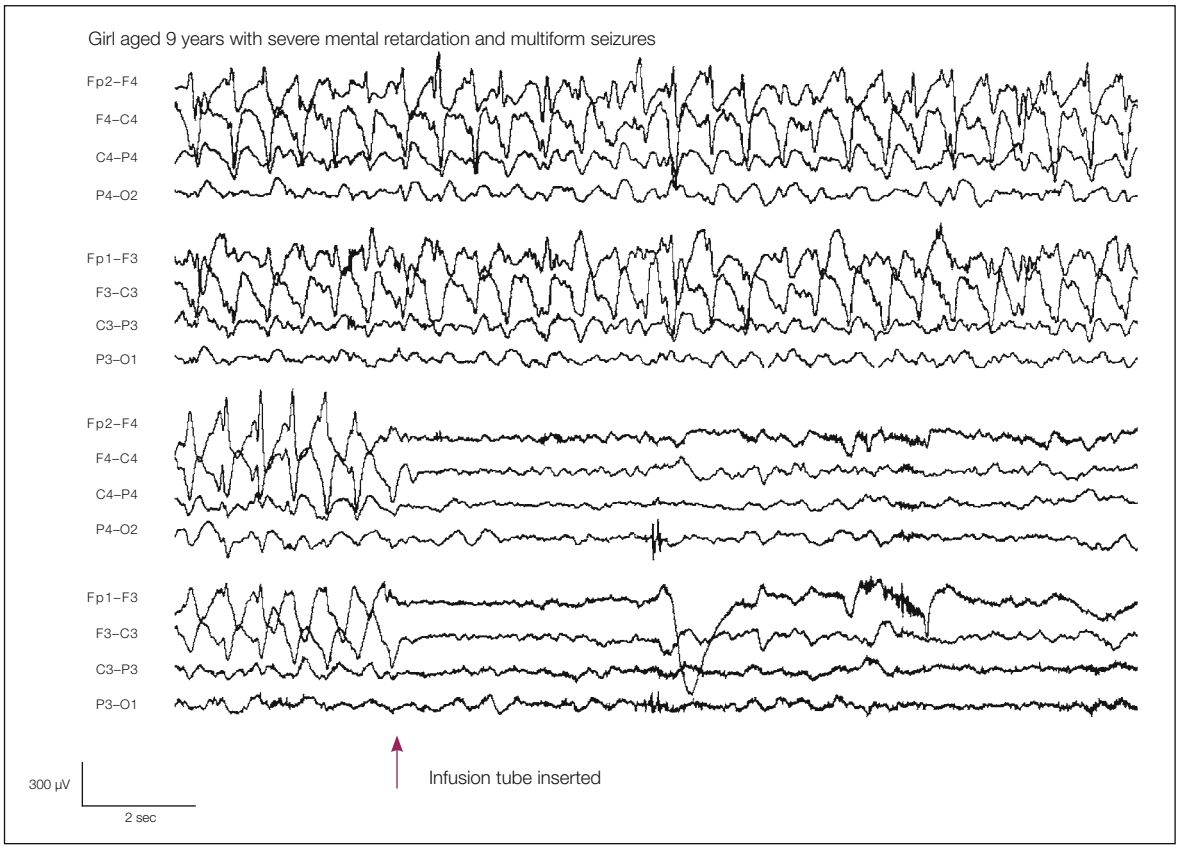

Figure 10.7 The EEG consisted of very-long slow GSWD at approximately 2 Hz. As a result of very severe learning disabilities, it was impossible to find any convincing differences in her behaviour and reactivity during or without EEG discharges. The discharge stopped simultaneously when the infusion tube was inserted before administering diazepam intravenously.

of falls resulting in severe injuries to the nose or teeth.

The patient collapses on the floor irresistibly without impairment of consciousness and then immediately stands up again.

Longer atonic seizures lasting from 30 s to up to 1 or 2 min are rare.

The patient remains on the floor unable to stand up.

In brief and milder attacks there is only head nodding or sagging at the knees.

Atonic seizures always alternate with tonic fits and atypical absences in Lennox–Gastaut syndrome. There may be a predominant tonic component (axial spasm) in these otherwise atonic seizures. In addition, myoclonic jerks may precede or less often intersperse with the atonic manifestations.

Myoclonic jerks occur in 11–28% of patients. They are very brief, shock-like, muscle contractions that may be isolated or repeated in a saccadic manner, usually for only a few seconds. The jerks are generally bilateral and symmetrical (massive myoclonus) and preferentially involve the axial flexor muscles and the abductors of the arms. They may cause falls.

Epileptic falls (drop attacks) may be the result of various types of seizures such as tonic (which are the most common), atonic, myoclonic–atonic and, more rarely, myoclonic seizures. These are often difficult

to differentiate clinically without polygraphic recording.[134] The falls result in recurrent injury.

Non-convulsive status epilepticus featuring all types of seizures such as atypical absences, tonic and atonic fits and myoclonic jerks occur in half the patients. They are often of very long duration (days to weeks), exhibit resistance to treatment and are repetitive. Depending on the predominant seizure type, status epilepticus in Lennox–Gastaut syndrome may be one of the following though these are often of mixed types:

- *absence status epilepticus,* a mild and less often severe confusional state that can last for days or weeks
- *tonic status epilepticus,* which is more often seen in adolescents than in children
- *myoclonic status epilepticus,* which is rare, occurring when the myoclonic jerks are the dominant seizure type
- *mixed tonic and absence status*, which is probably more common. It consists of a repetitive uninterrupted or discontinuous series of brief tonic seizures alternating with atypical absences. There is usually profound impairment of consciousness or stupor, mixed with serial tonic attacks and sometimes with myoclonic–atonic falls.

Aetiology

The aetiology is extensive and diverse. Symptomatic Lennox–Gastaut syndrome due to severe and, less often, mild brain disorders of any type is by far the most common, probably accounting for 70% of all cases. The pre-, peri- and postnatal causes are similar to those responsible for West syndrome (Table 10.1), but Aicardi syndrome and lissencephaly, which are common in West syndrome, are rare causes in Lennox–Gastaut syndrome. Malformations of cortical development are increasingly identified as a common cause of Lennox–Gastaut syndrome (Figures 6.6 and 10.4). Focal cortical dysplasia can produce a typical or an incomplete form of the syndrome.

A third of all Lennox–Gastaut syndrome cases occur with no antecedent history or evidence of brain pathology (idiopathic or cryptogenic cases). There is no evidence of a genetic predisposition.

Pathophysiology

Lennox–Gastaut syndrome is a non-specific, age-dependent, diffuse epileptic encephalopathy of unknown pathophysiology.[124]

The electrographic abnormalities are probably a severely abnormal response of the maturing brain in early childhood to a diffuse, or occasionally localised, brain damage. The response may be similar to that of infants developing West syndrome but at a different age of maturation. The electrical discharges are thought to reflect excessive neocortical excitability and arise from neuronal networks and oscillations peculiar to the immature brain. Secondary bilateral synchrony may be the main pathophysiological mechanism in a third of cases of typical Lennox–Gastaut syndrome.[135] Secondary bilateral synchrony refers to bilateral and synchronous EEG discharges generated by a unilateral cortical focus (Figure 2.7). Contrary to secondary bilateral synchrony, primary bilateral synchrony manifests with more rapid symmetrical and synchronous GSWD caused by a generalised epileptic process independent of any focal hemispheric lesion (Figure 2.7).

The pathophysiology of the development cognitive and behavioural abnormalities is thought to be similar to any other type of epileptic encephalopathy. Abundant epileptogenic abnormalities of slow GSWD and fast rhythms/rapid spikes play a pivotal role in the development of cognitive and behavioural impairment by altering brain connectivity and neurotransmission of the maturing brain. A reason for this may be that these electrical discharges divert the brain from normal developmental processes towards seizure-preventing mechanisms.[12] AEDs, sleep disruption and social isolation are significant contributing factors.[12]

Diagnostic procedures

A thorough clinical neurodevelopmental assessment, ophthalmological and ultraviolet skin examination may reveal the underlying cause, particularly in symptomatic cases. The cause may already be known in those who develop Lennox–Gastaut from West syndrome. Biochemical, haematological, metabolic

and other relevant screenings are rarely abnormal depending on the cause.

Brain imaging with high-resolution MRI and PET is abnormal in nearly all patients.[136–139] Two-thirds of patients have abnormal MRI, which are needed for the detection of subtle focal lesions. Functional brain imaging is highly sensitive in detecting focal cortical abnormalities in almost a third of patients, even when the MRI is normal.[136–139]

Electroencephalography[61,124,140–142]

The inter-ictal EEG features at onset may consist of an abnormal background with or without slow GSWD. The background abnormalities are found in almost all cases from the onset of seizures. They consist of a slow and fragmented alpha rhythm, an excess of diffuse slow waves and EEG disorganisation. Focal slow-wave abnormalities typically occur in symptomatic cases.

Commonly, EEGs of abnormal background contain paroxysms of fast rhythms characterising tonic seizures and slow (<2.5 Hz) GSWD characterising atypical absences (Figures 10.7 and 10.8). These EEG patterns may be clinically silent (inter-ictal) or manifest with inconspicuous or violent seizures (ictal).

Episodic abnormalities are frequent and mainly consist of (1) slow (<2.5 Hz) GSWD and (2) paroxysms of fast activity or rhythmic rapid spikes, which are characteristic features occurring almost exclusively during NREM sleep.[5]

Multiple independent spike foci mainly occur in the transition from West to Lennox–Gastaut syndrome. The EEG patterns differ among individuals and change from day to day and even from moment to moment.

Useful clarification

An EEG with multi-focal independent spike foci is not a specific diagnostic feature. Although most of the reports emphasise their association with severe childhood epilepsies and Lennox–Gastaut syndrome,[8,143] multiple independent spike foci are a main EEG feature of Panayiotopoulos syndrome (page 347).

Sleep activates paroxysmal abnormalities.

Ictal EEG: atypical absences are associated with slow (<2.5 Hz) GSWD (Figures 10.6 and 10.7).

Tonic seizures have accelerating fast paroxysmal activity, which is bilateral and often predominates in the anterior regions and the vertex (Figures 10.4, 10.5 and 10.9). This may be of two types:[132]

1. very rapid (20±5 Hz) and initially of low amplitude, progressively increasing to 50–100 μV
2. a more ample and less rapid rhythmic discharge at 10 Hz, identical to that of the tonic phase of the GTCSs (epileptic recruiting rhythm), except that it may be of high amplitude from the onset.[66]

Flattening of all EEG activity alone or in combination with fast paroxysms is also common (Figures 10.3 and 10.4). Fast ictal paroxysms may be preceded by slow GSWD or EEG suppression.

Atonic attacks occur with generalised polyspikes, slow GSWD and accelerating fast paroxysms alone or in combination.[132]

Myoclonic attacks have mainly generalised discharges of polyspikes with or without slow waves and fast rhythms.

A combination of clinical manifestations and ictal EEG patterns is common (Figure 10.8). Massive myoclonus, atonic seizures and myoclonic–atonic seizures mainly consist of a mixture of slow spike–wave, polyspikes and decremental events.

Post-ictally, there is diffuse slowing or slow GSWD instead of EEG flattening.

Differential diagnosis

There are a number of epileptic and non-epileptic conditions that should be differentiated from Lennox–Gastaut syndrome (Table 10.3). However, recognition of Lennox–Gastaut syndrome in a child is relatively easy because of the characteristic multiple seizure types, pre-existing or developing impairment of cognition and behaviour, and EEG features.

The main differential diagnostic problem is between idiopathic Lennox–Gastaut syndrome and EM-AS (see Table 10.4). This is relatively easy in typical

A video-EEG-recorded seizure of the same patient depicted in Figure 10.4

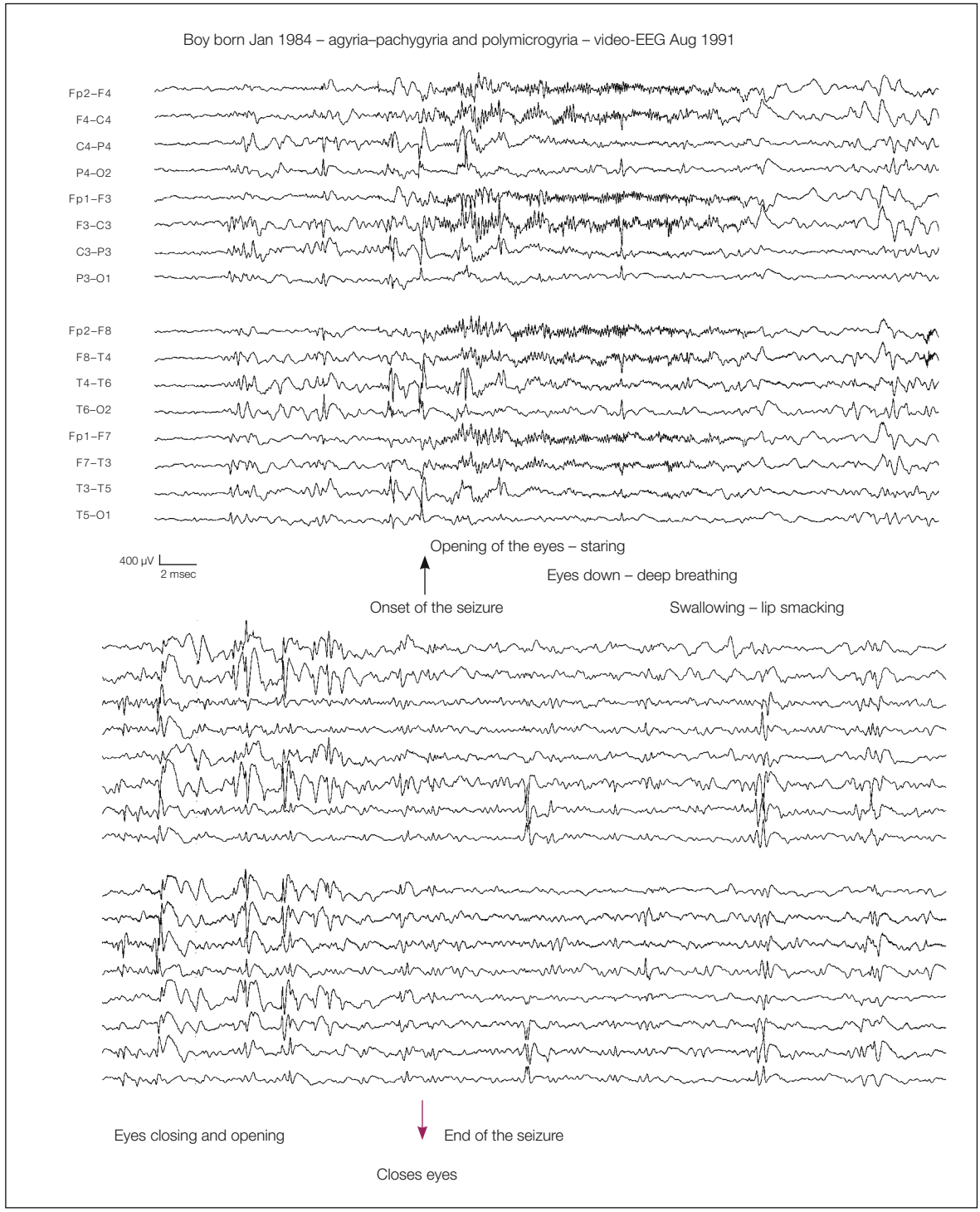

Figure 10.8 Note that the ictal discharge contains features of tonic (episodic fast activity) and absence (slow spike–waves) seizures. The annotated clinical manifestations were mild.

Ictal fast paroxysms of various frequencies in Lennox–Gastaut syndrome

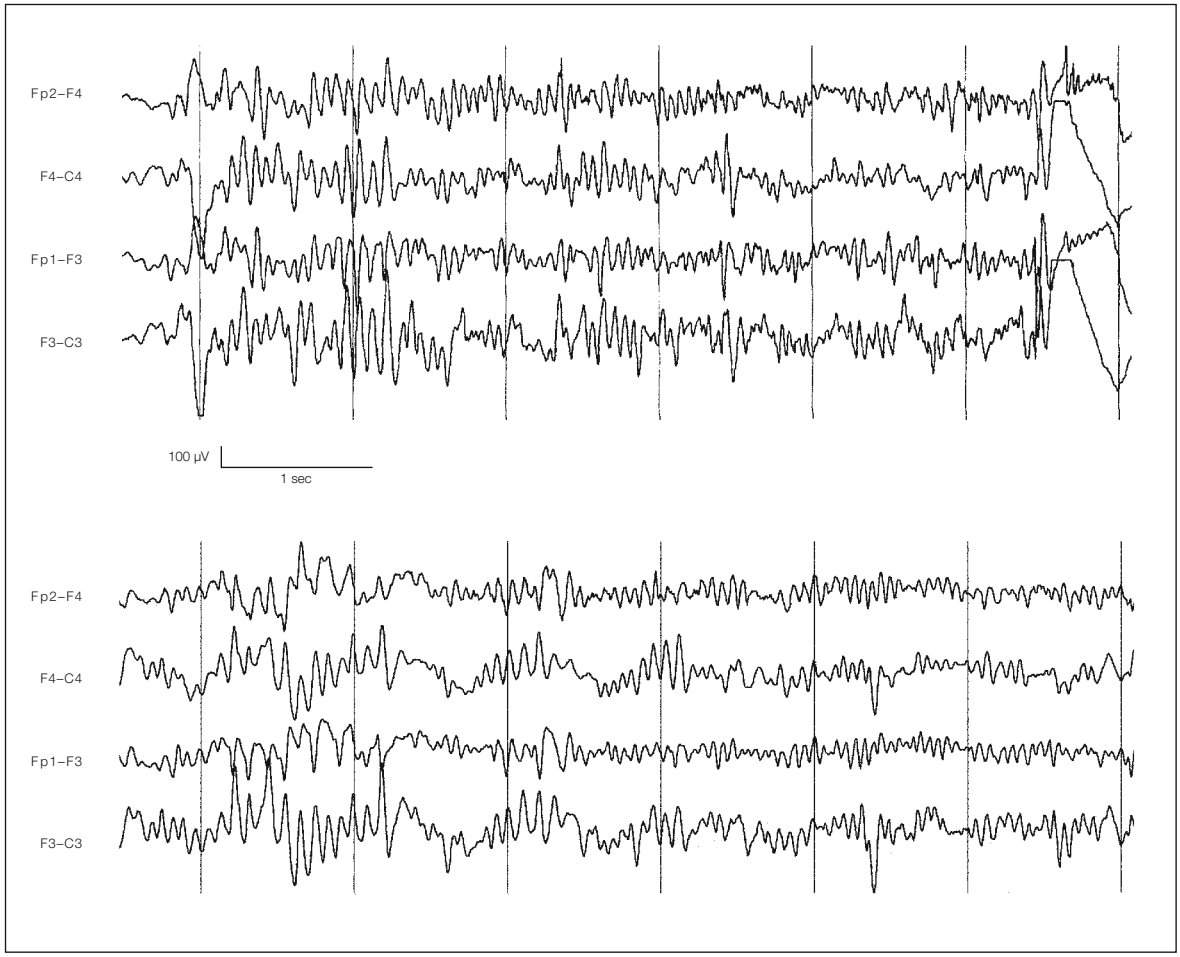

Figure 10.9

presentations (Table 10.4), but many patients present with overlapping features.[126,144]

Prognosis

The prognosis is appalling:[121,130,131,135,145–148] 5% die; 80–90% continue having seizures in adult life; and almost all (85–92%) have severely impaired cognition and behaviour. Many patients are finally institutionalised. A patient achieving a normal mental and motor development is a rarity.

Cognitive impairment is more likely to develop in symptomatic or West syndrome-related cases, when the onset is before 3 years of age, and frequent seizures and status epilepticus occur. Other prognostic factors are provided in Table 10.5.

Diagnostic tips

Recognition of Lennox–Gastaut syndrome is easy due to the characteristics of the multiple seizure types, pre-existing or developing impairment of cognitive functioning, and behavioural abnormalities.

Differential diagnosis may be problematic between Lennox–Gastaut syndrome and EM-AS of Doose (Table 10.4).

Non-epileptic and epileptic conditions to differentiate from Lennox–Gastaut syndrome

Non-epileptic conditions

- Non-epileptic falls, syncope and cataplexy
- Nocturnal paroxysmal dystonia

Epileptic syndromes

- Late-onset West syndrome
- Myoclonic epilepsies of early childhood
- Dravet syndrome
- Epilepsy with myoclonic absences
- Epilepsy with myoclonic–astatic seizures of Doose
- Myoclonic epilepsy of infancy associated with a fixed encephalopathy
- Progressive myoclonic epilepsies and neurodegenerative conditions
- Atypical benign partial epilepsy of childhood
- Epileptic encephalopathy with CSWS
- Focal epilepsies with secondary bilateral synchrony

Table 10.3

Lennox–Gastaut syndrome versus EM-AS of Doose

	Lennox–Gastaut syndrome	EM-AS of Doose
Main seizures	Tonic, atonic and atypical absences	Myoclonic, atonic and myoclonic–atonic
Tonic seizures	Common and characteristic; diurnal and nocturnal	Probably an exclusion criterion (nocturnal tonic seizures are accepted by some authors)
Tonic drop attacks	Common	Incompatible
Atypical absences	Common; they also occur independently of other seizures	Uncommon; they usually accompany myoclonic or atonic episodes
Developmental abnormalities before onset of seizures	Common	Exceptional, if any
Aetiology	Symptomatic or possibly symptomatic (idiopathic cases are accepted by some authorities)	Idiopathic[1] (although symptomatic or possibly symptomatic cases are included in the 1989 ILAE classification[18])
Genetic predisposition	None	Common
Development from West syndrome	Common	Incompatible
EEG background	Abnormal by rule	Usually normal, particularly at onset
EEG episodic fast activity and rapid spikes	Common and often characteristic	Exceptional and mainly in sleep
EEG GSWD	Usually <2–2.5 Hz	Usually 2–3 Hz
Prognosis	Commonly bad	Commonly relatively good

Table 10.4

Prognostic factors in Lennox–Gastaut syndrome

Worse prognosis is associated with:

- Symptomatic causes
- Pre-existent West or Ohtahara syndrome
- Early-onset
- Frequent and intractable seizures
- Repeated episodes of status epilepticus
- Constantly slow EEG background
- Localised and mainly multifocal EEG abnormalities

A better prognosis may be indicated for patients who have:

- Normal development prior to the onset of seizures
- Faster rather than slower generalised spike–wave activity
- Normal brain imaging
- Near-normal background EEG
- Activation of generalised spike–wave by hyperventilation

Table 10.5

Management[120,122–124,149–152]

My 13-year-old daughter has Lennox–Gastaut syndrome. She is on Sabril, Lamictal and Frisium. It seems multiple drug therapies work best for these children. I have found the best control is when the drug level or types are changed. The initial control is good usually reducing the seizures for a month or so, but they then start up again. Hence, we are always juggling the doses up and down.

From an internet description by a mother

Lennox–Gastaut syndrome requires a multidisciplinary approach to management that is demanding and often frustrating for the family and the treating health care professionals and can only be supportive and palliative. A management strategy should include the following elements:

- treatment of epileptic seizures with appropriate medications and nonpharmacological methods
- treatment of behavioural and cognitive problems with appropriate educational programmes
- physical therapy for the patient's physical disabilities
- family support.

AED treatment

AED treatment of Lennox–Gastaut syndrome is largely empirical and the few RCTs have failed to make any significant breakthrough in the evidence-based recommendations. Avoiding AEDs that may worsen seizures, cognition and behaviour is an important aspect of management.

Lennox–Gastaut syndrome is highly resistant to antiepileptic medication, often requiring rational polytherapy that is rarely successful. Only a few RCTs have been performed and many of the AED treatment recommendations have little or no evidence-based support. Tonic attacks, which may be life threatening and can be numerous during sleep, are the most difficult to treat, while atypical absences and myoclonic and atonic seizures are more amenable to treatment. As a rule, multiple medications lead to patients suffering from sedation and other adverse effects. Often this causes a vicious cycle, with sedation increasing the incidence of seizures. Another problem is that some AEDs beneficial in controlling one type of seizure may

aggravate other types of seizure. More than three AEDs are probably unacceptable.

The beneficial effects of drugs are often transient, lasting at best around 4 months. AEDs are usually used in combinations according to the predominant seizure type. In regard to seizure severity, patients may have spontaneous good and bad days or weeks, but a seizure-free state cannot be achieved. A realistic aim of AED treatment in Lennox–Gastaut syndrome is to:[120,150]

- minimise the number of serious and disabling seizures such as drop attacks.
- minimise the number of daytime seizures
- prevent and treat prolonged convulsive seizures and non-convulsive status epilepticus.

Older AEDs

Valproate is the preferred first-line AED in most recommendations because it has beneficial efficacy in all types of seizure.[120,150–152] Uncontrolled studies found a greater than 50% improvement in seizure control in 55% of patients with drop attacks and in 25–30% of patients with atypical absences and myoclonic seizures.[120] Lower responder rates were reported for tonic and tonic–clonic seizures.[120]

Younger children, particularly those on polytherapy, are at greater risk of hepatic failure and acute haemorrhagic pancreatitis.

Clonazepam,[120] *clobazam,*[153] and *nitrazepam*[154] are mainly effective in myoclonic jerks and tonic attacks.[150] Nitrazepam has been widely used from the Marseilles school of Gastaut.[151] Clobazam has been recently re-assessed in a RCT as an effective adjunctive therapy for drop seizures in patients with Lennox–Gastaut syndrome.[153] Higher doses (target 1.0 mg/kg/day) were more effective than lower doses (target 0.25 mg/kg/day). Other seizure types were also reduced. Also, clobazam is not as sedative and does not induce as much drooling as the other benzodiazepines.

Phenytoin may reduce tonic and vibratory tonic seizures and it is used for the treatment of tonic status epilepticus.[151]

Carbamazepine is an excellent AED in focal seizures, but may exacerbate other types of generalised seizures such as absences and myoclonic jerks. The Marseilles school considers carbamazepine to be an effective AED against tonic seizures, particularly in combination with valproate.[151] However, carbamazepine probably aggravates all other types of seizure in Lennox–Gastaut syndrome and therefore it should be used with caution.

Ethosuximide is very effective in atypical absence seizures, negative myoclonus and atonic seizures with falls (see page 576).[155,156]

Phenobarbital and *primidone* may control convulsive seizures, but often aggravate absences and are associated with serious cognitive, behavioural and sedative ADRs.

Newer AEDs

Randomised controlled trials (RCTs) in Lennox–Gastaut syndrome are scarce and do not provide unquestionable evidence regarding the best AEDs for particular types of seizures in this syndrome. Specific limitations of current RCTs include:

- most RCTs use short-term assessments, but we know that the beneficial effects of AEDs in Lennox–Gastaut syndrome are often transient, lasting for a few weeks; this may also explain the high percentage of placebo responders
- efficacy measures rely on observers' counts of seizures, although we know that these are unreliable, particularly for absences, myoclonic jerks and nocturnal tonic seizures, which may be numerous and clinically undetectable. Most RCTs use a reduction in drop attacks as the primary outcome variable, but, again, whether these drop attacks are atonic or tonic seizures is not defined. Objective video EEG monitoring of seizures has not been used in any of these RCTs. We have found that less than 30% of tonic seizures documented in long video-EEG monitoring have been identified by specialised personnel in a dedicated in-patient hospital (unpublished study).
- all RCTs so far have studied the effect of an AED as adjunctive treatment, usually with valproate; thus we do not know whether the results would be the same in combination with another AED or in monotherapy
- there are no head-to-head comparisons of AEDs in Lennox–Gastaut syndrome

- RCTs examined mixed populations of children and adults, despite the likelihood of response and ADRs having significant age-related differences

Seven RCTs are for add-on treatment with lamotrigine, topiramate, felbamate and rufinamide in Lennox–Gastaut syndrome and these have been recently reviewed.[120,149–152] The Cochrane review[149] assessed that each of the 7 existing RCTs looked at different populations, assessed different therapies and considered different outcomes. Therefore, a meta-analysis was impossible to perform and the authors concluded that "the optimum treatment for Lennox–Gastaut syndrome remains uncertain and no study to date has shown any one drug to be highly efficacious; rufinamide, lamotrigine, topiramate and felbamate may be helpful as add-on therapy".[149]

Felbamate significantly reduced all seizures compared with placebo (–19% vs +4%; p=0.002), including drop attacks and GTCS.[120,149,150,152,157] The effect on atypical absences was not reported. As felbamate can cause fatal side effects it is now only available for specific cases. It should be used with caution and for no longer than 2 months if there is no clear response (see Pharmacopoeia).

Lamotrigine significantly reduced all seizures compared with placebo (–32% vs –9%; p=0.02), including drop attacks and GTCS.[149,158,159] These results have been confirmed in case series and other small studies.[150] The effect of treatment on tonic, atonic, myoclonic or partial seizures was not reported in the two RCTs.[149,158,159]

Lamotrigine efficacy may be at its best in combination with valproate because of their beneficial pharmacokinetic interactions (page 181). The major ADR of lamotrigine is a skin rash that may be very severe and life threatening (page 197). Children receiving lamotrigine in comedication with valproate have a higher risk of skin rash, anticonvulsant hypersensitivity syndrome and hepatic failure.

Topiramate significantly reduced the frequency of drop attacks and tonic clonic seizures but not of overall seizures (–21% vs –9%,NS).[160] In addition, small trials have confirmed the efficacy of topiramate in drop attacks and tonic clonic seizures. A complete loss of the efficacy of topiramate was seen by 30 months,[161] which is a typical pattern with therapy for Lennox–Gastaut syndrome

The many cognitive, behavioural and physical side effects, such as oligohydrosis, may outweigh the benefits of topiramate treatment.

Rufinamide is a new AED licensed for the treatment of Lennox–Gastaut syndrome (see pharmacopoeia).[149–152] In a RCT of add-on treatment of Lennox–Gastaut syndrome,[162] the rufinamide group had, compared with placebo, a greater median percentage reduction in total seizure frequency (32.7% vs 11.7%, p=0.0015) and in the frequency of drop attacks (p<0.0001), a greater improvement in seizure severity (p=0.0041) and a higher 50% responder rate for total seizures (p=0.0045) and tonic-atonic seizures (p=0.002). Somnolence and vomiting were the main ADRs.

Levetiracetam has not been assessed in RCTs for Lennox–Gastaut syndrome. Small studies have shown that it is effective for all types of seizures except, probably, tonic seizures.[163,164] Levetiracetam is relatively safe and does not interact with other AEDs in polytherapy.

Vigabatrin is probably efficacious in Lennox–Gastaut syndrome, though it may exacerbate absences and myoclonic jerks.[150] In one study vigabatrin added to monotherapy with valproate had a beneficial effect in 85% of children, who experienced a 50–100% seizure reduction.[165] However, the risk of irreversible visual field defects may be too high. As with West syndrome, it may be patients with Lennox–Gastaut syndrome of cortical dysplasia who benefit most from vigabatrin, but this has not been tested.

Zonisamide has been also considered as a useful AED in the treatment of Lennox–Gastaut syndrome.[166] In a recent study of 62 patients maintained on zonisamide add-on medication for for at least 12 months 3 became free of seizures, 29 had reduction in seizure frequency and 24 (38.7%) had no seizure reduction. Oligohydrosis and other major ADRs could be a problem.[166]

Management tips

With increasing seizures, reduction may be a better option than increase in AEDs.

Evaluate the predominant, severe and disabling seizure type in preparation for selection of the next AED and withdrawal of the current ineffective drug.

Any AED change, whether addition or removal, may be temporarily beneficial.

Treatments for Lennox–Gastaut syndrome

First-line drugs (in order of priority)

- Valproate: all seizures.
- Lamotrigine: all but myoclonic seizures. Lacks sedative effects and is particularly useful as an add-on to valproate.
- Clobazam: probably all types of seizures. Less sedative than other benzodiazepines.
- Rufinamide: probably all seizures but has not yet been widely used in clinical practice.
- Zonisamide: probably all seizures.
- Levetiracetam: probably all but tonic seizures.
- Topiramate: probably all seizures but with many and serious adverse reactions.
- Clonazepam: mainly myoclonic jerks.
- Phenytoin: tonic seizures.
- Felbamate: probably all seizures but with serious, sometimes fatal, adverse reactions.

Second-line drugs

- Ethosuximide: absences and negative myoclonus
- Carbamazepine: focal seizures, secondarily GTCSs and probably tonic seizures in combination with valproate.
- Corticosteroids and ACTH: if seizures worsen and in periods of status epilepticus.
- Intravenous immunoglobulins: probably worth trying in patients for whom other treatments are of little benefit.

Non-pharmacological treatments

- The ketogenic diet is undergoing a mini-renaissance.
- Vagus nerve stimulation may be an option to consider but expectations should be kept low.
- Neurosurgical resections in selective cases.

Drop attacks are more responsive to felbamate, lamotrigine, rufinamide, and topiramate; vagus nerve stimulation and corpus callosotomy are surgical options.

Hormonal and other non-AED treatment

Corticosteroids and ACTH may be helpful particularly in idiopathic/cryptogenic Lennox–Gastaut syndrome, particularly at onset (as for West syndrome)[151] and in periods of marked seizure exaggeration.[124,150] Given their long-term adverse effects, they should not be tried more than once or twice in the course of the disease and only at times of desperation.[124] They are also used to treat episodes of nonconvulsive status epilepticus not responding to conventional AEDs.[150,151]

Intravenous immunoglobulin was found to be useful in a few case reports and sometimes improvement was evident after the first dose.[150] It may be tried at times of seizure exacerbations not responding to other medications. Intravenous immunoglobulin is costly and administration is inconvenient but it does not interfere with other drugs and is usually well tolerated.

Amantadine, tryptophane, flumazenil, imipramine and other non-epileptic drugs have had limited success in some patients and they may even exacerbate seizures.

Non-pharmacological treatments

The ketogenic diet is undergoing a mini-renaissance in epileptic encephalopathies (see page 228) including the Lennox–Gastaut syndrome.[120,167–169] In a recent report,[167] the effect of a ketogenic diet was studied in a blinded randomised cross over study in 20 children with intractable Lennox–Gastaut syndrome. The patients fasted for 36 hours and then were randomised to receive the classic ketogenic diet in conjunction with a solution containing either 60 g/day of glucose to negate the ketosis or saccharin. A crossover to the ketogenic diet with the alternate solution occurred following the sixth day and a repeat fast. After administration of the solution, there was moderate evidence of a reduction in parent-reported seizures between the glucose and saccharin arms, with a median difference of 1.5 seizures per day ($p=0.07$). There was no reduction in the number of EEG-identified events, with a median reduction of 7 events per day ($p=0.33$). Ketosis was not completely eliminated in the glucose-added arm.[167] A supplementary study[168] attempted to clarify whether the effectiveness of the ketogenic

diet could be explained by a placebo effect or by parental expectations and commitment. In this study, the additional glucose did not significantly alter the frequency of EEG-assessed events, but did decrease the frequency of parent-reported "drop" seizures (P=0.07). Fasting had substantial effects on both drop attacks and EEG-assessed events. The diet remained effective in decreasing seizures at 12 days, 6 months, and 12 months.[168] The popular Atkins diet may be a less restrictive alternative when appropriately modified.[170]

Vagus nerve stimulation in childhood epileptic encephalopathies, including Lennox–Gastaut syndrome, has been found to be effective, particularly in tonic and atonic seizures, and to improve the quality of life of these patients.[120,150,171–172] It has been assessed to be as good as corpus callosotomy.[172] However, the results of another promising study report when follow-up assessments were made suggests that caution may be warranted.[173]

Neurosurgery: Corpus callosotomy is the only surgical procedure for devastating atonic seizures with traumatic falls (drop attacks).[151,152] Resective neurosurgery is appropriate in the few cases with distinctively localised epileptogenic lesions.[174]

Treatment of status epilepticus in Lennox-Gastaut syndrome[120,150,151]

Episodes of non-convulsive status epilepticus are is common and may last for hours to weeks; attempts should be made to prevent these as much as possible. Home-administered benzodiazepines are the first option in treating impending or established non-convulsive status epilepticus. Midazolam (buccal or nasal) and diazepam (rectal) are preferred; some authorities also recommend oral intake of relatively high doses of clonazepam, clobazam or nitrazepam, although these are not of proven efficacy by oral administration. Hospital management includes intravenous administration of mainly nitrazepam, phenytoin, diazepam, clonazepam or midazolam. Intravenous immunoglobulins or corticosteroids may also be used when the status epilepticus is prolonged and resistant to AED. The treatment of status epilepticus is detailed in chapter 3 (page 82).

Intravenous benzodiazepines may, rarely, induce tonic status epilepticus.

Treatment-induced aggravation of seizures, cognition and behaviour

Treatment-induced aggravation of seizures, cognition and behaviour is a major problem with Lennox–Gastaut syndrome. It is much more common than reported and may be a significant cause of the bad prognosis of Lennox–Gastaut syndrome. The effect is difficult to detect and often assumed to be a spontaneous fluctuation or part of the progress of the disease, and is hard to attribute to a specific treatment, particularly if the treatment concerned has improved other types of seizure. Parents often value highly a treatment that improves major seizures at the cost of adverse effects.

Gabapentin is contraindicated because it worsens seizures. However, any one of the AEDs cited in the above section has the potential to aggravate seizures, cognition and behaviour or to have other serious physical consequences. Seizures may also be increased by sedative AEDs that affect alertness.

Finding the right balance of risk versus benefit of any treatment and for each individual patient is probably more demanding in Lennox–Gastaut syndrome than for any other condition.

Attention to seizure precipitants

Detection and prevention of seizure facilitating factors are part of the appropriate management of Lennox–Gastaut syndrome.[151] Intercurrent febrile illnesses, vomiting, changes in treatment regimens, sedation and psychological stress may facilitate seizures and status epilepticus. Children with Lennox–Gastaut syndrome are particularly vulnerable in an unstable and non-stimulating environment in which they experience irregular patterns of sleep, diet and medication.

Educational management

Almost all patients have cognitive and behavioural dysfunction, which is often severe, and require extensive educational, behavioural and psychological support. Patients and their families have immense needs from the time that Lennox–Gastaut syndrome is first diagnosed. Medical therapeutic support is important, but alone is not sufficient to achieve an acceptable quality of life. This requires a coordinated approach involving a wide range of healthcare professionals (physicians, specialist nurses, psychologists, psychotherapists and pharmacists), teachers and social workers.

Landau–Kleffner syndrome

Synonym: LKS, acquired epileptic aphasia.

LKS is a partly reversible, epileptic encephalopathy of childhood manifesting with acquired verbal auditory agnosia and other predominantly linguistic deficits that often occur together with other cognitive and neuropsychological behavioural abnormalities.[175–187] Seizures are infrequent and not a prerequisite for LKS.

The Landau-Kleffner syndrome has been expertly reviewed in a recent Epilepsia special issue (August 2009).[187]

Considerations on classification

In the 1989 ILAE classification, this disorder was placed under the descriptive name 'acquired epileptic aphasia' attached to the eponymic name 'Landau–Kleffner syndrome'.[18] It was considered to be a different syndrome from 'epilepsy with CSWS', although both were classified among 'epilepsies and syndromes undetermined as to whether they are focal or generalised'.[18] The new ILAE diagnostic scheme[1] discarded the descriptive in favour of the eponymic nomenclature, and retained LKS and epilepsy with CSWS as separate diagnostic entities, classifying them among the 'epileptic encephalopathies'.The new ILAE report, however, now considers them to be a single entity called 'epileptic encephalopathy with CSWS including LKS'.[17]

The ILAE's justification for this is that 'there is insufficient evidence for mechanistic differences between LKS and CSWS to warrant considering them as separate syndromes. It is unknown whether these conditions are idiopathic, symptomatic, or both'.[17] This is in agreement with the views of Tassinari, the leading authority, who has described CSWS and epilepsy with CSWS. He considers that LKS is a clinical variant of epileptic encephalopathy with CSWS and that both syndromes are 'two facets of the same entity', in which the type of neuropsychological dysfunction depends on the location of inter-ictal foci (frontal in epilepsy with CSWS and temporal in LKS).[175] However, this syndromic unification creates a problem with regard to patients with typical clinical features of LKS who do not have epileptic seizures and lack the EEG abnormalities of CSWS. Furthermore, a recent study found significant differences between LKS and epilepsy with CSWS, which led the authors to conclude that these two disorders could be classified in a dichotomous manner rather than as two points along a continuum.[179]

On terminology, the new ILAE report rightly abandons the term 'slow-wave sleep', following the suggestion made in the previous edition of this book discouraging the use of 'slow-wave sleep' (stages III and IV of sleep) in favour of 'NREM sleep':

> Continuous spike–wave appears as soon as the patient falls to sleep and continues through all NREM I–IV sleep stages. It is interrupted during REM stage and repeats the same cycle again in NREM and REM stages.[175,180]

Demographic data

Onset is at age 2–8 years (peak at 5–7). There is a 2:1 male to female ratio. One or two cases are seen every year in highly specialised centres.

Clinical manifestations

> Our son was normal in every way until approximately age 2 years. At first he seemed to be losing his hearing but not for environmental sounds. We thought that he was going deaf, but the hearing test was normal … When he was 3 years old he didn't say anything for over a month. He improved for a few months and then we saw a very minor seizure.
>
> From an internet description by a mother

All children suffer from linguistic abnormalities, but only three-quarters of them also have seizures.

Linguistic abnormalities

The first symptom is usually verbal auditory agnosia, occurring in an initially normal child who had achieved developmental milestones at appropriate ages and had already aquired age-appropriate speech. Children with LKS become incapable of attributing a semantic value to acoustic signals, thus making them appear hypoacoustic or autistic. The parents notice a gradual inability of the child to respond to their calls despite raising their voices. Verbal auditory agnosia may later progress to complete word deafness and non-linguistic sound agnosia such as not hearing, for example, a doorbell. The diagnosis is often delayed, and mistaken for acquired deafness or elective mutism. Many of these children have an audiogram that is normal.

The language deficit may be initially undermined because of other behavioural or cognitive problems.

The onset may be subacute progressive or stepwise (stuttering); it gradually worsens and affects other linguistic functions with impairment of expressive speech, paraphasias, stereotypies, perseverations and phonological errors. Probably all types of aphasia can occur. The children express themselves in a telegraphic style or in very simple sentences and some cases may develop fluent aphasia or 'jargon'. Finally, the child may also become entirely mute, failing to respond to even non-verbal sounds.

One of the most puzzling features of LKS is the fluctuating course of the linguistic disturbances, characterised by remissions and exacerbations.

Cognitive and behavioural abnormalities

Cognitive and behavioural abnormalities occur in more than three-quarters of patients with LKS. Behavioural disorders such as hyperactivity and attention deficit are common and in rare cases there is progression to severe disinhibition and psychosis.

The relative severity of the linguistic, behavioural and cognitive problems can vary over time in the same child and between children. Long-term follow-up studies have shown that LKS is not always associated with intellectual deterioration.

Seizures

Clinically, seizures occur in three-quarters of patients, but are usually infrequent and of good prognosis. Onset is between 4 and 6 years. Only 20% of patients continue having seizures after the age of 10 years and occurrence of seizures after the age of 15 is exceptional.[181]

Seizure symptoms and seizure type are not well described. They are mainly nocturnal and often heterogeneous. GTCSs and focal motor seizures (Figure 10.10) are emphasised by the ILAE Commission.[18] However, atypical absences, atonic seizures with head drop, minor automatisms and secondarily GTCSs are reported. Subtle seizures with minor motor or subjective symptoms may be frequent, but often remain undetected.[182,183] A third of patients may suffer from a single GTCS or isolated convulsive status epilepticus occurring mainly around age 5–10 years. Complex focal seizures of temporal lobe origin are exceptional. Tonic seizures are probably incompatible with LKS.

The frequency and severity of seizures are not determined by the severity of either EEG abnormalities or severity of linguistic and behavioural problems.

From a video-EEG recording of an 8-year-old boy with Landau–Kleffner syndrome before a PET scan

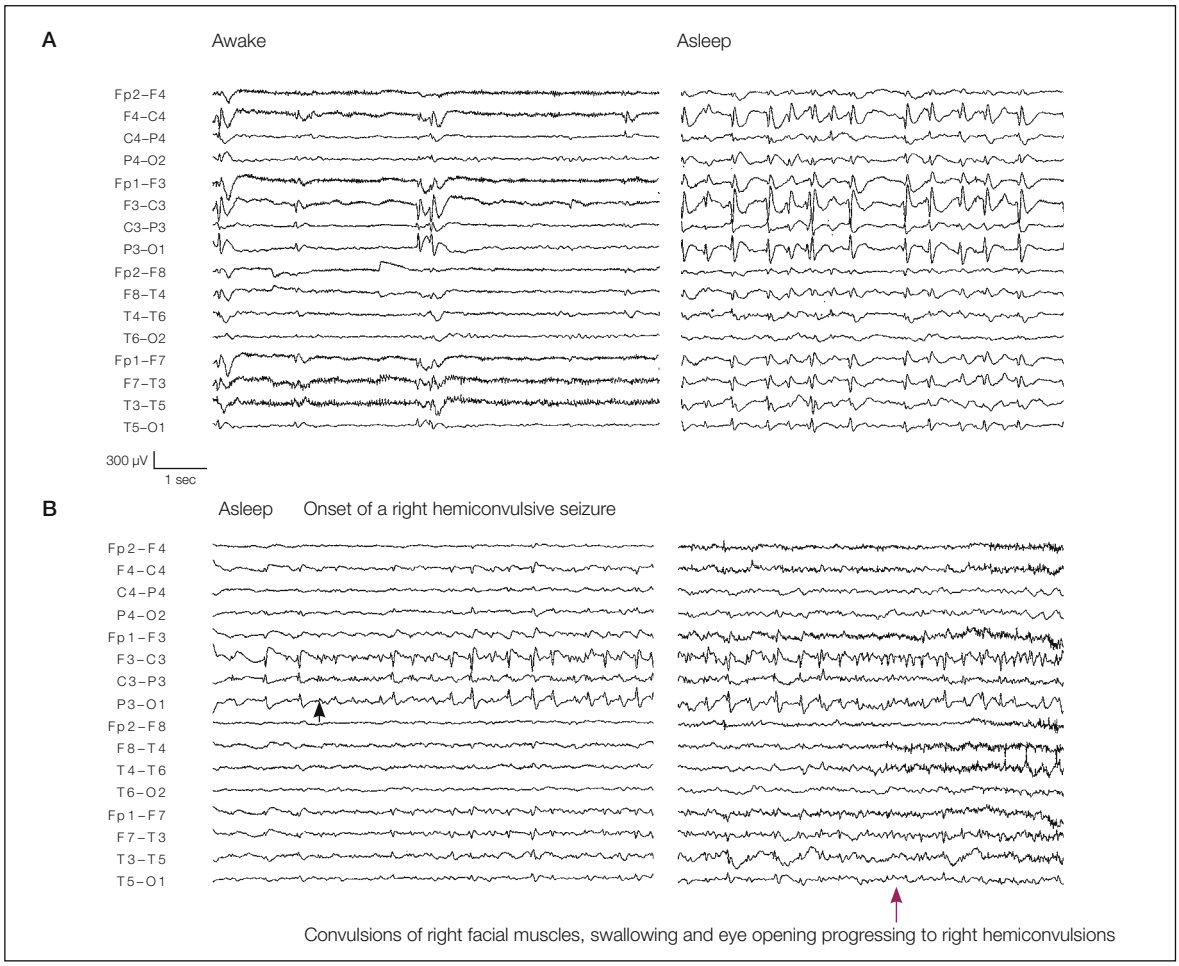

Figure 10.10 This boy had infrequent seizures, one of which was incidentally captured on a video-EEG recording before a PET scan. (**A**) Inter-ictally, there were clusters of sharp–slow-wave focal discharges, maximal around the left rolandic regions (left). They became continuous during natural sleep (right). (**B**) Ictal discharge starts from the left central regions (black arrow indicates its onset) and rapidly spreads to the neighbouring regions. The first clinical signs consisted of right facial convulsions (red arrow; also note muscle artefacts on the right) progressing to hemiconvulsions.

Aetiology[175,177,184]

This is unknown. A family history of epilepsy is found in about 12% of cases with LKS who also have seizures. This is reduced to 5% in those cases who do not have seizures. Siblings may be affected.

Commonly, there is no detectable underlying structural abnormality and the MRI is normal. However, according to some reports, 3% of patients have an encephalopathy and a variety of abnormalities were found in brain biopsy specimens of neurosurgical series.[185–187]

Pathophysiology[175,177,178,184–1187]

LKS is probably the result of an epileptogenic 'functional lesion' in the speech cortex during a critical period of child development. In other words,

focal epileptogenic activity is thought to cause a *functional ablation of eloquent speech areas*.

LKS and epilepsy with CSWS are considered to have a common pathophysiological mechanism. They are both functional disorders occurring at an age where cortical synaptogenesis with abundant axonal sprouting and elemental functional network is being established in the brain. The number of synapses rapidly increases in excess of the ultimate number needed. Neuronal activity or synaptic use is critical in determining which of these synapses will be established or discarded before the age of 10 years. Aggressive epileptic activity, such as that of CSWS at this active period of brain organisation is detrimental for the establishment of appropriate neuronal connections, normal brain development and functioning.[7] It is likely that epileptic discharges activate and perpetuate synaptic arrangements that are functionally improper.[183] Intense epileptic activity in the dominant temporal region would affect linguistic capabilities, as in LKS.[183] Conversely, the mainly frontal localisation of CSWS primarily affects higher cognitive and executive functioning.[7,175,186]

In my opinion, the idiopathic cases of LKS and epilepsy with CSWS are probably exceptional and extreme parts of benign childhood seizure susceptibility syndrome (BCSSS; see Chapter 12), which is derailed to an epileptic encephalopathy.[188,189] This extreme deviation results in a more aggressive condition of seizures, neuropsychological manifestations and EEG abnormalities of various combinations and degrees of severity, as in LKS, epilepsy with CSWS and APEC.[189] The reason for this derailment of otherwise benign seizure susceptibility is unknown, but may be related to location (temporal spikes in LKS, frontal spikes in epilepsy with CSWS) or other intrinsic and external superimposed factors. Additional evidence to support this pathophysiological proposition comes from the atypical evolutions of the rolandic and Panayiotopoulos syndrome to produce the clinical and EEG features of LKS, epilepsy with CSWS and APEC (for more detail, see chapter 12).[190–192]

Diagnostic procedures

Routine brain CT and MRI are often normal, but functional brain imaging shows abnormalities in the temporal lobes.[178,194] MRI volumetric analysis demonstrated volume reduction specifically in the planum temporale and superior temporal gyrus (25–57%), where receptive language is localised.[195] Magnetoencephalography studies have suggested that in more than 80% of patients with Landau-Kleffner syndrome, the bilateral epileptic discharges are generated in the auditory- and language-related perisylvian cortex.

Electroencephalography

The EEG is characterised by mainly posterior temporal lobe foci of sharp–slow-wave complexes that are often multi-focal and bisynchronous, markedly facilitated by NREM sleep (Figure 10.11).[195–197] CSWS occur at some stage of the illness in almost all cases, but this is not a prerequisite for diagnosis. They may also persist or deteriorate during REM sleep (a finding that does not happen in epilepsy with CSWS) (see page 259).[197]

Differential diagnosis

Many cases of LKS are initially investigated for deafness or misdiagnosed as autistic or other psychiatric disorders.

Acute or subacute aphasia in children 2–8 years of age with no unilateral acquired paresis or symptoms of encephalitis is most probably due to LKS. This is because receptive or expressive aphasia is unusual in young children unless they have a bitemporal lobe dysfunction.

The main differences between LKS and epilepsy with CSWS are outlined in Table 10.6.

Prognosis

Seizures and EEG abnormalities are age dependent and often remit by the age of 15. Language and other neuropsychological disturbances gradually improve at the same age as the disappearance of EEG epileptiform activity. Only half the patients with

From a video-EEG recording of a 4-year-old boy referred for possible 'absence seizures' because of 'frequent episodes of inability to understand commands'

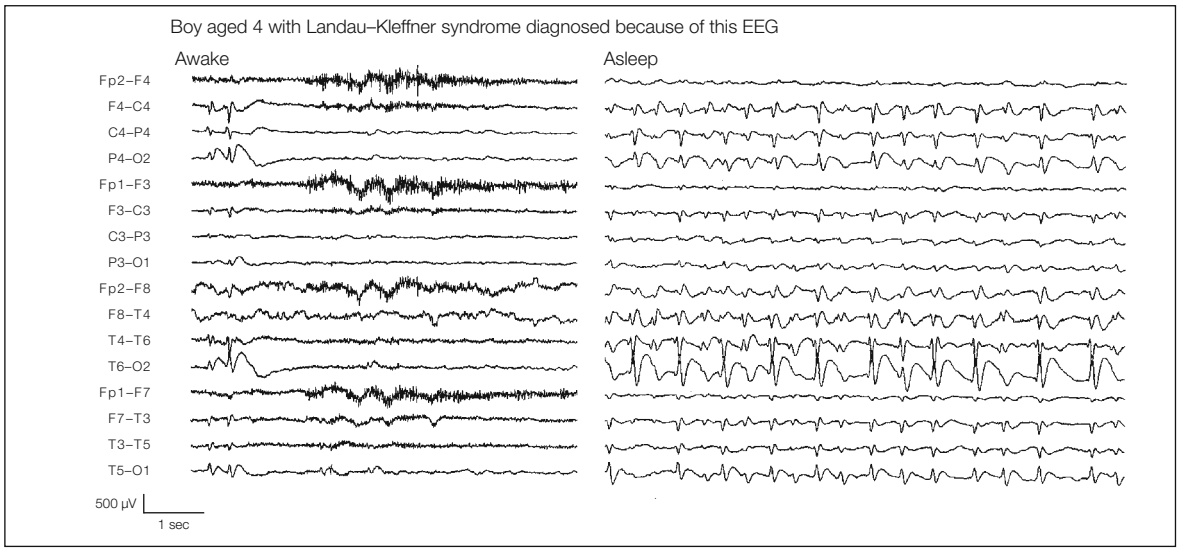

Figure 10.11 The EEG showed clusters of sharp–slow-wave focal discharges maximum around the right posterior temporal regions (left). Although this was a request for a routine EEG, the technologist allowed time to proceed with a sleep EEG during which the paroxysms became continuous (right). The possibility of LKS was raised and this was confirmed with appropriate clinico-psychological testing.

Landau–Kleffner syndrome versus epilepsy with CSWS

	Landau–Kleffner syndrome	Epilepsy with CSWS
EEG aspects		
CSWS	80%	100%
Main spike localisation	Temporal	Frontal
Clinical aspects		
Seizures	Three-quarters of patients	All patients
Symptomatic causes	Rare (~10% abnormal MRI)	One-third (~33% abnormal MRI)
Primary language impairment	Verbal auditory agnosia	Expressive > receptive aphasia
Psychomotor/behavioural deficits	Common (45%)	Nearly all (95%)
Onset of cognitive impairment	Verbal auditory agnosia	Global
Prognosis	Half reach near-normal life	One-quarter reach near-normal life

Table 10.6 Linguistic disturbances are a prerequisite for the diagnosis of LKS, whereas an EEG with CSWS is a prerequisite for the diagnosis of epileptic encephalopathy with CSWS.[197]

LKS may be able to live a relatively normal life, with 10–20% achieving complete normalisation. The other half is left with permanent sequelae that may be very severe.

Outcome is not influenced by the frequency and type of epileptic seizures. However, there is a strict correlation between the length of the CSWS and persistence of language impairment.[198] Early onset of LKS is related to the worst prognosis with regard to language recovery.

Conversely, a recent study showed that the age of onset of language dysfunction does not seem to correlate with the prognosis for recovery of language function.[199]

Rarely, spontaneous remissions may occur within weeks or months from onset.

Management

The goal of management is to:

a. eliminate or reduce by pharmaceutical or surgical means the epileptiform EEG discharges, assuming that these are responsible not only for the seizures but also for the overall clinical manifestations of LKS. Seizures are infrequent, age limited and often easily controlled with AEDs.
b. treat the linguistic, behavioural and other neuropsychological abnormalities that make up the majority of these children's problems with appropriate educational programmes, expert speech therapy, including sign language, and psychotherapy. Continuous monitoring of these symptoms is required in order to assess severity, progression or remission.

The treatment of LKS is by large empirical and involves AEDs, corticosteroids, ACTH, intravenous immunoglobulins, ketogenic diet, and surgical procedures. The results are of variable success and often disappointing. Treatment is usually effective for seizure control and eventual seizure remission. However, the response for language and behaviour is often poor.

The effect of treatment should be monitored with appropriate neuropsychological evaluation and serial awake and sleep-stage EEGs.

Medical treatment:[175,176,185,187] All traditional AEDs as well as sleepmodifying drugs such as amitriptyline and amphetamine, have been tried. By expert assessment, valproate is the first line option, usually in combination with clobazam. Ethosuximide, sulthiame, clonazepam and, of the newer AEDs, levetiracetam, topiramate, vigabatrin and zonisamide have been used, mainly in combination regimens, and there have been case reports of success, particularly with levetiracetam. High dose diazepam protocols lasting several weeks have also been used and have claimed better results than chronic administration of other benzodiazepines. It is important to avoid AEDs such as phenytoin, phenobarbital and carbamazepine because these drugs may worsen the EEG discharges and neuropsychological deficit.[189]

In the likelihood that optional AED treatment fails to elicit any signs of clinical and EEG improvement, then ACTH or prednisolone (hydrocortisone may also be used) should be employed (see chapter 7, page 229). This is particularly important in new and younger patients who may respond better, need shorter corticosteroid treatment and are at a high risk of significant residual neuropsychological sequelae. Oral corticosteroids are used more often than high doses of intravenous pulse corticosteroids. There is an empirical view that the results depend on early treatment with high initial doses of corticosteroids for at least 3 months. Continuation of treatment after this period depends on response and side effects. Probably 75% of patients with LKS respond well to this treatment but around 40% of them relapse, usually upon discontinuation of corticosteroids. The latter patients may need to continue receiving corticosteroid medication for years. Corticosteroids are usually combined with valproate or benzodiazepines, which continue after the corticosteroids have been weaned off.

The value of intravenous immunoglobulins and the ketogenic diet in the treatment of LKS is equivocal despite some case reports of success.

Surgical treatment: In medically intractable cases of LKS, multiple subpial intracortical transections (see page 224) have been used with relative success.[183,200] This surgical technique has been designed to eliminate the capacity of cortical tissue to generate seizures

while preserving the normal cortical physiological function. Its success depends on the selection of cases with severe epileptogenic abnormality that can be demonstrated to be unilateral in origin despite a bilateral electrographic manifestation.

The ILAE Subcommission for Pediatric Epilepsy Surgery considers multiple subpial transections as the surgical procedure of choice in LKS.[83]

Epileptic encephalopathy with continuous spike-and-wave during sleep

Synonyms: epilepsy with CSWS, encephalopathy with electrical status epilepticus during slow-wave sleep.

Epileptic encephalopathy with CSWS[175,180,185–187,197,201–204] is a partly reversible, age-related childhood epileptic encephalopathy characterised by the triad of:

- EEG CSWS (Figure 10.12)
- seizures
- neuropsychological impairment.

Continuous spikes and waves during NREM sleep is a prerequisite for the diagnosis of this syndrome.

Clarifications on classification

See page 251.

Demographic data

Epileptic encephalopathy with CSWS is age dependent, occurring only in children. Onset of seizures is between 2 months and 12 years, with a peak at 4 or 5 years. The EEG abnormality of CSWS probably starts 1 or 2 years from the first seizure with a peak at age 8 and a range of 3–14 years. There may be a male preponderance (62%).[175] The prevalence is no higher than 0.5% of all children with seizures.[203]

Clinical manifestations[175]

Half the affected children are normal before the onset of the disease. The other half have pre- or perinatal illness, neonatal convulsions and neurological abnormalities such as congenital hemiparesis or tetraparesis, ataxia, psychomotor or language deficits.

There are three stages of evolution.

The first stage is before the discovery of the CSWS: The first seizure is usually nocturnal in half of cases and in 40% consists of unilateral convulsions, often lasting for more than 30 min (hemiclonic status epilepticus). In others, seizures may be simple focal motor clonic, complex focal, myoclonic absence seizures and GTCSs. Seizures are infrequent and mainly nocturnal.

The EEG shows multi-focal spikes and bisynchronous generalised sharp or spike–wave discharges.

The second stage (with CSWS) commonly starts 1 or 2 years after the first seizure. The discovery of CSWS is usually due to an increase in seizures and the appearance or deterioration of neuropsychological symptoms that prompt a sleep EEG. The active duration of CSWS is difficult to assess ranging from several months to up to 6 or 7 years.

Seizures: The habitual seizures of the patient become frequent and new types of seizure emerge. Patients may have one or multiple forms of seizures. These include hemifacial, hemiconvulsive, GTCSs, atypical or typical absences, negative myoclonus, nonconvulsive status epilepticus and atonic seizures. Convulsive seizures are predominantly nocturnal. Tonic seizures do not occur at any stage and are probably incompatible with the diagnosis of epilepsy with CSWS.

This case supports the links between benign neonatal seizures, rolandic seizures and epilepsy with CSWS

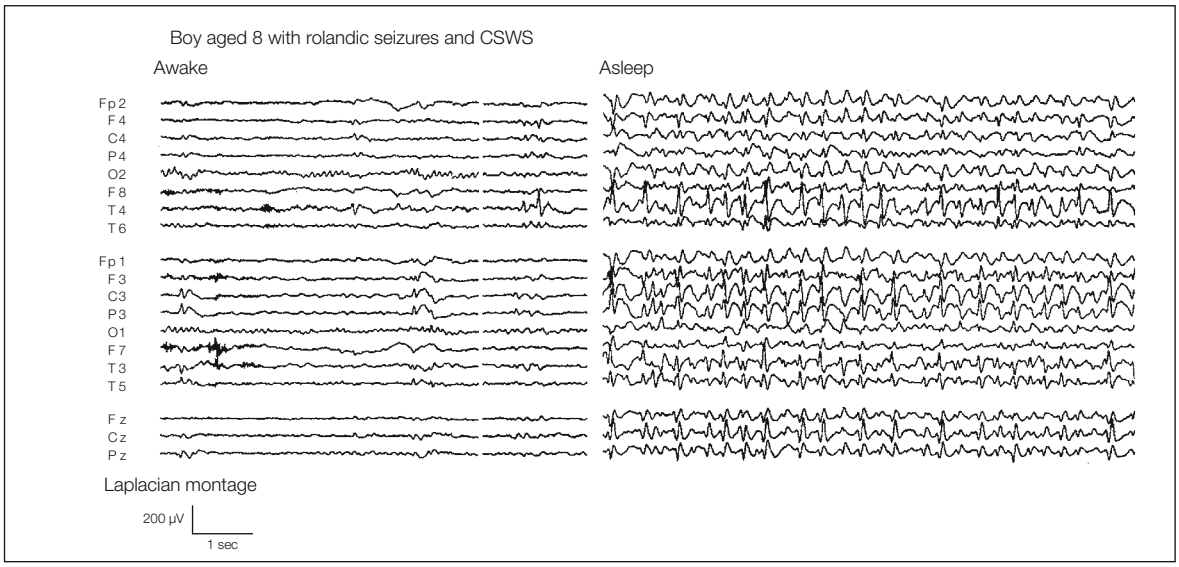

Figure 10.12 From a video-EEG recording of an 8-year-old boy who, at age 8 weeks, had three focal seizures of right-sided convulsions involving the face and upper limbs (Figure 9.1). Subsequent development was excellent, but at age 7 he started having rolandic seizures and later developed epilepsy with CSWS associated with impaired scholastic performance (case 17.2 in Panayiotopoulos[189]). When alert, the EEG shows infrequent clusters of focal sharp–slow-wave discharges (left), which became continuous during sleep (right).

Over 90% of patients have numerous seizures, sometimes several a day. Infrequent seizure occurrence is unusual (10%).

Neuropsychological decline: The decline of the neuropsychological state is the most disturbing clinical feature. This is usually of insidious onset and progression, while sudden commencement is rare. The neuropsychological deficits are largely dependent on spike localisation.

Frontal or prefrontal CSWS disrupt the higher cognitive and executive functioning before damaging language function, and produce a frontal lobe type of mental and behavioural deterioration. This presents as hyperkinesia, agitation, disinhibition, aggressiveness and inattention, often leading to extensive cognitive decline or psychosis described as dementia of frontal lobe syndrome.

Temporal lobe CSWS produces mainly linguistic disturbances with a tendency towards expressive aphasia rather than the verbal auditory agnosia of LKS.

Motor disturbances consist of ataxia, hemiparesis and dyspraxia. Some children may develop the clinical features of 'acquired epileptiform opercular syndrome' with orofaciolingual deficits of severe oral motor dysfunction, drooling, dysarthria, speech arrest or weakness of the face and tongue.[186,205,206]

The third stage of clinico-EEG remission starts after a variable period of months to usually 2–7 years from onset. Seizures remit in all patients. The EEG gradually improves to a relatively normal appearance. The neuropsychological state also improves but children rarely attain average normality. Despite some improvement, many of these children suffer from permanent complex and severe neuropsychological impairment.

Aetiology

The aetiology is unknown. More than a third of patients with epilepsy with CSWS have an abnormal

pathology such as unilateral or diffuse cortical atrophy, focal porencephaly and malformations of cortical development. Cases of epilepsy with CSWS evolving from benign childhood focal seizures (see Chapter 12) are well reported.[192] Usually, there is no evidence of familial epileptic disorders and a family history of epilepsy is very uncommon (approximately 10%). However, epilepsy with CSWS and rolandic epilepsy could, in rare instances, co-exist in members of the same family.[207]

Pathophysiology

This is similar to that described in LKS (see page 305). The neuropsychological impairment is attributed to the effect of CSWS.[7,175,180,186] The acquired deterioration of cognitive function with CSWS is probably caused by an alteration of the maturation of one or several associative cortices, primarily involving local interneurones and cortico-cortical associative networks.[208] The pattern of neuropsychological derangement depends on the location of the inter-ictal focus. Linguistic impairment relates to epileptogenic abnormalities over one or both temporal lobe regions, whereas mental deterioration and autistic behaviour relates to frontal lobe epileptogenic foci. Motor impairment such as dyspraxia and dystonia, are attributed to the dysfunction of the motor cortex by CSWS and the negative myoclonus during wakefulness.

Tassinari and colleagues hypothesised that prolonged focal epileptic activity during sleep (as occurs in epilepsy with CSWS) interferes with local slow wave activity at the site of the epileptic focus, impairing neural processes and, possibly, the local plastic changes associated with learning and other cognitive functions.[196,209] In order to emphasise their view they proposed to label epilepsy with CSWS as the "Penelope syndrome: Spinning during the day, spiking during the night," in which the diurnal "spinning" to make up a thread (a neuronal network) is erased by the "EEG spiking" during sleep.[196]

The CSWS-generating mechanism is attributed to secondary bilateral synchrony (Figure 2.7). Focal epileptogenic foci rapidly propagate within and between hemispheres to produce diffuse slow GSWD.

Diagnostic procedures

Brain imaging, particularly MRI, is mandatory. More than a third of patients with epilepsy with CSWS have abnormal brain imaging. Functional brain imaging (PET or single photon emission CT [SPECT]) is usually abnormal even in patients with a normal brain MRI.

Electroencephalography[175,179,180,186]

Epilepsy with CSWS is mainly defined by EEG CSWS. The testing procedures include routine EEG, prolonged video-EEG recording or ambulatory monitoring. The syndrome can be suspected with brief sleep EEG recordings (Figure 10.12), but an all-night sleep EEG is usually needed for proper quantification.

EEG in the first stage (before the development of CSWS): The first EEG is usually obtained after the onset of seizures.

Inter-ictal awake EEG shows focal or multi-focal slow spikes in more than two-thirds of patients, mainly localised in the frontotemporal, centrotemporal and less often in the parieto-occipital electrodes. Often these are morphologically similar to the functional spikes of benign childhood focal seizures. These are activated by sleep without altering their morphology. In 80% of cases, there are additional diffuse slow GSWD at 1–3 Hz, often with an apparent focal driving spike that suggests secondary bilateral synchrony.

Sleep patterns and the cyclic organisation of sleep are normal.

The background EEG varies in accordance with the cause of epilepsy with CSWS. Focal slow waves, fast spikes and polyspikes may occur in symptomatic cases.

EEG in the second stage (with CSWS): The characteristic EEG pattern in this stage occurs during sleep. In wakefulness the EEG is similar to that of the first stage, but the abnormalities are more pronounced.

Continuous spikes and waves during NREM sleep are the defining EEG pattern of epilepsy with CSWS.

The classical CSWS consists of NREM sleep-related, continuous or almost continuous, bilateral and bisynchronous sharp–slow waves, which are morphologically similar to the functional spikes of rolandic epilepsy with a repetitive rate of 1.5–2 Hz (faster rates of 3 or 4 Hz may be present). These are of higher amplitude in the anterior or central regions. There are significant variations so that the discharges can be grossly asymmetrical, unilateral or predominantly focal[210] and spikes may be devoid of the slow waves.

This pattern is generally found between the ages of 4 and 14 years and seems to develop 1 or 2 years after the appearance of seizures.

The duration of CSWS is quantitatively expressed as the spike–wave index (SWI), which is the sum of all spike–slow-wave complexes in minutes multiplied by 100 and divided by the total duration of NREM sleep in minutes. The SWI is usually more than 85% (sometimes 100%) of the total duration of NREM sleep. Less stringent criteria of an SWI greater than 50% are also accepted provided that the clinical symptomatology resembles that of classical cases and the dramatic activation of the epileptiform discharges occurs in NREM sleep rather than wakefulness. Patients with an SWI of less than 85% have better performance tests than those with a higher SWI. The percentage of CSWS is more marked during the first cycle of sleep (95–100%) than in the following cycles (80–70%). An EEG with mainly anterior spikes during wakefulness tends to produce a higher SWI (85–100%) than those with posterior spikes (64%):

> As soon as the patient falls asleep continuous bilateral and diffuse slow spikes and waves appear, mainly at 1.5–2.5 Hz, persisting through all the slow wave sleep stages. An SWI in the range of 85–100%, calculated during all-night sleep EEG recordings, is considered as an essential feature for the diagnosis of epilepsy with CSWS. This criterion was useful in identifying the tip of the iceberg.[175]

The diffuse or generalised CSWS frequently originate from focal spikes (secondary bilateral synchrony). These focal spikes are often seen in the inter-ictal awake or REM sleep EEG, at the onset of spike–wave stretches or with clearly higher amplitude in relation to the others. They are also discernible during the rare short period of fragmented diffuse spike–wave discharges in NREM sleep.[175]

Polyspikes are rare, and fast episodic activity is exceptional.

NREM-sleep EEG patterns (spindles, K complexes or vertex spikes) are seldom discernible during CSWS. However, these are preserved and become apparent when CSWS is fragmented, in the late cycles of sleep and in patients with a low SWI. The cyclic organisation of sleep is grossly preserved, 80% of sleep is NREM and there are no apparent sleep disorders.

In REM sleep the EEG is very similar to that of wakefulness.

EEG progression towards relative normalisation: Longitudinal sleep EEG recordings show a progressive improvement over the years towards normalisation after an average age of about 11 years. The discharges during sleep EEG become shorter, less frequent and more fragmented. Physiological sleep patterns become discernible. Rare, focal, sharp–slow-wave complexes may persist, particularly in sleep EEG, long after clinical improvement. Normalisation, if finally achieved, may take more than 15 years.

In all cases, sleep organisation and sleep stages are normal after CSWS remission.

Differential diagnosis[7,175,186,189]

The differential diagnosis of epileptic encephalopathy with CSWS from LKS when CSWS occur in EEG has been outlined in Table 10.6. Briefly, in LKS:

- acquired aphasia is the most predominant linguistic impairment
- epileptic seizures may not occur
- the inter-ictal EEG foci are mainly temporal, whereas they are mainly frontal in epilepsy with CSWS.

The differential diagnosis of epilepsy with CSWS from rolandic epilepsy and other benign focal seizure susceptibility phenotypes has been emphasised in all relevant reviews[7,186,189] because of similar EEG features, exaggeration of spikes during sleep, focal

motor seizures, mild cognitive impairment and atypical evolutions (see Chapter 12).

Differentiating epilepsy with CSWS from Lennox–Gastaut syndrome is easy because tonic seizures and EEG fast paroxysms are prominent in Lennox–Gastaut syndrome, whereas these are almost completely absent in epilepsy with CSWS. Furthermore, focal motor seizures and remissions are rare in Lennox–Gastaut syndrome.

Prognosis

Spontaneous resolution of the epileptiform discharges and seizures occurs in the mid-teens, which coincides with stabilisation or improvement of the behavioural and neuropsychological deficits. The persistence and severity of residual behavioural, cognitive and linguistic deficits depend on the age at onset and the duration of the active phase of electrographic epileptiform activity.

Seizures gradually become less frequent and less severe before they finally remit in all patients, commonly at about the age of 10–15. Seizure improvement may be simultaneous with (30%), precede (30%) or follow (40%) the resolution of CSWS. Seizure outcome is independent of aetiology with remission of seizures also in symptomatic cases such as multilobar polymicrogyria.[211] Delayed resolution of seizures occurs in patients with more severe epilepsy, such as those manifesting with generalised motor or atonic seizures or absences. The total duration of the active seizure period varies from 4 to 17 years.

Cognitive and behavioural abnormalities show a global improvement, which starts after the end of CSWS, but recovery is always slow and often only partial. The majority of affected children never return to normal functioning, particularly in the verbal areas and attention.[203,212]

Less than a quarter of the patients will resume acceptable social and professional levels, and these are more likely to include those who had a normal pre-morbid neuropsychological state and a shorter duration of the active period in CSWS.

Management

Management is similar to that described for LKS (see page 308).

Seizures are not a major problem because their final prognosis is good. The treatment of CSWS, which is responsible for the neuropsychological impairment, is entirely empirical and usually of transient efficacy. The following schemes, alone or in combination, have been proposed:[7]

- Oral benzodiazepines (diazepam, clobazam, clonazepam or lorazepam) combined with valproate.[175] Short cycles (3 or 4 weeks each) of diazepam (0.5 mg/kg) following a rectal bolus of 1 mg/kg of diazepam have been used with some benefit.[213]
- ACTH (80 IU daily with a taper of 3 months) or high-dose prednisolone (2–5 mg/kg daily with a taper of 3 months) when CSWS is diagnosed.[7] The earlier the treatment is initiated, the shorter the time for which steroids need to be taken and the better the ultimate outcome.

In cases with severe linguistic impairment, subpial intracortical transections have been used with success.[183,200]

Myoclonic encephalopathy in non-progressive disorders

Synonym: myoclonic status in non-progressive encephalopathies, non-progressive myoclonic epilepsy in infancy.

Myoclonic encephalopathy in non-progressive disorders is characterised by:[214–217]

- a fixed, non-progressive encephalopathy
- recurrent episodes of prolonged and erratic atypical myoclonic-absense status epilepticus.

Clarifications on classification

Myoclonic status in non-progressive (fixed) encephalopathies was considered to be 'a syndrome in development' in the 2001 diagnostic scheme of the ILAE.[1] It is now believed that there is sufficient evidence to support it as a syndrome of an important form of epileptic encephalopathy.[17] It has been renamed 'myoclonic encephalopathy in non-progressive disorders'.[17]

Demographic data

Onset is from day 1 of life to 5 years of age (peak at 12 months). There is a twofold female preponderance. Incidence and prevalence are unknown but may occur in 0.5–1% of a selected population of severe childhood forms of epilepsy.

Clinical manifestations

All patients have pre-existing neuropsychological deficits of a fixed encephalopathy characterised by severe axial hypotonia, ataxia, continuous jerky movements, tremor, and severe cognitive and learning abnormalities.

The defining seizure manifestation is repetitive and long (sometimes for days) episodes of atypical and subtle myoclonic status epilepticus, consisting of myoclonic jerks and discontinuous absences. The myoclonic jerks, which involve the eyelids, face and limbs, are mostly erratic and asynchronous, becoming more rhythmic and synchronous during the absences. They are often inconspicuous and babies may just appear to be apathetic and ataxic. Myoclonic status epilepticus may be the first seizure manifestation. In others, onset is with focal motor seizures, myoclonic absences, massive myoclonias and, more rarely, generalised or unilateral clonic convulsions, recurring in some cases only during febrile illness. Tonic seizures do not occur.

Many patients also have frequent and sudden spontaneous massive startle attacks, which consist of brief and abrupt loss of postural tone and long-lasting episodes of positive/negative myoclonus and tremor.

On electroclinical grounds two main groups are recognised:

1. *The first group* has a mixed pattern of myoclonic absence seizures, inhibitory phenomena and cortical myoclonus. The myoclonic status is usually sporadic but may also be frequent for years. This pattern occurs mainly in chromosomal abnormalities such as Angelman syndrome.[218,219]
2. *The second group* shows a marked predominance of inhibitory phenomena resulting in complete motor inhibition. The status is always permanent throughout the evolution. All patients are females with unknown aetiology.

Aetiology

Half of cases suffer from chromosomal disorders, mainly Angelman and 4p syndromes. Around 20% of patients have prenatal brain anoxia–ischaemia or malformations of cortical development. The aetiology is unknown in the remaining cases. A fifth of all patients have a family history of epileptic seizures.

Metabolic diseases such as non-ketotic hyperglycinaemia may present with similar electroclinical features.

Pathophysiology

This is unknown but may be multiple. A loss of GABAergic inhibition has been implicated because Angelman syndrome and some patients with 4p syndrome have a chromosomal deletion eliminating a cluster of $GABA_A$-receptor genes.[216]

Diagnostic procedures

As a result of different aetiologies these children require brain MRI, chromosomal analysis and metabolic screening. Seizures may need confirmation with video-EEG.

Electroencephalography

The inter-ictal EEG is diffusely slow with frequent focal or multi-focal abnormalities of slow waves and spikes.

The ictal EEG shows continuous or subcontinuous brief bursts of diffuse slow spikes and waves.

Differential diagnosis

Myoclonic status epilepticus is often difficult to recognise without polygraphic or video-EEG recordings because of the severe learning disabilites and the continuous abnormal movements of these babies. The diagnosis of non-progressive encephalopathy needs exclusion of progressive diseases manifesting with similar seizures/status such as certain forms of progressive myoclonus epilepsy (see Chapter 17).

Prognosis

Prognosis is poor even for those who initially appear only hypotonic. The initial hypotonic state progressively deteriorates to, sometimes severe, neurocognitive deficits. The myoclonic status improves with age but the patients rarely achieve a relatively normal state.

Management

Stopping myoclonic status epilepticus with benzodiazepines is often associated with a global improvement of the patient, although commonly this improvement is transient. In some patients with chromosomal abnormalities there may be some beneficial effect of valproate combined with ethosuximide or clobazam, but ACTH treatment is often needed.

Atypical benign partial epilepsy of childhood

Atypical benign partial epilepsy of childhood (APEC)[33,189,220–224] is correctly not recognised as an epileptic syndrome by the ILAE. However, it has been included in this book for two reasons. First, because it poses significant problems in its differentiation from some epileptic encephalopathies (Lennox–Gastaut syndrome, LKS and epilepsy with CSWS), EM-AS (see Chapter 13) and atypical evolutions of benign childhood focal seizures (see Chapter 12).[33,189,220] Second, because it is of an intermediate severity between LKS and epilepsy with CSWS and benign childhood focal seizures (see Chapter 12).[222]

Clarifications on nomenclature

Aicardi and Chevrie[220] used the term 'benign' for this atypical benign partial epilepsy of childhood, not because of possible similarities with rolandic seizures, but mainly in order to distinguish it from the Lennox–Gastaut syndrome 'for which it is regularly mistaken'.[220] Others have called it 'pseudo-Lennox syndrome'.[222]

Retrospectively, Aicardi considered that it now appears that APEC bears a close relationship to epilepsy with CSWS. It may be a mild and intermediate form of epilepsy with CSWS.[33]

Demographic data

Onset is at 2–6 years of age. APEC is rare, probably one case per 130 patients with rolandic epilepsy.[225]

Clinical manifestations

Children have normal development and neurological examinations before the onset of seizures.

All patients have at least two different seizure types: atonic seizures and nocturnal focal 'rolandic-like' seizures.

Atonic seizures occur in clusters lasting for 1 week to several weeks, usually separated by free intervals of several weeks or months. They may involve the whole axial musculature and/or both lower limbs with multiple daily falls. Atonic seizures may also

be subtle and localised, manifesting with brief (1 or 2 s), abrupt drop of the head or hands. Focal atonia of transient dropping of one arm may be very brief (100–150 ms) and is observed when the patients are asked to keep both arms outstretched in front of the body.[226] The brief focal atonia of the arm occasionally progresses to atonic seizures or atonic absence seizures.

Nocturnal focal seizures similar to rolandic seizures often occur as a presenting symptom and are infrequent. Diurnal focal sensorimotor fits are exceptional.

Other type of seizures: Some patients may also have GTCSs, brief absences and, occasionally, jerks. In some patients, absence seizures may be prominent.

Behavioural and cognitive problems: At the active seizure periods there is some degree of mental slowing or behavioural disturbance, which is often subtle and disappears during seizure-free periods.

Diagnostic procedures

All tests except the EEG are normal.

The inter-ictal awake EEG shows centrotemporal spikes, which are often bilateral. Generalised spikes and waves at 3 Hz are frequent, with or without clinical absences. The sleep EEG is similar or identical to the CSWS. This occurs mainly during the active period of atonic seizures and may disappear in between.

The ictal EEG in unilateral, brief (100–150 ms), focal atonia corresponds exactly with a single sharp–slow-wave complex arising from the contralateral centro-temporo-parietal region. With progress to atonic or atonic–absence seizures, the localised epileptic discharge spreads into generalised discharges.[226,227]

Differential diagnosis

Atypical benign partial epilepsy of childhood has a good outcome with no evidence of residual mental or behavioural deterioration.

In contrast with Lennox–Gastaut syndrome, there are no tonic fits.

APEC may also imitate EM-AS because of repeated falls, absences and diffuse slow spike–wave activity mainly in the sleep EEG.[33,189,220] The main differentiating points are as follows:

- nocturnal focal seizures, similar to rolandic seizures, are often the initial seizure type.
- EEG centrotemporal and other functional spikes in various locations.

Similar to APEC, clinico-EEG features may occur in atypical evolutions of rolandic epilepsy[190,228] and Panayiotopoulos syndrome,[191,192] but these are preceded by typical presentations of these syndromes (see Chapter 12).

A similar but reversible clinico-EEG condition may be induced by carbamazepine, oxcarbazepine or lamotrigine in a few children with rolandic epilepsy and Panayiotopoulos syndrome.[189,229–231] This possibility should be considered in children with these syndromes who show a dramatic deterioration after treatment with carbamazepine, oxcarbazepine, lamotrigine or some other drugs, such as vigabatrin.

Prognosis

The long-term outcome appears to be good with complete remission of seizures, no gross cognitive or behavioural sequelae and children attending mainstream schools.[33]

Management

Most of the traditional AEDs are often ineffective against the seizures and the EEG paroxysms. ACTH or corticosteroids were tried unsuccessfully in a few cases. Sulthiame or sulthiame/clobazam has been recommended as an effective treatment.[232–235] Lamotrigine[236] and phenobarbital[237] may have a deteriorating effect.

Hypothalamic epilepsy

Synonyms: Gelastic seizures with hypothalamic hamartoma.

Hypothalamic epilepsy is a rare epileptic disease of hypothalamic hamartomas manifesting with gelastic seizures. This often evolves to a generalised epileptic encephalopathy with severe seizures and cognitive and behaviour decline. Despite earlier views to the contrary, there is now good evidence to suggest that all these clinical features are caused, either directly or indirectly, by the hamartoma.[20,238–245]

A multi-expert authoritative review of hypothalamic epilepsy has been published in *Epileptic Disorders*.[241]

Clarifications on classification

The 1989 ILAE Commission[18] classified gelastic seizures resulting from hypothalamic hamartomas among the 'symptomatic generalised epilepsies of specific aetiologies'.[18] The position of the ILAE Task Force was similar and considered hypothalamic epilepsy among 'an example of a classification of diseases frequently associated with epileptic seizures or syndromes'.[1] The updated ILAE Task Force report now correctly considers 'gelastic seizures with hypothalamic hamartoma' to be an epileptic syndrome and probably a disease (Table 5.2),[17] as was proposed in the first edition of this book.

In the new (unpublished) report of the ILAE commission on classification and terminology, "hypothalamic hamartoma with gelastic seizures" represents a clinically distinctive constellation on the basis of a specific lesion (hypothalamic hamartoma) rather than an electro-clinical syndrome per se.

Demographic data

Onset of habitual seizures typically begins in the neonatal period or early childhood with a peak at 2 or 3 years. Boys are twice as likely to be affected. Hypothalamic epilepsy appears to be extremely rare, probably 0.1% among patients with seizures. In my experience of a series of 1500 of both adult and child patients with seizures, only two had hypothalamic epilepsy.

Clinical manifestations

Laughter is the defining, inaugural and starting clinical ictal manifestation of hypothalamic epilepsy.

Hypothalamic seizures may manifest only with laughter, particularly at onset. The laughter may be silent, a facial expression of a smile, or loud, with the natural vocalisations at various intensities and combinations. There is no emotional element of pleasure or amusement associated with this: it is a mirthless laughter. The attacks come out of the blue, are out of place and are inappropriate. Although unmotivated as a rule, some of the attacks may be triggered by a pleasant situation and may not even be recognised as pathological.

Dacrystic (crying) attacks alone or together with laughter may occur in 13% of the patients.[243]

Gelastic seizures are usually brief (10–30 s), of sudden onset and termination, and occur on a daily basis. The attacks are usually diurnal, but exceptionally they may also occur during sleep.

Subjectively, patients may be conscious of laughing, but they cannot prevent it or stop it. They feel embarrassed about this, often inventing various excuses to justify it if this occurs at school, church or social meetings.

A few patients report a warning that they cannot describe well:

> A 13-year-old girl had onset of gelastic seizures from age 3 years. The laughter might precede or occur simultaneously with a feeling of her being light as 'if flying in the air'. The ictal laughter is similar to her natural laughter, but her parents can recognise the pathological one. MRI demonstrated a small hypothalamic hamartoma in the right wall of the third ventricle. Despite numerous gelastic seizures, which became longer and more severe with time, she remains highly intelligent with normal behaviour.

Other ictal subjective symptoms concurrent with laughter include disorientation, localised tingling and auditory sensations.

Gelastic seizures may be associated with impairment of consciousness in half of patients. The more common pattern is that of the gelastic seizures becoming longer with impairment of consciousness and other-than-laughter clinical ictal manifestations such as automatisms.

Autonomic symptoms associated with the attacks of laughter occur in a third of patients. These symptoms include cardiorespiratory and blood pressure changes, pallor or flushing, pupillary dilatation, sniffing and urinary incontinence. Gelastic seizures are accompanied by an abrupt sympathetic system activation, probably due to the direct paroxysmal activation of limbic and paralimbic structures or other autonomic centres of the hypothalamus and medulla.[246]

Other types of seizures: More than half the patients (66%) also suffer from other types of seizure in addition to gelastic attacks. These are usually generalised seizures such as tonic, atonic, tonic–clonic and absences alone or in combination. Complex focal seizures without laughter are less common. These additional seizure types may start at the same time with laughter attacks or usually later within 1 year to a few years.

A small number of patients with hypothalamic hamartoma present with infantile spasms (as an initial or early seizure type).[247]

Post-ictal state: There are no objective or subjective post-ictal symptoms in non-convulsive seizures of hypothalamic epilepsy. Pre-ictal activity continues as if nothing had happened.

Aetiology

Hypothalamic epilepsy is due to hypothalamic hamartomas (Figure 10.13). Hamartoma is a non-neoplastic, developmental tumour-like nodule that results from aberrant differentiation.[248] Mature small neurones are the most prominent and most consistent histological feature of hypothalamic hamartomas.

Patients with Palister-Hall syndrome may also develop hypothalamic epilepsy.[241] Pallister-Hall syndrome is an autosomal dominant disorder resulting from mutations of GL13. It is characterised by a spectrum of anomalies that include central polydactyly, asymptomatic bifid epiglottis, hypothalamic hamartoma and endocrine dysfunction.

Pathophysiology[240,249]

Hypothalamic hamartomas are directly involved in the pathogenesis of gelastic and dacrystic seizures and they have intrinsic epileptogenicity.[250] Intracranial recordings documented that the gelastic seizures of hypothalamic epilepsy arise from the hamartoma itself.[249] That seizures may also respond to the long-acting gonadotrophin-releasing hormone (GnRH) analogue prescribed for precocious puberty may indicate that the epileptogenic generators reside in the same cells that autonomously produce GnRH.[251]

The acquired cognitive and behavioural symptoms probably result from a direct effect of the seizures. Children with hypothalamic hamartomas and precocious puberty but without seizures do not develop cognitive and behavioural problems.

Diagnostic procedures

A clinical diagnosis of hypothalamic gelastic epilepsy would demand confirmation with high-resolution MRI (Figure 10.13).[252]

MRI showing hypothalamic hamartoma of a child with gelastic seizures

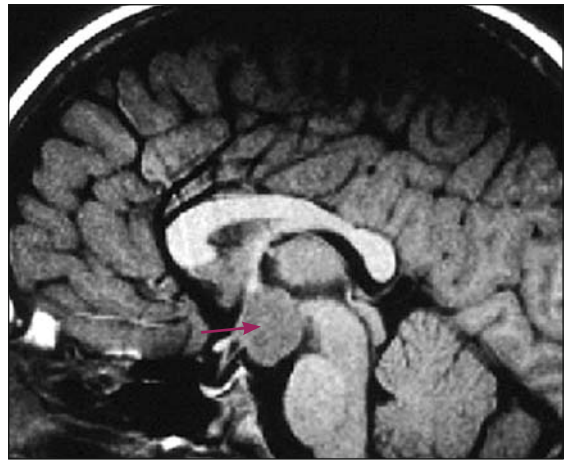

Figure 10.13 *Courtesy of Dr. Rod C. Scott, Institute of Child Health, London, UK.*

The diagnosis is obvious in patients with Palister-Hall syndrome because of polydactuly and other apparent anomalies. GL13 is routinely available for genetic testing.[241]

Electroencephalography

The inter-ictal EEG is not informative. It may be normal or more commonly show non-specific and non-lateralising episodic abnormalities.

Ictal gelastic seizures express rhythms on surface EEG compatible with epileptic activity originating in subcortical generators and secondarily involving cortical ones.[253] A typical *ictal pattern* in the surface EEG consists of low-voltage episodic fast rhythms with simultaneous suppression of background activity (Figure 10.14).

Differential diagnosis

Hypothalamic seizures need differentiation from non-epileptic conditions and from seizures arising from other brain locations. Gelastic seizures may

Surface ictal EEG of a girl aged 3 years and 3 months with normal neuropsychological development and frequent daily gelastic seizures[245]

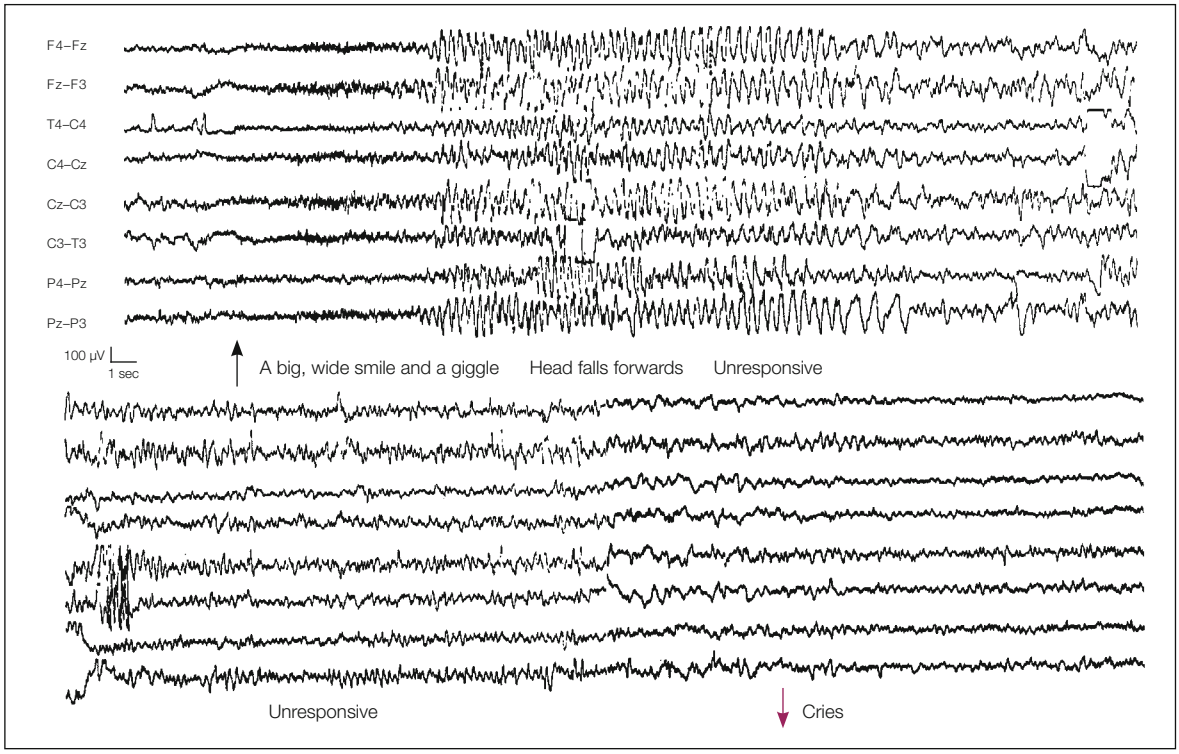

Figure 10.14 First noticed at age 2 years when her parents observed that, when told 'how beautiful' she is or 'come and get these candies', she reacted with a 'facial grimace', something like a 'frozen smile', 'a smile that freezes' and 'right-sided deviated lips with a smile'. This initially lasted for only a few seconds, occurred every fortnight and was always provoked as above. Subsequently, within months, this occurred daily, almost every morning, without precipitating factors, became longer and it was also associated with small giggles.[245] At the black arrow, her mother said 'here is her big smile'. The girl suddenly had a big and wide smile, which was associated with a mild giggle. This lasted for only a few seconds followed by head falling forwards and complete unresponsiveness until the end of the seizure when recovery was manifested by a cry (red arrow). The inter-ictal EEG was normal with a well-organised and symmetrical alpha rhythm. The seizure started (black arrow) with fast episodic activity at approximately 22 Hz, which is widely spread with some left-sided emphasis. This was concordant with the gelastic manifestations of the seizure. The rest of the EEG ictal events are self-evident.

initially be so mild and appear so natural that they are understandably unrecognised as pathological. (Figure 10.14) It is only after the appearance of other more traditional seizure manifestations and impairment of consciousness that medical advice is sought.

It is difficult to establish exact differential criteria between gelastic seizures of hypothalamic versus cortical (frontal or temporal lobe) origin. However, gelastic seizures of hypothalamic epilepsy are unique with regard to:

- seizure onset of laugher as the first and often the only ictal manifestation
- daily seizure frequency
- lack of mirth
- awareness of ictal laughter.

This clustering of events does not occur in either temporal or frontal lobe gelastic seizures. For example, laughter occurring in the middle of other ictal manifestations, laughter associated with emotions, infrequent seizures of laughter or gelastic seizures starting in adolescence are not features of hypothalamic epilepsy.

Prognosis

Hypothalamic gelastic epilepsy is often a progressive seizure disorder. Typically, neonates or children are normal before the onset of seizures. Gelastic seizures become more frequent and longer with associated impairment of consciousness. Later generalised seizures of any type appear. In addition, most patients develop progressive cognitive and behavioural impairment.[20,254,255] More than half (59%) of patients with hypothalamic epilepsy suffer from precocious puberty.[243]

In hypothalamic epilepsy of patients with Palister-Hall syndrome, seizures start later and are less frequent and easier to control than those patients with isolated (non-syndromic) hypothalamic hamartomas.[241]

Management[19,238,256–259]

Medical treatment of hypothalamic epilepsy is often ineffective with minimal reduction of seizure frequency. Polytherapy may cause more harm than good.[243] Two patients treated with a GnRH analogue for precocious puberty became free of gelastic seizures.[251] Further trials with GnRH in patients with and without precocious puberty are needed.

Surgical removal of the hamartoma is technically difficult, but it is highly effective if successful. Choices include a transcallosal approach (good for intraventricular lesions), a pterional approach (useful for interpeduncular lesions), a transventricular endoscopic approach[260,261] or destruction of the lesion with radiofrequency probes or gamma knife radiosurgery.[262] Stereotactic radiofrequency lesioning of the hamartoma may result in seizure remission with significantly fewer complications than operative procedures.

Complete lesionectomy results in freedom from seizures and prevents neurobehavioural deterioration.[19] Improvement may occur with incomplete removal.

Depending on procedure, the percentage of patients achieving Engel class I or II outcome (seizure freedom, auras only, rare seizures only) ranges from 60–66% (endoscopic procedures or transcallosal resections, respectively) to 36–38% (pterional/frontotemporal approaches to resection/disconnection or Gamma Knife surgery, respectively) to 27% (stereotactic radiofrequency ablations).[238]

In a recent report, MRI-guided stereotactic radiofrequency thermocoagulation resulted in freedom from seizures in all but 2 of 25 patients with hypothalamic epilepsy. More impressively, 19 patients (76.0%) achieved complete seizure remission as well as improvement of their behavioural and intellectual states.[263]

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Severe neocortical epileptic syndromes in infancy and childhood

The following are severe neocortical epileptic syndromes with onset in infancy and childhood:[1,2]

- Kozhevnikov–Rasmussen syndrome
- migrating partial epilepsy of early childhood.

Rightly, hemiconvulsion–hemiplegia epilepsy is no longer recognised as an epileptic syndrome in the revised report of the ILAE Task Force.[3]

Kozhevnikov–Rasmussen syndrome

Synonyms: Kozhevnikov type 2 syndrome, Rasmussen syndrome.

Kozhevnikov–Rasmussen syndrome is a severe, probably acquired, subacute, lateralised encephalitis of unknown cause, characterised by progressive brain hemiatrophy, intractable and mainly focal motor seizures, epilepsia partialis continua (EPC) and progressive neuropsychological deterioration, with hemiparesis, and cognitive and linguistic deficits.[4–20]

The syndrome has recently been thoroughly assessed in a European consensus statement, which is recommended for further reading.[13]

> Kozhevnikov–Rasmussen syndrome should not be equated with 'epilepsia partialis continua', which is a form of focal motor status epilepticus of various causes and prognoses as detailed on page 402. Only 60% of patients with Kozhevnikov–Rasmussen syndrome manifest with EPC.

Author's note: The UK spelling of the name Kozhevnikov is used throughout this book, as opposed to various other forms, such as Kojewnikow[1,21] or Kojevnikov,[2] that have appeared in the literature.

Clarifications on nomenclature

There is significant misunderstanding surrounding the history and hence the eponymic designation of this syndrome.[10,19,20]

The formal ILAE nomenclature

In 1985, the officially recognised name given for this disorder in the ILAE classification was:

> Kozhevnikov type 2 syndrome: Childhood disorder, suspected to be of viral aetiology, has onset between 2 and 10 years (peak, 6 years) with seizures that are motor partial seizures, but are often associated with other types.[21]

However, following a symposium in the Montreal Neurological Institute (June 1988),[6] the name

'Rasmussen syndrome' was introduced into the currently valid 1989 ILAE classification as a synonym, not a substitute, of 'Kozhevnikov type 2 syndrome':[1]

> Two types of Kozhenikov's syndrome are recognized, one of which is also known as Rasmussen's syndrome and is included among the epileptic syndromes of childhood noted under symptomatic seizures.[1]

The ILAE Task Force preferred 'Rasmussen syndrome',[2,3] eliminating the name Kozhevnikov based on a misinterpretation of historical information.

Historical facts

Focal motor status epilepticus (EPC) was first described by Kozhevnikov in 1894[16] (see the translation in reference 6). He detailed four patients with EPC that he attributed to 'chronic encephalitis':

> In recent years I happened to observe several cases of cortical epilepsy... that it may be called *epilepsia corticalis sive partialis continua*, in that here the convulsive manifestations were continuous... The question of the nature of the disease process is much more difficult.... in all cases the illness developed little by little and once it had developed persisted for a very long time, so that we can postulate only chronic processes here... Thus, of the chronic processes, encephalitis with transition to secondary hardening of the brain, or sclerosis cerebri, is almost the only possibility... Thus, not knowing precisely what we are dealing with, [I propose] the presence of chronic encephalitis.[16]

Rasmussen later superbly refined and documented this syndrome from 1958[17] onwards (for further details see references 6,10,13).

Misconceptions

The misconceptions resulting in the removal of Kozhevnikov's name by the ILAE Task Force are as follows:

- Kozhevnikov described acute and not chronic encephalitis, which is in direct conflict of his report, quoted above.[16]
- Kozhevnikov's epilepsy was known only in francophone countries. However, his name was well used throughout the world, including in American literature,[22] from the beginning of the previous century with the confirmation of encephalitis, although it is true that it was better known in France (Dereux' thesis of 1955 is on 100 cases of Kozhevnikov syndrome with many having chronic encephalitis).[23,24]
- Kozhevnikov described tick-borne spring–summer encephalitis.[14] It is incorrect that Kozhevnikov's four patients had tick-borne encephalitis, a disease described in 1937, 38 years after his death. Furthermore, only one of his four cases had acute illness: 'in all cases the illness developed little by little'.[16] That acute encephalitis or cysticercosis was a cause of EPC in patients reported by other Russian authors, including Omorokow (see their translations in reference 6), is irrelevant to what Kozhevnikov described. In addition, Kozhevnikov was practising in Moscow, whereas the cases of Omorokow were seen in Siberia.

Despite all these facts,[19,20] the relevant official chapter of the ILAE Task Force still informs us:

> Both the clinical aspects and the pathological features (of Rasmussen syndrome) are strongly in favour of an underlying infective cause, as evidenced by the close resemblance of the clinical picture to that seen in Russian spring–summer tick-borne encephalitis, described by Kozhevnikov (Kozhevnikov 1991).[14]

The historical truth should be at least known.

> Kozhevnikov–Rasmussen syndrome is the only nomenclature that properly honours both these great men who independently described this epileptic syndrome of chronic encephalitis, half a century apart.

Demographic data

Onset is in childhood at ages 1–10 years (median age 6).[4] Onset in adolescence or adulthood is rare. Both sexes are equally affected. Kozhevnikov–Rasmussen syndrome is a very rare disease; one case per year is seen in specialised tertiary referral centres.

Clinical manifestations[13–15,24]

Typically, affected children are initially normal. Onset is usually with focal motor seizures, EPC,

hemi or generalised clonic or tonic–clonic convulsions, or sometimes complex focal seizures with no automatisms. Status epilepticus may be the presenting feature in about 20% of patients. Half of cases have a history of upper respiratory tract infection, otitis media or tonsillitis, which precedes the seizures by about 6 months (see also Takahashi, *et al*[25]).

Initially, the focal motor seizures involve a small group of mainly distal muscles (thumb, fingers, corner of the mouth or the eye), but with time they progress to neighbouring regions, become erratic and more diffuse, and also persist during sleep. Seizures of any type, usually a combination, gradually become more frequent and longer in duration, and are often associated with post-ictal hemiplegia. EPC occur in 60% of patients and may last for days, often interspersed with hemitonic–clonic convulsions, which may also become generalised. Hemiplegia is initially post-ictal and transient, but gradually becomes permanent. Histologically confirmed cases of Kozhevnikov–Rasmussen syndrome with no seizures have been reported.[26]

The clinical course follows three stages.[4,5]

The first stage is characterised mainly by simple motor or somatosensory seizures. Less frequently, onset may comprise of EPC, complex focal seizures without automatisms or secondarily generalised tonic–clonic seizures (GTCSs). A combination of these types of seizure may occur. Gradually, over weeks or months, seizures become more frequent.

The second stage is characterised by worsening of the seizures and progressive neurological symptoms with mainly unilateral hemispherical involvement. This stage usually starts about 3 months after seizure onset, but may be delayed for as long as 10 years after the first symptoms of the disease. Seizures become more frequent and widespread, and last longer. Permanent psychomotor deficits appear with progressive intensity, consisting of hemiparesis, hemihypoaesthesia, hemianopia with cognitive and linguistic elements (including dysphasia and dysarthria).

Progressive deterioration of the neurological and psychological state, either with or without seizure deterioration, is a typical feature of Kozhevnikov–Rasmussen syndrome.

In the third stage, the disease appears to abate with regard to seizure frequency and severity, as well as progression of neurological deficits, although patients present with serious neurocognitive residuals.

Aetiology

The aetiology is unknown, although lateralised chronic encephalitis is believed to be the main causative factor, as postulated 100 years ago by Kozhevnikov[16] and 50 years ago by Rasmussen.[17]

Pathology reveals an inflammatory process, which is initially relatively localised, but later progresses to more extensive unilateral or bilateral, mainly cortical, involvement.[27,28] The lesion appears to extend in a confluent rather than a multifocal manner.[29] Robitaille[30,31] classified the pathological specimens into four groups from those of active to those of remote disease. Most of the brain damage occurs during the first 8–12 months.[8]

A more recent report found significant heterogeneity in the stages of cortical pathology and the multifocal nature of the disease.[32] These stages varied from early inflammation defined by infiltration of T lymphocytes and neuroglial reactions, to more severe stages with extensive neuronal cell death and cavitation of the cerebral cortex. A greater burden of pathology was significantly associated with an early age at onset and longer duration of disease. The burden of pathology was similar in all brain regions except the occipital lobe, where it was significantly lower.[32]

A number of patients with typical Kozhevnikov–Rasmussen syndrome may have, in addition to the pathological changes of chronic encephalitis, other pathology such as vascular abnormalities resembling cavernous angiomas, tuberous sclerosis and tumours.[33] Familial occurrence of Kozhevnikov–Rasmussen syndrome is exceptional.[34]

The causes of the pathological changes are hypothetical and include:

- chronic viral infection (but so far no virus has been isolated)

- acute viral infection leading to a local immune response
- independent autoimmune process, not linked to infection, although results have been both for and against it; however, it is likely that an autoimmune process may be important in the pathogenesis of this syndrome.[11]

Diagnostic procedures[13]

There is no specific diagnostic procedure or abnormality in Kozhevnikov–Rasmussen syndrome.

At onset, all tests for functional and structural abnormalities may be normal. It is the progression of symptoms and signs, and their localisation, that may be consistent with the diagnosis.

Serial CT brain scans, and preferably MRI, show progressive hemiatrophy (Figure 11.1). This usually starts unilaterally in the temporoinsular region with enlargement of the temporal horn and sylvian fissure. The abnormalities usually spread from one discrete area to an adjacent region or multifocally at the same time.[35]

Functional brain imaging with single photon emission CT (SPECT) and 5-fluoro-D-glucose positron emission tomography (PET) demonstrates inter-ictal hypoperfusion and hypometabolism in the affected side, which is widely distributed and more intense in the rolandic and temporoinsular regions, worsens with progression of the disease and may be abnormal at a stage when the MRI scan is normal.[36] Ictally, there is regional hyperperfusion corresponding to the epileptogenic locus.[37]

Antibodies to glutamate receptor GluR3 are detected in the serum of some, but not all, patients. Cerebrospinal fluid (CSF) shows non-specific abnormalities in 50% of patients. Oligoclonal or monoclonal banding may be found.

Electroencephalography[10,13,38,39]

Inter-ictal EEG: The background EEG may be normal at the onset of the disease. Subsequent abnormalities consist of focal slow, usually high-amplitude delta waves, which gradually dominate in one hemisphere and often become bilateral with lateralised prevalence. Gradual disappearance and poverty of physiological rhythms (alpha, photic following, sleep spindles and drug-induced fast activity) in the affected side are the rule. Almost all the EEGs show inter-ictal spikes or sharp–slow waves. A single focus is rare. Multiple independent foci in the same hemisphere occur in 50% of patients and, in a third, are bilateral with lateralised emphasis. In addition, 50% of cases show bilateral synchronous discharges that are often bifrontal, but also generalised. Again, they frequently predominate on the affected side.

Ictal EEG: The onset of ictal EEG patterns is variable. Exceptionally, they remain localised. Commonly, seizures have a multi-focal onset either confined to one hemisphere or, less frequently, moving from one side to the other. The discharge appears to have higher amplitude in the secondarily involved hemisphere. Focal motor seizures may occur without concomitant EEG changes. Conversely, ictal EEG paroxysms may frequently occur without discernible clinical manifestations.[27,38,40]

EPC is notorious with regard to the lack of clinico-EEG correlations. The myoclonic jerks do not have a chronological relationship to the inter-ictal spikes.[27,38,40] It is exceptional to have jerks associated with EEG discharges.

Similarly, in electrocorticography, inter-ictal epileptiform activity is widespread and the onset of seizures occurs in multiple independent sites.[38] Stereo-EEG correctly identifies the origin of the discharge and the clinico-EEG sequence.[41,42]

Differential diagnosis

The diagnosis of Kozhevnikov–Rasmussen syndrome relies on:[13,14,43]

- progressive neurological deficit, mainly hemiparesis
- progressive hemispherical atrophy on brain imaging
- biopsy evidence of chronic encephalitis, in neurosurgical cases.

A particular challenge is the early recognition of the disease, which is often possible within 4 months of the onset of the first symptoms.[9] In most chronic

Brain MRI of a 5-year-old boy with Kozhevnikov–Rasmussen syndrome confirmed by histology

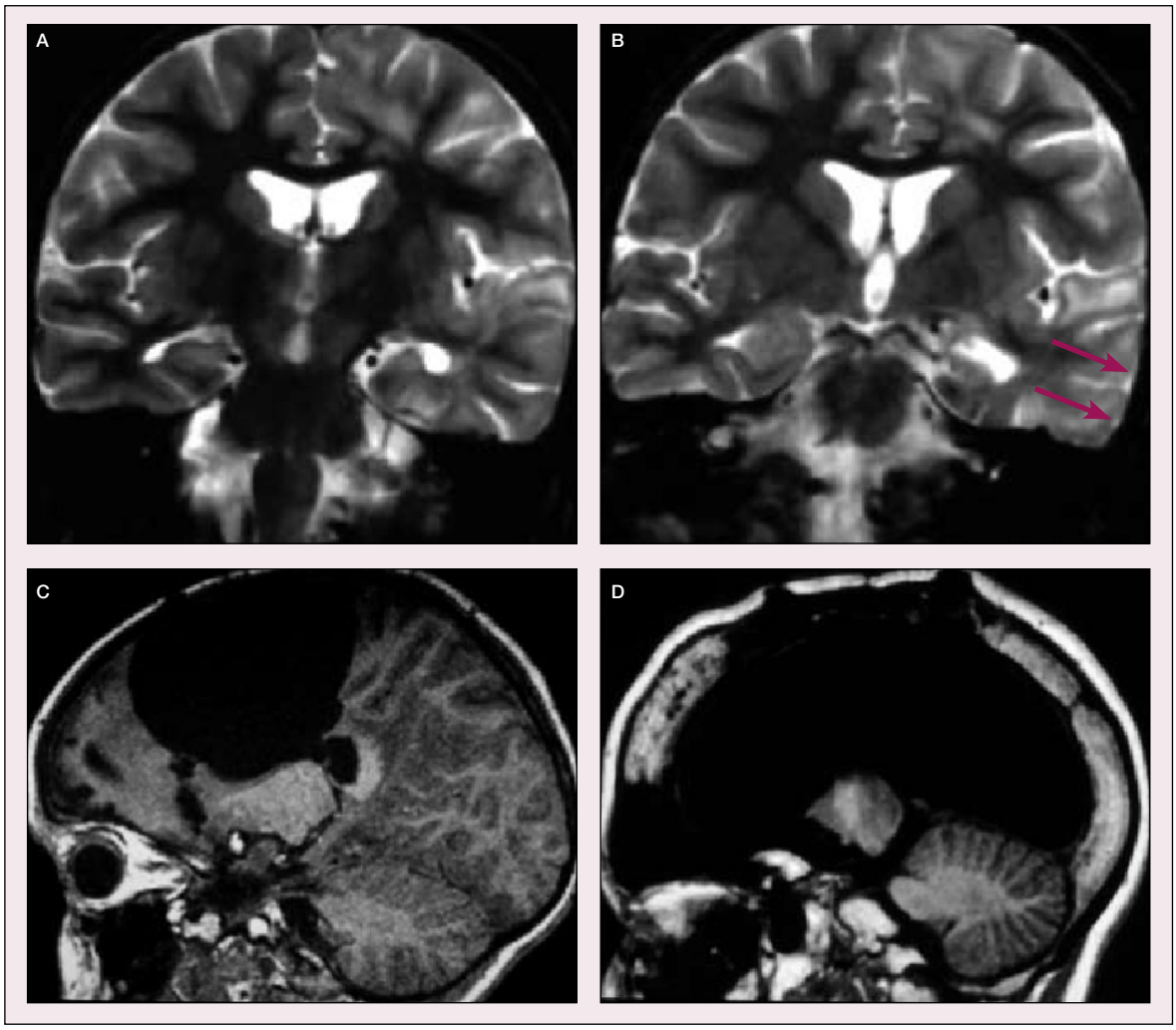

Figure 11.1 Progression of the disease in brain MRI before (A,B) and after (C,D) functional hemispheroctomy. The images on the right (B,D) were obtained 5 months after those on the left (A,C).
Courtesy of Dr. Rod C. Scott, Institute of Child Health, London, UK.

patients (i.e. after a disease duration of >1 year), differential diagnoses are few.

In the initial stages (before progressive hemiatrophy and the progressive loss of neurological functions are evident), the diagnosis is difficult, particularly in patients with no EPC. High-resolution brain imaging is mandatory to exclude other more common causes of focal seizures, such as malformations of cortical development, brain tumours, tuberous sclerosis, vascular anomalies, parasitic diseases (e.g. cysticercosis) and other infectious disorders (Table 15.2). An EEG is also mandatory at this stage because it may reveal functional spikes of rolandic seizures or other ictal and inter-ictal abnormalities that may suggest another epileptic syndrome. These tests also play an important role as baseline measurements for follow-up comparisons.

Other more serious diseases, such as MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), are less likely to cause diagnostic difficulties despite the high prevalence of EPC. Acute encephalitis of any cause that leads to hemiplegia and seizures should also be apparent from the onset. In endemic areas, Russian spring–summer and other tick-borne encephalitides should also be considered in patients with acute onset of symptoms.

Prognosis

This is a progressive disorder of increasing seizure frequency and severity with the development of neurological, cognitive and language deficits ranging from mild to often severe.[8,11,13]

Management

There is no effective treatment other than dramatic hemispherectomy, which appears to arrest the disease process in most patients at the expense of the consequent neurological disability.[10,13,44–46] Hemispherectomy should be reserved for patients with profound neurological deficits.[13] Limited focal resection is of little lasting benefit.

Anti-epileptic medication is usually ineffective, although a reduction of secondarily GTCSs may be achieved.

Antiviral treatments produce no definite benefit. Corticosteroids, adrenocorticotrophic hormone (ACTH), plasmapheresis, other immunosuppressive treatments (tacrolimus) and immunomodulatory trials with immunoglobulins, alone or in combination, and thalidomide may arrest the disease temporarily but with no sustained benefits. This may be useful in patients with status epilepticus and in the evaluation of patients before surgery when residual function may be unmasked by the reduction in seizure frequency.[39]

These treatments may be more effective if given in the early stage of the disease, before permanent neuronal damage has occurred.

Migrating focal seizures of infancy

Synonym: Malignant migrating partial seizures in infancy, epilepsy with migrating focal seizures in infancy.

Migrating focal seizures of infancy[47–54] is a devastating syndrome with early onset of almost continuous multi-focal seizures arising independently from multiple regions of both hemispheres, and relentless psychomotor deterioration.[47–49,55–57]

Considerations on classification

Initially considered by the ILAE Task Force as a new syndrome in development,[2] the latest report states that 'this has been sufficiently described by several independent investigators to merit recognition as a syndrome'.[3]

Demographic data

Less than 50 cases have been reported. Both sexes are equally affected. Age at onset is between the first day of life and 7 months of age (mean age 1 month).

Clinical manifestations

Patients are normal prior to the onset of seizures and there are no apparent antecedent factors. Seizures manifest with motor and autonomic symptoms, alone or in combination. Lateral deviation of the head and eyes, unilateral eyelid and eye jerking, and unilateral tonic or clonic convulsions of one limb are common motor manifestations that frequently progress to secondarily GTCSs. Both sides are alternately affected. Autonomic manifestations of apnoea, cyanosis, flushing, hiccups,

sweating and hypersalivation are striking, and may not be recognised as seizure symptoms. The same patient has mild or severe, short or prolonged seizures and status epilepticus, with a variable clinical expression and a polymorphous combination of ictal manifestations. Epileptic spasms are exceptional (one reported case).

Within a few weeks of onset, the seizures get relentlessly worse in frequency, duration and symptomatology. They usually occur in clusters, mainly on awakening and during drowsiness, and finally become virtually continuous.

Aetiology

The aetiology is unknown but a functional or metabolic disorder is suspected. There is no family history of epilepsies or neurological disorders. In two of three patients examined, mutational screening of the *CLCN2* gene revealed a homozygous mutation G2003C (exon 17), leading to a serine/threonine substitution at codon 668.[53] However, the same variation was found in 38 of 100 control alleles.

In two cases, postmortem brain pathology showed only severe hippocampal neuronal loss and accompanying gliosis, but this was normal in another case.[58]

Diagnostic procedures[48,53,56]

CT and MR brain scans are normal. Electroretinography and evoked potentials are normal.

Electroencephalography

The inter-ictal EEG shows slow activity from the onset of the seizures, which becomes rapidly worse over time, with alternating side emphasis from one EEG to the next. Spikes are initially sparse, but soon become frequent and multi-focal.

Ictal EEG discharges involve multiple independent sites randomly, moving from one cortical area to another in consecutive seizures. Morphologically, they consist of rhythmic alpha or theta activity, spreading to involve an increasing area of the cortical surface. Consecutive seizures overlap and the next seizure starts before the end of the previous one, with the topographical ictal onset markedly shifting from one area to another on either hemisphere.

Illustrated cases with video-EEG recording can be seen in the companion CD of Panayiotopoulos[20] and in Hahn, *et al.*[59]

Prognosis

All children regress developmentally and develop severe psychomotor abnormalities. They become quadriplegic with major axial hypotonia, pyramidal and extrapyramidal signs, and athetosis.

Death often occurs soon after onset of the disease, within 1 year or, rarely, after a few years. Control of the seizures and normal development are exceptional.

Management

Anti-epileptic drug (AED) treatment and a ketogenic diet are ineffective.[60] Potassium bromide,[49] stiripentol combined with clonazepam[61] and, more recently, levetiracetam[62,63] have had a temporary beneficial effect in individual cases.

Hemiconvulsion–hemiplegia epilepsy

Hemiconvulsion–hemiplegia is a rare dramatic sequence comprising a sudden and prolonged unilateral clonic seizure, followed by permanent ipsilateral hemiplegia.[57,64–72] The event occurs suddenly in an otherwise normal child, often during a febrile illness. Subsequently, 80% of patients develop focal epilepsy of what is considered to be the complete 'hemiconvulsion–hemiplegia epilepsy'.

Considerations on classification

The ILAE diagnostic scheme[2] recognised 'hemiconvulsion–hemiplegia epilepsy' as a syndrome, but this has now rightly been discarded in the new report,[3] in line with the 1989 ILAE classification[1] and as suggested in the first edition of this book.

Demographic data

Peak age of onset occurs in the first 2 years of life (range of 5 months to 4 years). This may be an extremely rare condition today, with improved emergency care for status epilepticus. There was only one (0.06%) equivocal case in the National Institute of Neurological and Communicative Disorders and Stroke Collaborative Perinatal Project in the USA.[73,74] Although Gastaut initially reported 150 cases,[64] the number of reported cases dramatically decreased in subsequent reports.[66,67,71]

Clinical manifestations

Hemiconvulsions occur suddenly, out of the blue, and consist of unilateral, often asynchronous, clonic jerks that last for hours or days if not appropriately treated. If very prolonged, convulsions may spread to the other side or more rarely change sides. Eye and head deviation may occur or be the first seizure symptom. Consciousness may be intact.

By definition, severe ipsilateral post-convulsive flaccid hemiplegia follows in all cases. It lasts for more than 7 days and becomes permanent in more than 80% of cases. The face is always affected and aphasia is present if the dominant side is involved. These signs distinguish acquired post-convulsive from congenital hemiplegia.[75]

Aetiology

The initial hemiconvulsion–hemiplegia event usually occurs in the course of a febrile illness that is often due to a CNS infection, such as herpes encephalitis. In a few cases, the cause may be traumatic or vascular. Leiden factor V mutation has been implicated in two cases.[76] Elevation of CSF interleukin-6 (IL-6) to levels seen in patients with encephalitis has been reported 2 hours after seizure onset in a child.[77]

However, frequently no cause is found, even though the family history may reveal a high incidence of febrile seizures.

Diagnostic procedures

Diagnostic procedures should include examination of the CSF, which is probably mandatory in children younger than 18 months in view of the high possibility of a CNS infection. Routine investigation for Leiden factor V mutation has been suggested.[76] If possible, brain imaging should precede lumbar puncture. In the acute stage, there is usually evidence of oedema in the affected hemisphere. Later, a rather characteristic, uniform hemiatrophy follows prolonged episodes (Figure 11.2). SPECT reveals hyperperfusion during the acute stage, followed later by hypoperfusion.[78]

Electroencephalography[72,79]

An EEG is not important in the acute stage, because it will simply confirm the clinical situation without offering any specific clues to the underlying cause and development.

Ictal EEG consists of a mixture of high-amplitude rhythmic slow waves of 2 or 3 Hz, mixed with spikes, sharp waves, spike–wave complexes and episodic fast activity of 10–12 Hz. The amplitude is higher and spikes predominate in the affected hemisphere with posterior emphasis. There is no consistent relationship between clonic convulsions and EEG discharges.

Prognosis

The prognosis depends on the cause and speed of effective acute management. Focal seizures of temporal, extratemporal or multifocal origin appear within 1–5 years of the acute episode in 80% of patients. Most patients also have secondarily GTCSs and often convulsive status epilepticus. Seizures

Severe hemiatrophy in a patient with long-standing hemiconvulsion–hemiplegia epilepsy

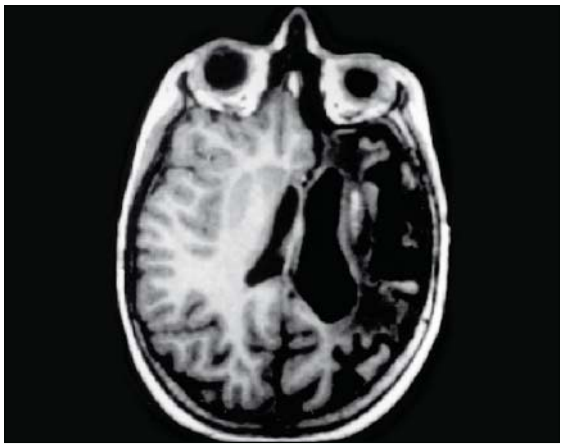

Figure 11.2 *Courtesy of Dr Rod C. Scott, Institute of Child Health, London, UK.*

are usually intractable to anti-epileptic medication. Learning difficulties are probably the rule.

Management

Immediate control of the seizure is a medical emergency as in status epilepticus detailed in Chapter 3. A benzodiazepine, usually intravenous diazepam or lorazepam, is probably the first choice. Treatment of the fever and the underlying illness is of equal importance. In the few cases with Leiden factor V mutation, careful consideration should be given to therapeutic and prophylactic anticoagulation, because this may improve the long-term outcome.[76] Apart from conservative management of the residual neurological deficits, little can be done after the establishment of hemiplegia. Hemispherectomy or other modes of neurosurgical intervention may be beneficial.[80]

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twelve

Benign childhood focal seizures and related epileptic syndromes

Benign childhood focal seizures and related epileptic syndromes are the most common and probably the most fascinating and rewarding topic in paediatric epileptology.[1] They affect 25% of children with non-febrile seizures and form a significant part of the everyday practice of paediatricians, neurologists and clinical neurophysiologists who care for children with seizures. Rolandic seizures are widely recognised. Panayiotopoulos syndrome (PS), a previously unrecognised common disorder with dramatic clinical and EEG manifestations, has now been formally recognised by the ILAE.[2,3] It has further been highlighted by editorials[4,5] and reviews in medical journals,[6,7] examined in an expert consensus,[8] featured as the main theme of a recent issue of *Epilepsia*[7,9–12] and is becoming more readily diagnosed by physicians. Less common phenotypes, such as the idiopathic childhood occipital epilepsy of Gastaut (ICOE-G) and idiopathic photosensitive occipital lobe epilepsy, have also been recognised and defined. Furthermore, there are also children who present with seizures of predominantly affective symptoms, and claims have been made for other benign childhood seizures associated with certain inter-ictal *functional EEG foci*, such as frontal, midline or parietal, with or without extreme somatosensory evoked spikes (ESESs). All these conditions may be linked together in a broad, age-related and age-limited, benign childhood seizure susceptibility syndrome (BCSSS), which may also constitute a biological continuum with febrile seizures and benign neonatal and benign infantile seizures. BCSSS should be properly re-examined and redefined.

The term 'functional spikes' refers to transient focal EEG abnormalities of sharp waves that occur in children with or without epileptic seizures and which disappear in the late teens.[13]

Functional spikes of childhood are of low epileptogenic potential and they occur in 2% to 3% of normal children (Table 12.1).

Considerations on classification

The ILAE Task Force recognises three syndromes of 'idiopathic childhood focal epilepsy' (Table 5.2):[2,3]

1. benign childhood epilepsy with centrotemporal spikes (BCECTS) (rating score 3)
2. early onset benign childhood occipital epilepsy (Panayiotopoulos type) (3)
3. late-onset childhood occipital epilepsy (Gastaut type) (2).

The rating score in parenthesis reflects on the certainty with which the ILAE Core Group believed that each syndrome represents a unique diagnostic entity on a range of 1–3 (with 3 being the most clearly and reproducibly defined).[3]

The 1989 ILAE classification recognised three 'age-related and localisation-related (focal, local, partial) epilepsies and syndromes' (Table 5.1):

1. BCECTS
2. childhood epilepsy with occipital paroxysms (which is now called 'late-onset childhood occipital epilepsy [Gastaut type]')
3. primary reading epilepsy.

EEG functional spikes in normal children (% median and range)				
Age (years)	**Centrotemporal spikes**	**Occipital spikes**	**Frontal spikes**	**Generalised discharges**
5–12	2.25 (0.7–3.5)	0.15 (0.0–0.4)	0.10 (0.1–0.6)	1.00 (0.1–1.1)
1–5	0.40 (0.3–0.4)	0.90 (0.8–1)	0.05 (0–0.1)	0.20 (0.1–0.3)

Table 12.1 *Modified with permission from Panayiotopoulos (1999).*[1]

'Reading epilepsy' is now rightly classified as a reflex epileptic syndrome (Table 5.2).

Considerations on classification and nomenclature are detailed in the individual description of each syndrome. Overall, benign childhood focal syndromes and their main representatives, BCECTS and PS, do not fulfil the diagnostic criteria of 'epilepsy' defined as 'chronic neurological condition characterised by recurrent epileptic seizures'.[14] BCECTS and PS are age limited (not 'chronic') and at least a third of patients have a single (not a 'recurrent') seizure. They should be classified among 'conditions with epileptic seizures that do not require a diagnosis of epilepsy', which is a new concept in the ILAE diagnostic scheme that incorporates 'febrile, benign neonatal, single seizures or isolated clusters of seizures and rarely repeated seizures (oligoepilepsy)' (Table 5.2).[2,3]

Benign childhood epilepsy with centrotemporal spikes

Synonyms: BCECTS, rolandic seizures, rolandic epilepsy.

BCECTS[1,15–22] is the most common manifestation of benign childhood seizure susceptibility syndrome (BCSSS).

Considerations on nomenclature

I use the terms 'BCECTS', 'rolandic seizures' and 'rolandic epilepsy' synonymously, although I prefer the term 'rolandic seizures' for the following reasons:

- the term 'rolandic seizures' has long been established and is better known than BCECTS among paediatricians
- most 'centrotemporal spikes' (CTSs) are rolandic spikes; they are rarely located in the temporal electrodes
- the word 'temporal' is misleading because children with this form of epilepsy do not have symptoms from the temporal lobes
- BCECTS may occur without CTSs and conversely CTSs may occur in children without seizures or other clinical phenotypes of BCSSS[23]
- similar clinical features may appear in patients with spikes in locations other than at centrotemporal sites.

Demographic data

Onset is from age 1 to 14 years; 75% start between 7 and 10 years (peak 8 or 9 years).[1,17] There is a 1.5 male predominance. Prevalence is around 15% in children aged 1–15 years with seizures. Incidence is 10–20 per 100,000 children aged 0–15 years.

Clinical manifestations

The cardinal features of rolandic seizures are infrequent, often single, focal seizures consisting of:

- unilateral facial sensorimotor symptoms (30% of patients)
- oropharyngolaryngeal manifestations (53% of patients)
- speech arrest (40% of patients)
- hypersalivation (30% of patients).[1]

Hemifacial sensorimotor seizures are often entirely localised in the lower lip or spread to the ipsilateral hand. Motor manifestations are sudden, continuous or bursts of clonic contractions, usually lasting from a few seconds to a minute. Ipsilateral tonic deviation of the mouth is also common. Hemifacial sensory symptoms consist of numbness in the corner of the mouth.

Hemifacial seizures are often associated with an inability to speak and hypersalivation:

> The left side of my mouth felt numb and started jerking and pulling to the left, and I could not speak to say what was happening to me.

Oropharyngolaryngeal ictal manifestations are unilateral sensorimotor symptoms inside the mouth. Numbness, and more commonly paraesthesias (tingling, prickling, freezing), are usually diffuse on one side or, exceptionally, may be highly localised even to one tooth. Motor oropharyngolaryngeal symptoms produce strange sounds, such as death rattle, gargling, grunting and guttural sounds, and combinations:

> In his sleep, he was making guttural noises, with his mouth pulled to the right, 'as if he was chewing his tongue'.

> We heard her making strange noises 'like roaring' and found her unresponsive, head raised from the pillow, eyes wide open, rivers of saliva coming out of her mouth, rigid.

Arrest of speech is a form of anarthria. The child is unable to utter a single intelligible word and attempts to communicate with gestures. There is no impairment of the cortical language mechanisms:

> My mouth opened and I could not speak. I wanted to say I cannot speak. At the same time, it was as if somebody was strangling me.

Hypersalivation is often associated with oropharyngolaryngeal or pure hemifacial seizures. Hypersalivation is not just frothing:

> Suddenly my mouth is full of saliva, it runs out like a river and I cannot speak.

Ictal syncope may occur, probably as a concurrent symptom of PS (page 349):

> She lies there, unconscious with no movements, no convulsions, like a wax work, no life.

Consciousness and recollection are fully retained in more than half (58%) of rolandic seizures:

> I felt that air was forced into my mouth, I could not speak and I could not close my mouth. I could understand well everything said to me. Other times I feel that there is food in my mouth and there is also a lot of salivation. I cannot speak.

Secondarily generalised tonic–clonic seizures (GTCSs) are reported in around half of children with rolandic seizures. Primarily GTCSs are not part of the syndrome of rolandic seizures (ictal EEG recordings), although the new ILAE report makes the unverified comment that 'some patients with this condition may have primarily GTCS as well'.[3]

Rolandic seizures are usually brief, lasting for 1–3 min. Three-quarters of seizures occur during non-rapid eye movement (NREM) sleep, mainly at sleep onset or just before awakening.

Status epilepticus

Although rare, focal motor status or hemiconvulsive status epilepticus is more likely to occur than secondarily generalised convulsive status epilepticus, which is exceptional. Opercular status epilepticus usually occurs in atypical evolutions of BCECTS[24–29] or, exceptionally, it may be induced by carbamazepine or lamotrigine,[30,31] and may last for hours to months. It consists of continuous unilateral or bilateral contractions of the mouth, tongue or eyelids, positive or negative subtle perioral or other myoclonus, dysarthria, speech arrest, difficulties in swallowing, buccofacial apraxia and hypersalivation (see page 82). These are often associated with continuous spikes and waves on an EEG during slow-wave sleep.

Aetiology

BCECTS is genetically determined, although conventional genetic influences may be less important than other mechanisms, which need to be explored.[32] There is evidence of linkage with chromosome 15q14.[33]

Autosomal dominant inheritance with age-dependent penetrance has been reported for subjects with CTSs on an EEG, and not for the clinical syndrome of BCECTS (see review in Panayiotopoulos[1]).[34,35] A recently published study found that the CTS EEG trait in rolandic epilepsy maps to Elongator Protein Complex 4 of chromosome 11p13.[35]

Siblings or parents of patients with BCECTS may rarely have the same type of seizures or other phenotypes of BCSSS, such as PS (page 350). Febrile seizures are common (10–20%) before rolandic seizures.

See also the unifying concept of benign childhood seizure susceptibility syndrome on page 365.[1,36]

Diagnostic procedures

Apart from the EEG, all tests are normal.

Brain imaging is not needed for typical cases, although 15% of patients with rolandic seizures may have abnormal findings because of static or other brain diseases unrelated to the pathophysiology of BCECTS.[37,38]

The presence of brain lesions has no influence on the prognosis of rolandic seizures.[37]

Electroencephalography

Inter-ictal EEG: CTSs are the hallmark of BCECTS (Figures 12.1, 12.2 and 12.3). They are age-dependent, appearing at a peak age of 7–10 years, often persisting despite clinical remission and usually disappearing before the age of 16 years. Although called CTSs, these are mainly high-amplitude, sharp and slow-wave complexes localised in the C3–C4 (central; Figure 12.2) or C5–C6 (midway between central and temporal) electrodes.[39] CTSs may be unilateral, but are more often bilateral, independently right or left. They are abundant (4–20/min) and usually occur in clusters.

CTSs amplify during stages I–IV of sleep by a factor of two to five times without disturbing sleep organisation. After sleep, the most common form of activation of CTSs (10–20%) is somatosensory stimulation, mainly of the fingers and toes (Figure 12.1).[1,40–47] These are extreme (giant) somatosensory evoked spikes (ESESs), which correspond to mid- or long-latency somatosensory evoked potentials with peaks at 35–80 ms, depending on the height of the individual and location of the site of stimulation (Figure 12.1). ESESs persist during sleep and, like spontaneous CTSs, occur in children with or without seizures and disappear with age. They may be detected in EEGs with or without spontaneous CTSs or other functional spikes of childhood.

Practical note

Elicitating ESESs in clinical EEG practice

In clinical EEG practice, asking the child to tap together the palmar surface of the tips of his or her fingers of both hands is an easy method of testing for ESESs. The child should be instructed to strike them with sufficient strength and at random intervals of varying frequency. This may elicit either bilateral or unilateral ESESs (Figure 12.1).

Rarely, children with rolandic seizures may have a normal EEG: the spikes may be very small or CTSs appear only during sleep stages (3–35%).[1] In serial EEGs, CTSs may appear right or left, infrequently or frequently, small or giant, and alone or with functional spikes in other locations. The reported prevalence of generalised discharges in rolandic seizures varies from as low as 0% to as high as 54%.[1] In my studies, generalised discharges occurred in about 4% of patients with rolandic seizures, and consisted of brief 1–3 s generalised bursts of 3–5 Hz slow waves, mixed with small spikes.[1] These brief generalised discharges are identical to those seen in PS (Figure 12.4).

Dipole and magnetoencephalography (MEG) studies show that the main negative spike component of CTSs can usually be modelled by a single and stable tangential dipole source along the rolandic region, with the negative pole maximum in

the centrotemporal region and the positive pole maximum in the frontal regions.[48–51] The tangential dipole and the location of CTSs have been confirmed with MEG.[52,53] More recently, combined spike-related functional MRI (fMRI) and EEG multiple source analysis (MSA) were applied.[54] EEG MSA confirmed the initial central dipole including the face or hand area. A second dipolar source was mostly consistent with propagated activity.[54]

The frequency, location and persistence of CTSs do not determine the clinical manifestations, severity and frequency of seizures or the prognosis.

Video-EEG of an 11-year-old girl with rolandic seizures who has been in remission since the age of 8 years

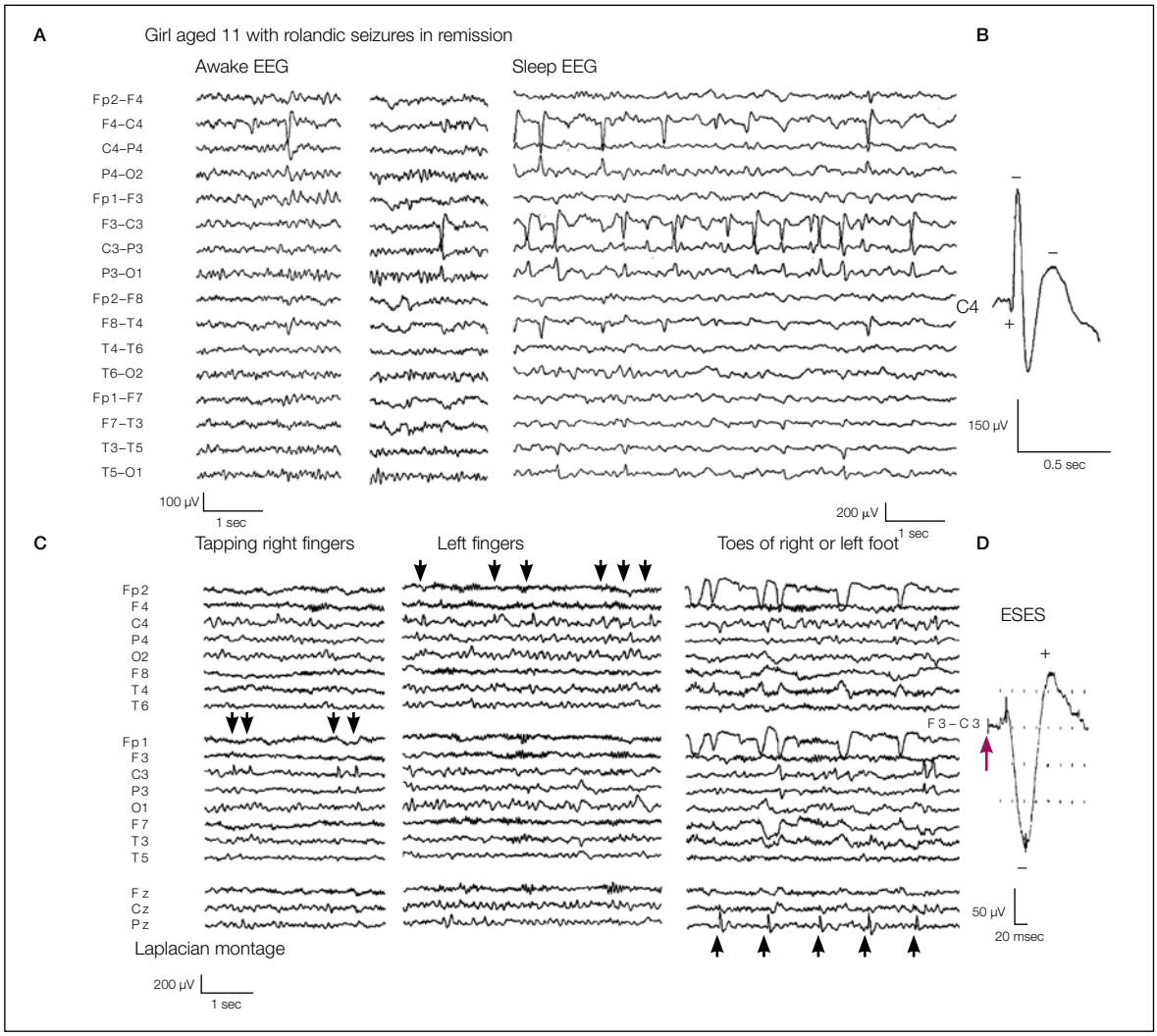

Figure 12.1 (**A**) High-amplitude CTSs (in fact, these are central spikes) occur independently on the right and left, and are markedly exaggerated during natural sleep. (**B**) Typical morphology and polarity of CTSs in laplacian montage. (**C**) ESESs, which are evoked by tapping fingers or toes. Note that their location corresponds to the location of the activating stimulus (black arrows). (**D**) ESES from another patient, which was evoked by electrical stimulation of the right thumb (onset at red arrow). Peak latency of the somatosensory evoked spike is 58 ms.

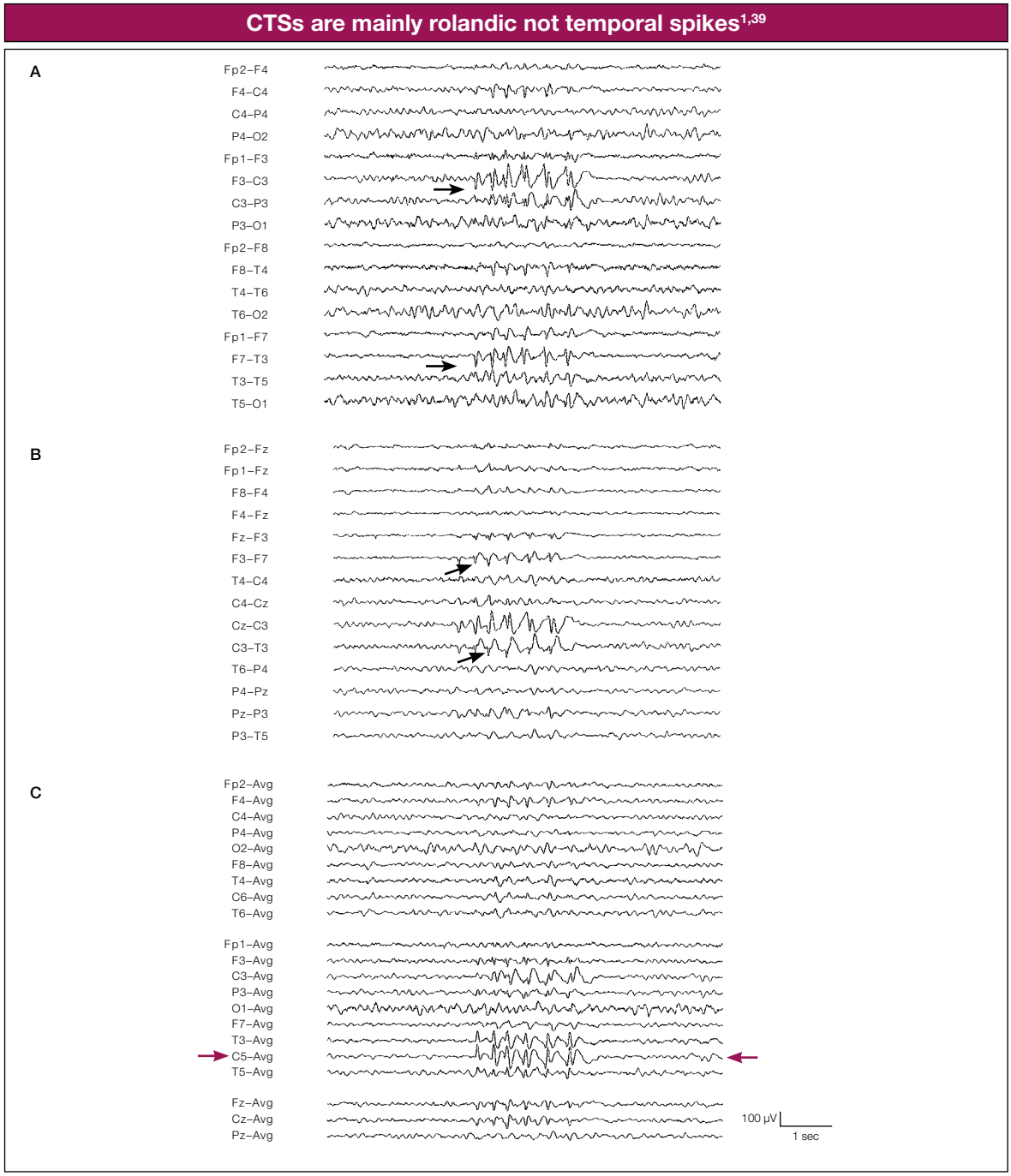

Figure 12.2 The same EEG sample is shown in three different montages. This is from an 8-year-old boy referred for an EEG because of: 'recent GTCSs and a 2-year history of unilateral facial spasms. Previously, the EEG and CT brain scan were normal. No medication. Focal seizures with secondarily generalised convulsions?' (**A**,**B**) The EEG showed frequent clusters of repetitive CTSs on the left. As the spikes appeared to be of higher amplitude in the temporal electrode (T3) (black arrows), the technician rightly applied additional electrodes at C5 and C6 (rolandic localisation) (**C**). This showed that the spike is of higher amplitude in the left rolandic region (C5) (red arrows). Another EEG 16 months later showed a few small spikes in the right frontal and central midline electrodes (not shown).

Video-EEG of a 10-year-old girl with rolandic seizures

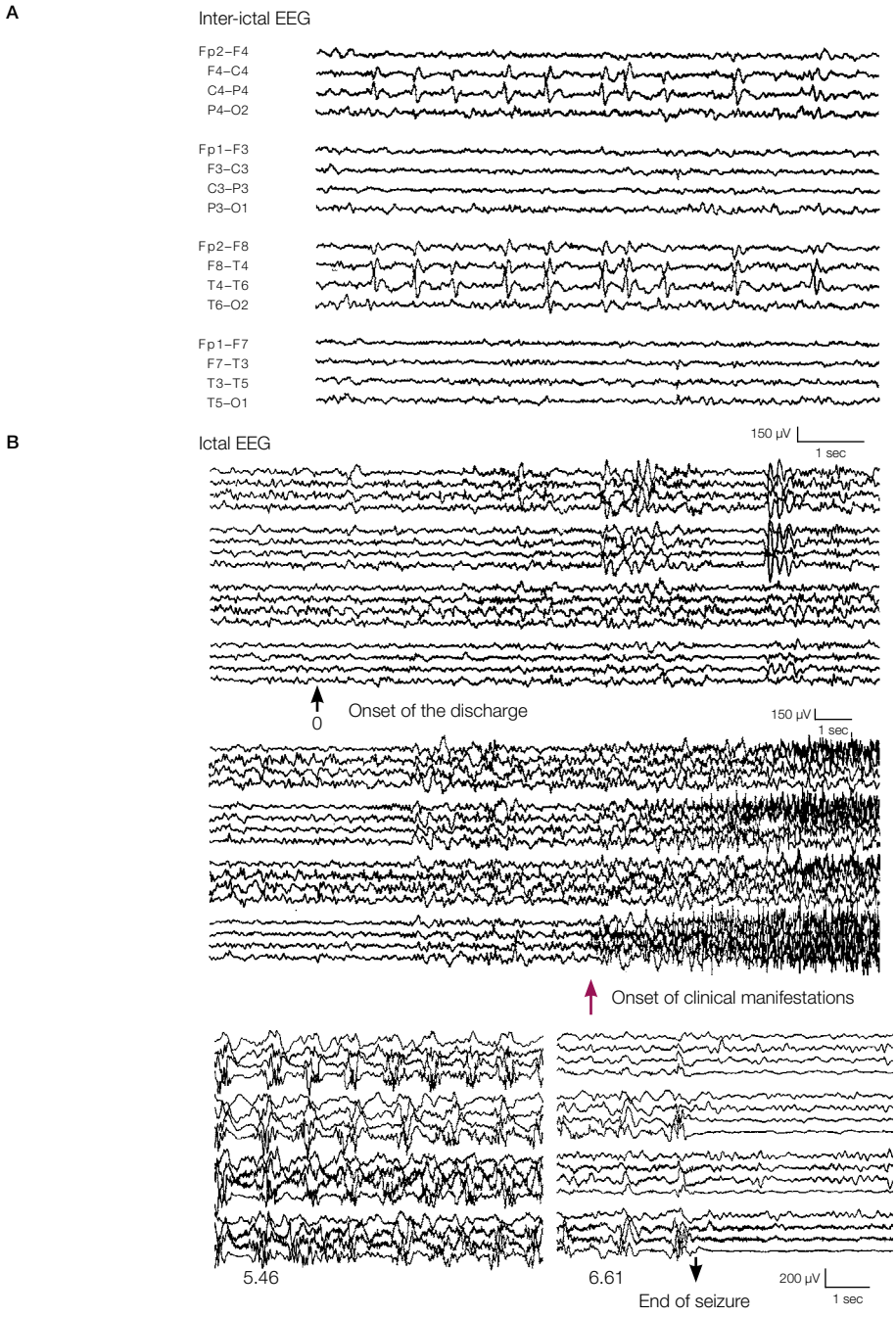

Figure 12.3 Case 5.1 in Panayiotopoulos.[1] (**A**) High-amplitude right-sided CTSs (C5 and C6 electrodes were not applied). (**B**) Onset of ictal discharge in the right centrotemporal regions during sleep (black arrow). Red arrow shows onset of clinical manifestations that started with contractions of the left facial muscles (note muscle artefacts on the left), progressing to a prolonged generalised clonic seizure, which lasted for 6.31 minutes from the ictal electrical onset. See video-EEG of this seizure in the companion CD of *A Practical Guide to Childhood Epilepsies*.[59]

CTSs may also occur in normal children.

It should be remembered that CTSs:

- occur in 2% to 3% of normal school-aged children, of whom less than 10% develop rolandic seizures (Table 12.1)[1,55–58]
- are common among relatives of children with rolandic seizures
- occur in a variety of organic brain diseases with or without seizures, such as cerebral tumours, Rett syndrome, fragile X syndrome and focal cortical dysplasia
- may incidentally be found in non-epileptic children with various symptoms, such as headache, speech, and behavioural and learning difficulties.

The combination of a normal child with infrequent seizures and an EEG showing disproportionately severe focal epileptogenic activity is highly suggestive of BCSSS.[1]

Ictal EEG: There are very few reports of ictal EEGs of rolandic seizures. One example captured with video-EEG is shown in Figure 12.3. There is an initial paucity of spontaneous CTSs before the onset of the ictal discharge, which appears in the ipsilateral rolandic regions and consists of slow waves mixed with fast rhythms and spikes. This ended with a SGTCS.

Evolution and prognosis

The prognosis for rolandic seizures is invariably excellent, with a risk of developing infrequent generalised seizures in adult life of less than 2%; absence seizures may be more common than GTCSs.[1,60–63]

Remission occurs within 2–4 years of onset and before the age of 16 years. The total number of seizures is low, the majority of patients having fewer than ten seizures; 10–20% have just a single seizure. About 10–20% may have frequent seizures, but these also remit with age.

Children with rolandic seizures may develop reversible linguistic and cognitive abnormalities during the active phase of their disease.[1,64–66] Mainly hospital-based studies emphasise learning or behavioural problems that require intervention (see review by Nicolai, *et al*[67]).[66,68–73] However, the effect of anti-epileptic drugs (AEDs), bias in selection of the most serious cases and other factors were not taken into consideration in most of these studies (see the note of caution).

A few patients (<1%) may progress to atypical evolutions of more severe syndromes of linguistic, behavioural and neuropsychological deficits, such as Landau–Kleffner syndrome, atypical benign partial epilepsy of childhood or epilepsy with continuous spike-and-wave during sleep.[27,28]

The development, social adaptation and occupations of adults with a previous history of rolandic seizures are normal.[1,62,63]

Note of caution

There is an increasing number of reports emphasising cognitive, linguistic and behavioural abnormalities of children with rolandic epilepsy. I am not in a position to dispute such findings. However, in most of these studies the findings are based on statistical comparisons of a group of children with rolandic epilepsy with matched normal control children. My reservations are that the groups of children with rolandic epilepsy include patients who are on AEDs, patients who may represent the worst spectrum of the disorder (i.e. hospital-based populations) or patients who have suffered bullying at school and social discrimination because of the stigma of 'epilepsy' with which they are often labelled. It is only if these factors are eliminated in studies of unbiased and newly diagnosed patients that we will learn of the true dimensions of the problem.[20]

Management

Children with rolandic seizures may not need AEDs, particularly if the seizures are infrequent, mild or nocturnal, or the onset is close to the natural age of remission of this age-limited disorder. Patients with either frequent seizures and secondarily GTCSs or comorbid conditions may need medication.[74] Some AEDs may significantly reduce GTCSs without reduction of focal seizures.[75] Empirically,

carbamazepine is the preferred AED. Recent studies found levetiracetam to be highly effective.[76–78]

Some children might experience learning difficulties, aggravation and new types of seizures when receiving either carbamazepine[1,30,31,78,79] or lamotrigine.[80,81]

> Within days after re-introduction of carbamazepine, she suffered nearly continuous, brief atonic attacks of head and arm drop and also absences (case 17.3 in Panayiotopoulos[1]).

For details see 'Management of benign childhood focal seizures' on page 368.

Panayiotopoulos syndrome

Panayiotopoulos syndrome (PS) is a common, childhood-related, idiopathic, benign susceptibility to focal, mainly autonomic seizures and autonomic status epilepticus.[4–12,20,23,82–101] Autonomic manifestations are the cardinal seizure symptoms in PS, and have immense pathophysiological, clinical and treatment implications, with all functions of the autonomic system possibly being affected during the ictus. Autonomic status epilepticus occurs in half of all patients.

A recent expert consensus defines PS as:

> A benign age-related focal seizure disorder occurring in early and mid-childhood. It is characterized by seizures, often prolonged, with predominantly autonomic symptoms, and by an EEG that shows shifting and/or multiple foci, often with occipital predominance.[8]

PS has been confirmed in long-term studies of over 1000 children worldwide. The importance of this syndrome and its impact on paediatric epileptology is signified by the June 2007 issue of *Epilepsia*, which featured PS as its main theme.[7,9–12]

Considerations on classification

PS has been recognised by the ILAE as 'early onset benign childhood occipital epilepsy (Panayiotopoulos type)'.[2,3] However, PS is not 'occipital' epilepsy:[7–11,20,90]

- onset is with autonomic manifestations, which are unlikely to be of occipital origin; of all the other seizure symptoms, only eye deviation, which is often not the first ictal symptom, may originate in the occipital lobes
- inter-ictal occipital spikes may never occur
- even ictal EEG has documented anterior or posterior origin.

Currently, most authors prefer the eponymous term 'Panayiotopoulos syndrome' to include all patients with this syndrome, irrespective of EEG spikes or topographical terminology,[4,5,23,90–94,97] as in the original study.[83] In this study, of the 21 children with ictal vomiting and normal neurological state evaluated,[83] 12 had occipital spikes 'epilepsy with occipital paroxysms'[98] and nine had extra-occipital spikes or normal EEG.[99]

Demographic data

Onset is from age 1 to 14 years; 76% of cases start at 3–6 years of age (peak 4 or 5 years). Both sexes are equally affected.[90] Prevalence is around 13% in children aged 3–6 years with one or more non-febrile seizures, and 6% in the age group 1–15 years. In the general population, two to three of every 1000 children are affected. These figures may be higher if cases currently considered to have atypical features are included.[6,90]

Clinical manifestations

Seizures comprise an unusual constellation of autonomic, mainly emetic, symptoms, behavioural changes, unilateral deviation of the eyes and other

more conventional ictal manifestations. Consciousness and speech, as a rule, are preserved at seizure onset. The seizure commonly starts with autonomic manifestations (81%), which are mainly emetic (72%). In a typical presentation, the child is fully conscious, able to speak and understand, but is complaining of feeling sick and looks pale:

> He complained of nausea and he looked pale. Five minutes later he vomited while still standing… He gradually became disorientated, but was still able to walk. However, 10 minutes from onset his eyes turned to the right and he became unresponsive.

Ictus emeticus: The full emetic triad (nausea, retching, vomiting) culminates in vomiting in 74% of seizures; in others, only nausea or retching occurs and, in a few cases, emesis may not be apparent. Emesis is usually the first apparent ictal symptom, but it may also occur long after the onset of other manifestations.

The initial manifestations do not suggest an epileptic seizure, as the child simply complains of feeling sick and being unwell, and vomits:

> On returning home from school, she looked tired and had a nap. After half an hour, she woke up looking pale and complained of feeling sick. She ran to the toilet and vomited repeatedly. Then her eyes deviated to one side and she became unresponsive and flaccid for 10 minutes. Soon after, she started recovering, answering simple questions and by 1 hour later she was playing again as if nothing had happened.

Autonomic manifestations other than ictus emeticus may occur concurrently or appear later in the course of the ictus. These include pallor or, less often, flushing or cyanosis; mydriasis or, less often, miosis; cardiorespiratory and thermoregulatory alterations; coughing; urinary and/or faecal incontinence; and modifications of intestinal motility. Hypersalivation (probably a concurrent rolandic symptom) may occur. Headaches and, more often, cephalic auras may occur, particularly at onset.

Pallor is one of the most common ictal manifestations. It occurs mainly at onset, usually with emetic symptoms. Pallor may be among the first symptoms with no apparent emesis.

Cyanosis is less common than pallor and occurs principally during the evolution of the seizures, often while the child is unresponsive.

Urinary and faecal incontinence occurs when consciousness is impaired before, or without, convulsions:

> He became unresponsive and incontinent of urine.

Mydriasis is sometimes so prominent that it may be reported spontaneously:

> Her pupils were as big as her eyes.

Miosis is rare and occurs with other severe autonomic manifestations while the child is unresponsive.

Hypersalivation is also rare in PS, which is in contrast to its common occurrence in rolandic seizures. Combined speech arrest and hypersalivation, as in rolandic seizures, is even rarer.

Cephalic auras, although rare, are of interest because they are considered to be autonomic manifestations and because they may cause diagnostic confusion with migraine if they are not properly evaluated. Cephalic auras commonly occur with other autonomic symptoms, mainly nausea and pallor, at seizure onset. Occasionally, the child may also complain of 'headache' but whether the complaint of 'headache' is a true perception of pain, discomfort or some odd sensation in the head is uncertain:

> 'Funny feeling in my head', 'warm sensation', 'pressure', 'headache'.

Coughing may occur as an initial ictal symptom either with or without ictus emeticus. It is described as 'strange coughing' or 'cough as if about to vomit'.

Thermoregulatory changes: Raised temperature may be subjectively or objectively documented during the seizure or immediately post-ictally. Whether this is a coincidental finding, a precipitating factor or an ictal abnormality is uncertain, as it could be any of these. However, pyrexia recorded immediately after seizure onset is probably an ictal autonomic manifestation.

Abnormalities of intestinal motility: Diarrhoea (3%) is occasionally reported during the progression of seizures.

Breathing and cardiac irregularities are rarely reported, but may be much more common in a mild form.

Breathing changes before convulsions include descriptions of 'heavy, irregular, abnormal breathing' or 'brief cessation of breathing for a few seconds'. Tachycardia is a consistent finding, sometimes at the onset of ictal EEG (Figure 12.5).

Cardiorespiratory arrest is rare, probably occurring in 1 per 200 individuals with PS.[8,90,100]

Ictal syncope (or syncopal-like symptoms) is a common and important ictal feature of PS.[6,8,10,90] In at least a fifth of seizures, the child becomes 'completely unresponsive and flaccid like a rag doll' before convulsions. Two-fifths have no convulsions or occur in isolation with no other symptoms.

> While talking to her teacher, suddenly and without warning, she fell on the floor pale, flaccid and unresponsive for 2 minutes. She had a complete recovery, but 10 minutes later she complained of feeling sick, vomited repeatedly and again became unresponsive and flaccid with pupils widely dilated for 1 hour. She had an unremarkable recovery and was normal after a few hours' sleep.

> She complained of 'dizziness' and then her eyes deviated to the left, she fell on the floor and she became totally flaccid and unresponsive for 5 minutes.

I proposed the descriptive term 'ictal syncope'[90,101] to describe this state, because 'unresponsiveness with loss of postural tone' is the defining clinical symptom of syncope.[102,103] However, 'syncopal-like symptoms' may be more appropriate.[104]

Ictal behavioural changes usually consist of restlessness, agitation, terror and quietness, which appear at the onset of seizures, often together with emetic or other autonomic manifestations. These symptoms are similar to those occurring in 'benign childhood epilepsy with affective symptoms' (page 363).

> At age 9 years, on returning from school, he looked tired and pale. He said that his head was killing him, 'something that would cause me to be sick'. In 10 minutes, he started screaming and banging his head on the wall. Within the next 20 minutes, he gradually became disorientated and floppy 'like a rag doll'. He was staring.

Conventional seizure symptoms

In PS, pure autonomic seizures and pure autonomic status epilepticus occur in 10% of patients. They start and end solely with autonomic symptoms. In all other seizures, autonomic manifestations are followed by the conventional seizure symptoms listed below.

Impairment of consciousness: Although initially fully conscious, the child gradually or suddenly becomes confused and unresponsive. Impairment of consciousness may be mild or moderate, with the child retaining some ability to respond to verbal commands, but often talking out of context occurs. In diurnal seizures observed from the onset, cloudiness of consciousness usually starts after the appearance of autonomic and behavioural symptoms. Good awareness may be preserved throughout the ictus in about 6% of seizures.

Deviation of the eyes: Unilateral deviation of the eyes is common, but it seldom occurs at onset. This pursuit-like deviation of the eyes may be brief (minutes) or prolonged (hours), continuous or less frequently intermittent.

Deviation of the eyes may occur without vomiting in 10–20% of patients and, in some children, the eyes may be open wide and remain in the midline before other convulsions occur.

Other ictal symptoms are, in order of prevalence, speech arrest (8%), hemifacial spasms (6%), visual hallucinations (6%), oropharyngolaryngeal movements (3%), unilateral drooping of the mouth (3%), eyelid jerks (1%), myoclonic jerks (1%), and ictal nystagmus and automatisms (1%). These probably reflect the primary area of seizure discharge generation. The seizures may end with hemiconvulsions, often with jacksonian marching (19%) or secondarily generalised convulsions (21%).

Ictal visual symptoms, such as elementary visual hallucinations, illusions or blindness, occur after more typical seizure symptoms of PS.

Seizure variations: The same child may have seizures with either marked autonomic manifestations or inconspicuous or absent autonomic manifestations. Seizures with no autonomic manifestations are rare (7%) and occur in patients who may also have additional autonomic seizures.[90]

The clinical seizure manifestations are roughly the same, irrespective of EEG localisations, although

there may be slightly fewer autonomic and slightly more focal motor features at onset in children with no occipital spikes.[90]

Duration of seizures and autonomic status epilepticus: Almost half (44%) of the seizures last for more than 30 min and can persist for many hours (mean about 2 hours), constituting autonomic status epilepticus. The rest of the seizures (56%) last from 1 to up to 30 min with a mean of 9 min. Lengthy seizures are equally common in sleep and wakefulness. Even after the most severe seizures and status, the patient is normal after a few hours of sleep. There is no record of residual neurological or mental abnormalities. The same child may have brief and lengthy seizures. Hemiconvulsive or convulsive status epilepticus is exceptional (4%).

Circadian distribution: Two-thirds of seizures start in sleep; the child may wake up with similar complaints while still conscious or else may be found vomiting, conscious, confused or unresponsive. The same child may suffer seizures while asleep or awake.

Precipitating factors: There are no apparent precipitating factors other than sleep. Fixation-off sensitivity is an EEG phenomenon that may not be clinically important. Many seizures have been witnessed while a child is travelling in a car, boat or aeroplane. There are two explanations for this: (1) the seizures are more likely to be witnessed during travelling; and (2) children are more vulnerable because travelling also precipitates motion sickness, to which children are particularly susceptible.

Aetiology

PS, similar to the rolandic seizures, is probably genetically determined. Usually, there is no family history of similar seizures, although siblings with PS or PS and rolandic epilepsy have been reported.[9,23,84,87,91] There is a high prevalence of febrile seizures (about 17%), and there may be a high incidence of abnormal birth deliveries, although these all need re-evaluation.[90] A mutation in the *SCN1A* gene was recently reported in two siblings[104] and in a single case of severe PS with many febrile precipitants of seizures.[105] However, no such mutations were found in another couple of siblings with typical PS and no febrile seizure precipitants (personal communication with J. Livingston). These data indicate that SCN1A mutations when found contribute to a more severe clinical phenotype of PS.

Pathophysiology

Autonomic symptoms of any type are often encountered in seizures, whether focal or generalised, in adults or children, and they are implicated in occurrences of sudden death.[106,107] However, autonomic seizures and autonomic status with ictus emeticus and ictal syncope, with the symptomatology and sequence detailed here, are specific in childhood.[101] This clinical picture does not occur in adults: only about 30 cases of ictal vomiting have been reported, and not in the same sequence as in children – adult patients usually have amnesia about the vomiting, which often occurs after the seizure has started with other symptoms.[107–110] An explanation for this is that children are vulnerable to emetic disturbances as exemplified by 'cyclic vomiting syndrome', a non-seizure disorder of unknown aetiology that is also specific to childhood.[111] Ictal syncope is even more difficult to explain.

Symptoms at the onset of seizures are important, because they indicate the possible location of the epileptic focus. However, autonomic and emetic disturbances are of uncertain value with regard to localisation in PS and may occur in seizures starting from the anterior or posterior regions. The localisation of ictal vomiting in adults (the non-dominant temporal lobe) does not appear to apply to children.

Clinical and EEG findings indicate that, in PS, there is a diffuse and multifocal cortical hyperexcitability, which is related to maturation. This diffuse epileptogenicity may be unequally distributed, predominating in one area, which is often posterior. The preferential involvement of emetic and other autonomic manifestations may be attributed to epileptic discharges triggering temporarily hyperexcitable low threshold central autonomic networks of vulnerable children.[90,101] In other words, it is likely that in these children a 'weak' epileptic electrical discharge (irrespective of localisation) activates, at its onset, susceptible autonomic centres to produce autonomic seizures and autonomic status

epilepticus. This happens before the generation of clinical manifestations from brain regions that are topographically related to the ictal electrical discharge (occipital, frontal, central, parietal and less often temporal) with clinical seizure thresholds higher than those of the autonomic centres.[20]

Koutroumanidis has proposed a modern view that PS is an important electroclinical example of benign childhood system epilepsy.[7]

Diagnostic procedures

Neurological and mental states and MRI are normal. The most useful laboratory test is the EEG (Figure 12.4).

The determinant of neurodiagnostic procedures is the state of the child at the time he or she first presents medically, as follows:[90]

1. The child has a typical brief or lengthy seizure of PS, but has fully recovered before arriving at the accident and emergency department (A&E) or being seen by a physician. A child with the distinctive clinical features of PS, particularly ictus emeticus and lengthy seizures, may not need any investigations other than an EEG. However, as about 10–20% of children with similar seizures may have brain pathology, MRI may be indicated.
2. The child with a typical lengthy seizure of PS has partially recovered, although he or she is still in a post-ictal stage, tired, mildly confused and drowsy on arrival at A&E or when seen by a physician. The child should be kept under medical supervision until full recovery, which, as a rule, occurs after a few hours of sleep. Then guidelines are the same as in (1).
3. The child is brought to A&E or is seen by a physician while ictal symptoms continue. This is the most difficult and challenging situation. Symptoms may dramatically accumulate in succession, and demand rigorous and experienced evaluation. A history of a previous similar seizure is reassuring and may help to avoid unnecessary investigation.

Electroencephalography

Inter-ictal EEG shows great variability. In about 90% of cases, the EEG reveals functional, mainly multifocal, high-amplitude, sharp–slow-wave complexes (Figure 12.4). Spikes may appear anywhere, often shifting from one region to another in a series of EEGs. Occipital spikes predominate but these do not occur in a third of patients. Spikes often appear independently in the same or the contralateral hemisphere. Clone-like, repetitive, multifocal spike–wave complexes may be characteristic features when they occur (19%).[90]

Small, and even inconspicuous, spikes may appear in the same or a previous EEG of children with giant spikes. Although rare, positive spikes or other unusual EEG spike configurations may occur.[90] Brief generalised discharges of slow waves, mixed with small spikes, may occur either alone (4%) or more often with focal spikes (15%).

Whatever their location, spikes are accentuated by sleep. EEG spikes may be stimulus sensitive; occipital paroxysms are commonly (47%) activated by the elimination of central vision and fixation,whereas CTSs may be elicited by somatosensory stimuli. Occipital photosensitivity is an exceptional finding.

The background EEG is usually normal, but diffuse or localised slow-wave abnormalities may also occur in at least one EEG in 20% of cases, particularly post-ictally.

EEG spikes may persist for many years after clinical remission or appear in only one of a series of EEGs.

A single routine EEG may be normal in 10% of patients. This should prompt a request for a sleep EEG.

> The frequency, location and persistence of spikes do not determine clinical manifestations, duration, severity and frequency of seizures or prognosis. The clinical seizure manifestations are roughly the same irrespective of EEG spike localisation.

The multifocal nature of epileptogenicity in PS has been also documented with dipole analysis.[112,113]

Ictal EEG: Ictal video-EEG has unequivocally documented the epileptic nature of the autonomic manifestations in PS.[85,93,114–116] These may start long after the onset of the electrical ictal discharge and

present as tachycardia, breathing irregularities, coughing or emesis, which would be impossible to consider as seizure events without an EEG. Other recognisable conventional seizure symptoms such as convulsions appear later in the ictal phase or may not appear at all. The seizure discharge mainly consists of rhythmic theta or delta activity, usually mixed with small spikes. Onset is unilateral, often posterior, but may also be anterior and not strictly localised to one electrode (Figures 12.5 and 12.6).

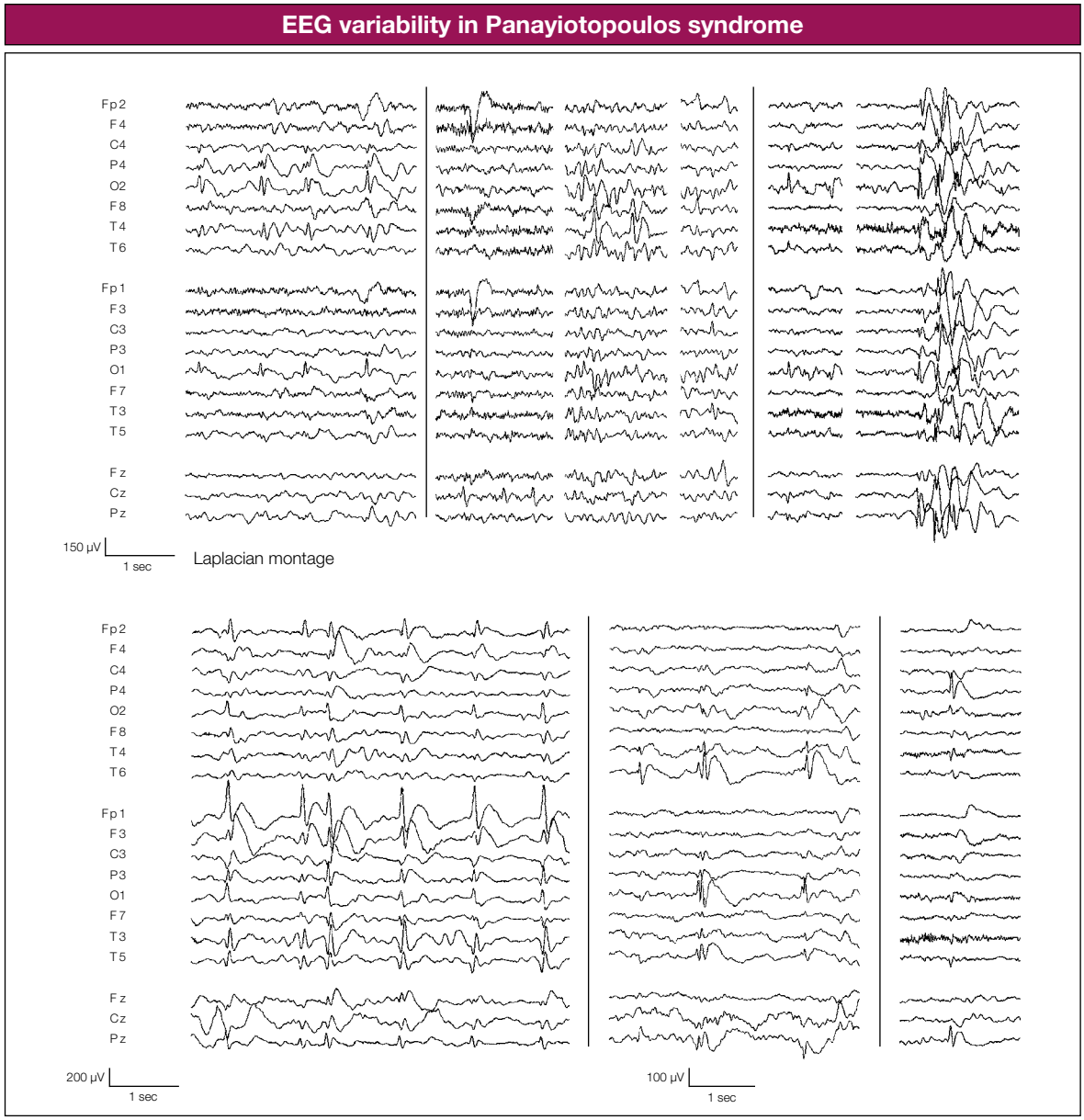

Figure 12.4 Samples from EEGs of six children with typical clinical manifestations of PS. Spikes may occur in all electrode locations, and they are usually of high amplitude and frequent or repetitive (clone-like repetitive multifocal spike–wave complexes), although they may also be small and sparse. Brief generalised discharges of small spikes and slow waves may be present.

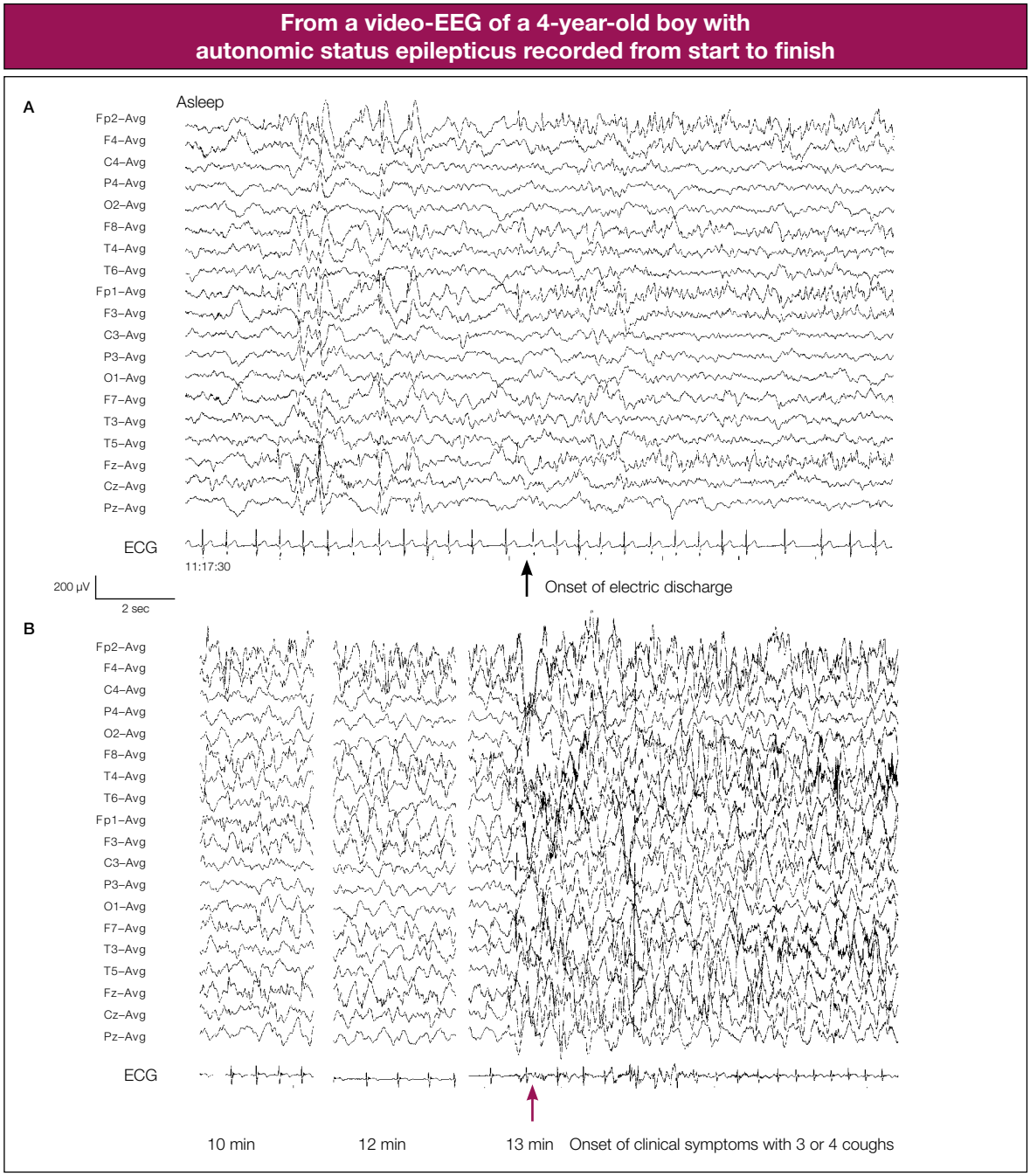

Figure 12.5 (**A**) High-amplitude spikes and slow waves are recorded from the bifrontal regions before the onset of the electrical discharge, which is also purely bifrontal (black arrow shows onset of ictal discharge). (**B**) First clinical symptoms with three or four coughs and marked tachycardia appeared 13 min after the onset of the electrical discharge (red arrow), when this had become bilaterally diffuse. Subsequent clinical symptoms were tachycardia, ictus emeticus (without vomiting) and impairment of consciousness. No other ictal manifestations occurred until termination of the seizure with diazepam 70 min after onset. Another lengthy autonomic seizure was recorded on video-EEG a year later. The onset of symptoms was different with mainly tachycardia and agitation.

Modified with permission from Koutroumanidis, et al *(2005).*[114]

Ictal EEG in Panayiotopoulos syndrome (A) and ICOE-G (B)

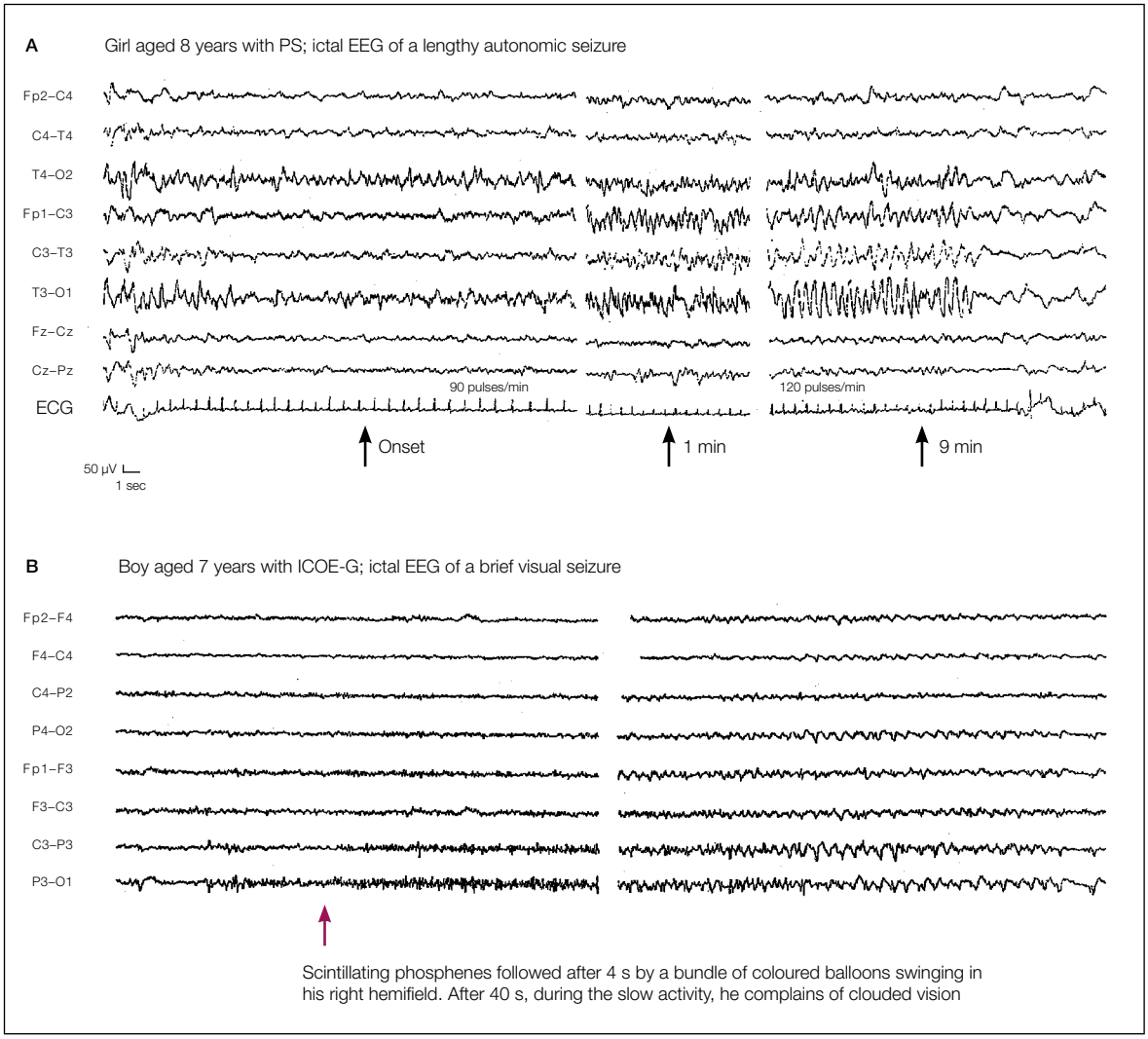

Figure 12.6 (**A**) Samples of continuous EEG recordings from the onset to the end of a 9-min seizure during sleep stage II in an 8-year-old girl. Clinically, the seizure manifested with awakening, eyes opening, frequent vomiting efforts and complaints of frontal headache.[116] The ictal EEG started with remission of the inter-ictal occipital paroxysms and the appearance of occipital sharp rhythms progressing to monomorphic rhythmic theta activity in the bioccipital regions, mainly involving the right hemisphere in a wider posterior distribution. The slow activity slowed down with the progress of the seizure and ended with no post-ictal abnormalities. The ECG showed significant tachycardia during the ictus.[116] (**B**) Ictal EEG during a visual seizure in a boy with ICOE-G. The seizure starts in the left occipital region with fast spikes associated with visual symptoms. This spreads, 4 s later, to the parietal regions and the child sees a bundle of coloured balloons swinging in his right hemifield. This lasted for 40 s and was followed by slow waves that progressively became slower and diffused over the whole brain. At this stage, he complained of clouded vision. This boy was normal physically and intellectually, and also had a normal CT brain scan. At the age of 3 years, he had a nocturnal, left hemiconvulsion. His first EEG showed occipital paroxysms with fixation-off sensitivity. From the age of 4 years, he had started having frequent, brief, visual seizures (simple, coloured, visual hallucinations) provoked by sudden darkness.
Modified with permission from Beaumanoir (1993).[116]

MEG in Panayiotopoulos syndrome of frontal origin

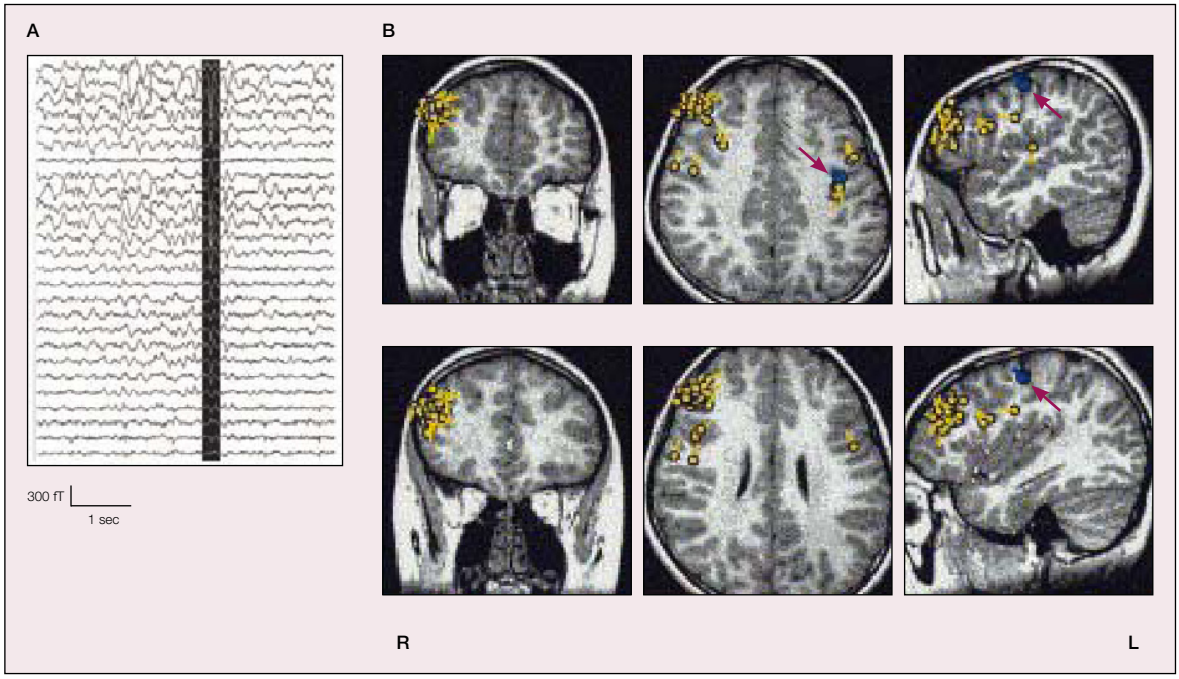

Figure 12.7 The patient had seizures typical of PS from the age of 4 years. EEGs initially showed occipital spikes, but at age 13 the EEG had bifrontal spikes and MEG was performed. His younger brother also had PS preceded by febrile seizures and followed by rolandic seizures. (A) MEG wave forms. The reversed coloured MEG wave forms in white in the vertical dark zone were analysed. (B) Magnetic source images revealed clustering equivalent current dipoles of spike discharges alongside the right inferior frontal sulcus, but the orientations were not so regular. All MRIs are T1-weighted. The pale-coloured solid circles and tails represent the locations and orientations of equivalent current dipoles of the spike discharges. The early somatosensory evoked field was modelled using a single equivalent current dipole approach to estimate the spatial source of response, whereas the dark-coloured solid circles and tails indicated by red arrows represent the locations and orientations of somatosensory evoked fields (N20).
Reproduced with permission from Saitoh, et al *(2007).*[119]

Magnetoencephalography

MEG revealed that the main epileptogenic areas in PS are along the parieto-occipital, calcarine or central (rolandic) sulci.[117,118] A more recent report of three children with PS (two were brothers) and frontal EEG spikes, showed equivalent current dipoles clustering in the frontal lobes (Figure 12.7).[119]

Differential diagnosis

PS is easy to diagnose, because of the characteristic clustering of clinical seizure semiology, which is often supported by inter-ictal EEG findings. However, despite sound clinico-EEG manifestations, PS escaped recognition for many years and is still misdiagnosed for a number of reasons:

- ictus emeticus was difficult to accept as a seizure event
- encephalitis or other acute cerebral insults were the prevailing diagnoses in the acute stage of a deteriorating level of consciousness followed by convulsions
- cardiogenic syncope, atypical migraine, gastro-enteritis, motion sickness and a first seizure were the likely diagnoses when seizures were brief or after recovery from the acute stage.

Similarly, ictal syncope has only recently been recognised as an important clinical manifestation of PS; it

may be misdiagnosed as cardiogenic syncope, pseudoseizure or a more severe encephalopathic state.[90]

The main problem is to recognise emetic and other autonomic manifestations as seizure events, and not to dismiss them or erroneously consider them as unrelated to the ictus and as a feature of encephalitis, migraine, syncope or gastroenteritis.

It should be remembered that 10–20% of autonomic seizures and autonomic status epilepticus are due to heterogeneous cerebral pathology and are also restricted to childhood. These cases are betrayed by abnormal neurological or mental symptomatology, abnormal brain imaging and background EEG abnormalities.

PS is significantly different from rolandic seizures and ICOE-G (page 362) despite some overlapping features.[20] See also the unifying concept of benign childhood seizure susceptibility syndrome on page 365.

PS should also be differentiated from febrile seizures, with which many of these children are diagnosed. However, febrile seizures are usually GTCSs from their onset. Conversely, GTCSs in PS occur only in a third of patients and happen after the onset of significant ictal autonomic manifestations (secondarily GTCS).

An EEG demonstrating multifocal spikes may be indispensable in the diagnosis of patients with PS if clinical information is inadequate or emetic manifestations are inconspicuous.

Prognosis

This syndrome is remarkably benign in terms of its evolution.[8,23,83–88,90–92,95,99,120] A quarter of patients with PS have a single seizure only and half have two to five seizures. The remaining quarter have more than six or sometimes very frequent seizures. Remission often occurs within 1 or 2 years of onset. Autonomic status epilepticus imparts no residual neurological deficit. Atypical evolution of PS with the development of absences, drop attacks and epilepsy with continuous spikes–waves during slow-wave sleep is extremely rare.[121,122]

A fifth of children with PS develop mainly rolandic seizures (13%) and less often occipital or other types of seizures during childhood and the early teens.[8,90,95] These are also age related and remit before the age of 16 years. The risk of epilepsy in adult life appears to be no higher than in the general population.[8,90]

Findings of subtle neuropsychological deficits in some studies[123] may be a genuine syndrome-related symptom in the active phase of PS, but are more probably the result of AEDs (most of the children were on AEDs, including phenobarbital and vigabatrin)[123] and/or other contributing factors.

Although the syndrome is benign in terms of its evolution, autonomic seizures are potentially life threatening in the rare context of cardiorespiratory arrest.[8,90,100] It is probably reassuring that normal children with epilepsy do not have an increased risk of death compared with the general population.[124]

Diagnostic tips

Paediatricians should be alerted by lengthy autonomic seizures, and electroencephalographers by frequent multifocal spikes in a normal child with one or a few seizures.

In terms of the EEG, it is important to remember that frequent epileptogenic foci in a normal child with infrequent seizures should raise the possibility of benign childhood focal seizures.

Management[6,8,10,20,90,101]

Current guidelines for febrile seizures, if appropriately modified, may provide the basis for similar guidelines for PS. Education about PS is the cornerstone of management. Prophylactic treatment with anti-epileptic medication may not be needed for most patients. Autonomic status epilepticus in the acute stage needs thorough evaluation; aggressive treatment may cause iatrogenic complications including cardiorespiratory arrest.

See page 368 for details of the management of benign childhood focal seizures.

Idiopathic childhood occipital epilepsy of Gastaut

Synonyms: ICOE-G, Gastaut-type of childhood occipital epilepsy, late-onset childhood occipital epilepsy (Gastaut type), childhood epilepsy with occipital paroxysms.

ICOE-G is a pure but rare form of idiopathic childhood occipital epilepsy.[1,20,95,125–129]

Considerations on classification

This purely 'idiopathic childhood occipital epilepsy' has been recognised in the new diagnostic scheme[2] as 'late-onset childhood occipital epilepsy (Gastaut type)' replacing the previous name 'childhood epilepsy with occipital paroxysms'.[130] Also note that 'benign' (used in all other benign childhood focal seizures) is not included in the descriptive terminology of this syndrome because ICOE-G is of uncertain prognosis.[2,130] Furthermore, the certainty by which the ILAE Core Group believed that this syndrome represents a unique diagnostic entity has been lowered to 2 on a score of 1–3 (3 being the most clearly and reproducibly defined).[3] My view is that ICOE-G is a definite but relatively rare epileptic syndrome of BCSSS.

The term 'idiopathic childhood occipital epilepsy of Gastaut' was chosen to (1) precisely describe that this is a purely occipital epilepsy, (2) honour this great epileptologist (Gastaut syndrome is an appropriate alternative but may be confused with Lennox–Gastaut syndrome) and (3) emphasisethat there is no other type of idiopathic childhood occipital epilepsy.

Demographic data

Onset is between 3 and 15 years of age with a mean of around 8. Both sexes are equally affected. The disorder accounts for about 2–7% of benign childhood focal seizures.

Clinical manifestations

Seizures are purely occipital and primarily manifest with elementary visual hallucinations, blindness or both (see also the detailed symptomatology of occipital lobe epilepsy in Chapter 15, page 474). They are usually frequent and diurnal, develop rapidly within seconds and are brief, lasting from a few seconds to 1–3 min, and, rarely, longer.

Elementary visual hallucinations are the most common and characteristic ictal symptoms, and are most likely to be the first and often the only clinical manifestation. They consist mainly of small multicoloured circular patterns (Figure 12.8) that often appear in the periphery of a visual field, becoming larger and multiplying during the course of the seizure, frequently moving horizontally towards the other side (see Chapter 15):

> I see millions of small, very bright, mainly blue and green coloured, circular spots of light, which appear on the left side and sometimes move to the right.

Other occipital symptoms, such as sensory illusions of ocular movements and ocular pain, tonic deviation of the eyes, eyelid fluttering or repetitive eye closures, may occur at the onset of the seizures or appear after the elementary visual hallucinations.

Deviation of the eyes, often associated with ipsilateral turning of the head, is the most common (in about 70% of cases) non-visual ictal symptom. It is often associated with ipsilateral turning of the head and usually starts after visual hallucinations, although it may also occur while the hallucinations still persist. It may be mild, but more often it is severe and progresses to hemiconvulsions and GTCSs. Some children may have seizures of eye deviation from the start without visual hallucinations. It is likely that these cases have a better prognosis and shorter seizure lifespan than those with ICOE-G.[128]

Forced eyelid closure and eyelid blinking occur in about 10% of patients, usually at a stage at which

consciousness is impaired. They signal an impending secondarily GTCS.

Ictal blindness, appearing from the start or, less commonly, after other manifestations of occipital seizures, usually lasts for 3–5 min. It can occur alone and be the only ictal event in patients who could, at other times, have visual hallucinations without blindness:

> Everything went suddenly black, I could not see and I had to ask other swimmers to show me the direction to the beach.[1,82]

Complex visual hallucinations, visual illusions and other symptoms resulting from more anterior ictal spreading rarely occur from the start. They may terminate in hemiconvulsions or generalised convulsions.

Ictal headache, or mainly orbital pain, may occur and often precedes visual or other ictal occipital symptoms in a small number of patients.[1,131]

Consciousness is not impaired during the visual symptoms (simple focal seizures), but may be disturbed or lost in the course of the seizure, usually before eye deviation or convulsions.

Ictal syncope is rare.[90]

Occipital seizures of ICOE-G may rarely progress to extra-occipital manifestations, such as hemiparaesthesia. Spread to produce symptoms of temporal lobe involvement is exceptional and may indicate a symptomatic cause.[1]

Post-ictal headache, mainly diffuse, but also severe, unilateral and pulsating, or indistinguishable from migraine headache, occurs in half the patients, in 10% of whom it may be associated with nausea and vomiting.

> I then have a left-sided severe throbbing headache for an hour or so.[1,131]

Circadian distribution: Visual seizures are predominantly diurnal and can occur at any time of the day. Longer seizures, with or without hemi or generalised convulsions, tend to occur either during sleep, causing the patient to wake up, or after awakening. Thus, some children may have numerous diurnal visual seizures and only a few seizures that are exclusively nocturnal or occur on awakening.

Frequency of seizures: If untreated, patients experience frequent and brief visual seizures (often several every day or weekly). However, propagation to other seizure manifestations, such as focal or generalised convulsions, is much less frequent (monthly, yearly or exceptionally).

Elementary visual hallucinations as perceived and drawn by patients with visual seizures

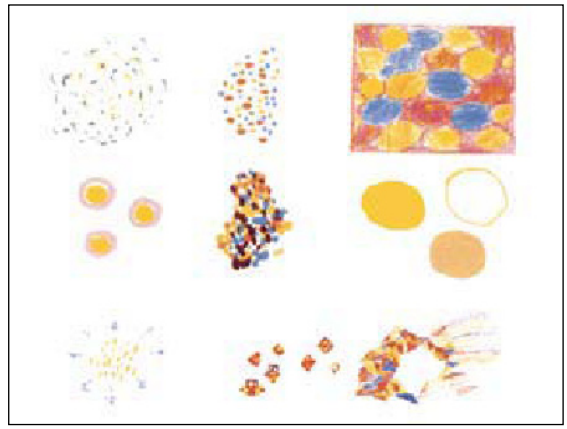

Figure 12.8 *Figure reproduced with permission from Panayiotopoulos (1999).*[1]

Aetiology

There may be an increased family history of epilepsies (37% of cases) or migraine (16% of cases),[126] but a family history of similar seizures is exceptional.[132]

ICOE-G is considered to be a late-onset phenotype of BCSSS (page 365).

Pathophysiology

The seizures are of a purely occipital lobe origin.[20,90]

The mechanisms for post-ictal headache, which is a common event after minor idiopathic or symptomatic visual seizures, with or without a predisposition to migraine, are unknown. It is likely that the occipital seizure discharge triggers a genuine migraine headache through trigeminovascular or brain-stem mechanisms.[131,133]

The occipital paroxysms are bilateral and synchronous when they occur, because they are activated in the bioccipital regions by the elimination of fixation and central vision (Figure 12.9).[90,134] They are not

due to thalamocortical activation, as proposed by Gastaut and Zifkin.[126]

Diagnostic procedures

By definition, all tests other than the EEG are normal. However, high-resolution MRI is probably mandatory because of the high incidence of symptomatic occipital epilepsies with the same clinico-EEG manifestations.

Electroencephalography

The inter-ictal EEG shows occipital paroxysms, often demonstrating fixation-off sensitivity (Figure 12.9). However, some patients may only have random occipital spikes, whereas others may have occipital spikes only in the sleep EEG, and a few may have a consistently normal EEG. Centrotemporal, frontal and giant somatosensory evoked spikes may occur, although less often than in PS. Whether or not occipital photosensitivity is part of this syndrome is debatable (see Chapter 16).

Occipital spikes are not pathognomonic of a particular syndrome, because they also occur in a variety of organic brain diseases with or without seizures, in children with congenital or early onset visual and ocular deficits, and even in 0.8–1% of normal preschool-age children (Table 12.1).[55,134–136] They are common in young children, with a peak age at first discovery of 4–5 years, and 'tend to disappear in adult life, and the subsidence of the EEG abnormality is usually accompanied by a cessation of seizures'.[55,135]

Ictal EEG, preceded by regression of occipital paroxysms, is characterised by the sudden appearance of an occipital discharge that consists of fast rhythms,

Occipital paroxysms in their classical form with fixation-off sensitivity in a 10-year-old boy with ICOE-G

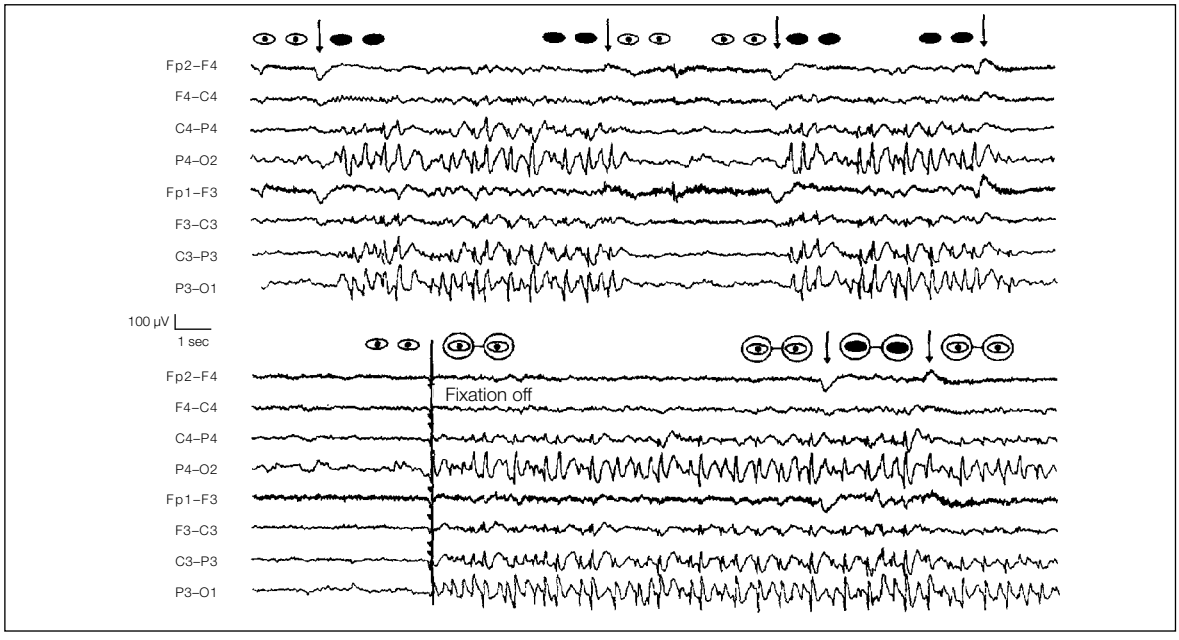

Figure 12.9 Case 26 in Panayiotopoulos.[1] Occipital paroxysms occur as long as fixation and central vision are eliminated by any means (eyes closed, darkness, +10 spherical lenses, Ganzfeld stimulation). Under these conditions, eye opening cannot inhibit the spikes. Symbols of the eyes open or closed without glasses denote that the recording was made with the lights on and whenever fixation was possible. Symbols of the eyes open or closed with glasses denote that the recording was made when fixation and central vision were eliminated by any of the above means.
Reproduced with permission from Panayiotopoulos (1999).[1]

Main features of rolandic epilepsy, Panayiotopoulos syndromes and idiopathic childhood occipital epilepsy of Gastaut

	Rolandic epilepsy	Panayiotopoulos syndrome	Idiopathic childhood occipital epilepsy of Gastaut
Prevalence amongst children aged 1–15 years with non-febrile seizures (%)	15	6	0.5–1
Peak age at onset (years)	7–10	3–6	8–11
Male to female ratio	1.5	1	1
Seizure characteristics			
Typical onset with	Hemifacial sensory-motor or oropharyngolaryngeal symptoms	Autonomic symptoms mainly with emesis	Visual symptoms mainly with elementary visual hallucinations
Hemifacial sensory-motor symptoms	Common and often from onset	Rare and not from onset	Rare and not from onset
Oropharyngolaryngeal symptoms	Common and often from onset	Rare and not from onset	Have not been reported
Speech arrest	Common and often from onset	Rare and not from onset	Has not been reported
Hypersalivation	Common and often from onset	Rare and not from onset	Has not been reported
Ictus emeticus	Rare and not from onset	Common and often from onset	Rare and not from onset
Autonomic disturbances other than vomiting and hypersalivation	Exceptional and not from onset	Common and often from onset	Exceptional and not from onset
Visual symptoms	Have not been reported	7% but exceptional from onset	Common and often from onset
Deviation of the eyes	Frequent during sensory-motor symptoms	Common but rarely from onset	Common but rarely from onset
Ictal behavioural changes	Exceptional and not from onset	Common and often from onset	Have not been reported
Duration for 1–3min	As a rule	Rare	As a rule
Duration of more than 5min	Rare	Common	Rare
Partial status epilepticus (>30min)	Exceptional	40%	Exceptional
Total number of seizures 1–15	As a rule	As a rule	Rare
Single seizures only (%)	10–20	30	Exceptional
Frequent seizures (%)	10	10	90
Nocturnal (sleep only) (%)	70	64	Exceptional

Table 12.2 *Continues on facing page.*

Main features of rolandic epilepsy, Panayiotopoulos syndromes and idiopathic childhood occipital epilepsy of Gastaut

	Rolandic epilepsy	Panayiotopoulos syndrome	Idiopathic childhood occipital epilepsy of Gastaut
Febrile seizures (%)	18	17	10
Prognosis	Excellent	Excellent	Uncertain
Remission within 1–2 years from first seizure	Common	Common	Exceptional or rare
Seizures after the age of 13 years	Rare	Exceptional	Common
Interictal EEG			
Centrotemporal spikes alone	As a rule and characteristic	Rare	Have not been reported
Occipital spikes	Have not been reported	65%	Probably 90%
Spikes in other locations	Probably uncommon	Frequent	Exceptional
Brief generalised discharged of 3–5Hz slow waves with small spikes (%)	5	10	Exceptional
Somatosensory evoked spikes	Common	Rare	Have not been reported
Fixation-off sensitivity	Has not been reported	Rare	May be less common than reported
Photosensitivity	Has not been reported	Exceptional	Probably 20–30%
Normal EEG or focal slow after first seizure (%)	~10	~10	~10
Ictal EEG	Slow activity with spikes	Slow activity with spikes	Fast spikes and fast rhythms
Ictal onset	Rolandic regions	Anterior or posterior regions	Occipital regions

Table 12.2 *Continued from facing page.*
Reproduced with permission from Panayiotopoulos et al (2008).[20]

fast spikes or both (Figure 12.6).[116,125,126,137–141] This is of a much lower amplitude than the inter-ictal occipital spikes. Elementary visual hallucinations are related to the fast-spike activity. Complex visual hallucinations may occur when the discharge is slower. In oculoclonic seizures, spikes and spikes and waves are slower, and a localised ictal fast spike rhythm may occur before deviation of the eyes. Ictal EEG during blindness is characterised by pseudo-periodic slow waves and spikes, which differ from those seen in ictal visual hallucinations.

There are usually no post-ictal abnormalities.

Differential diagnosis

The differential diagnosis of ICOE-G is mainly from cryptogenic or symptomatic occipital epilepsy, coeliac disease, migraine with aura, and basilar or acephalgic migraine where misdiagnosis is high.[1,131]

The differential diagnosis from migraine should be easy if all clinical elements are properly assessed and synthesised (Table 4.4), as described on pages 125–130.

Basilar migraine with occipital spikes does not exist; the relevant reports described cases with genuine ICOE-G (see Chapter 4, page 130) imitating basilar migraine.[131,142]

Symptomatic occipital epilepsy often imitates ICOE-G; neuro-ophthalmological examination and brain imaging may be normal. Thus, high-resolution MRI is required to detect subtle lesions.

Occipital seizures of mitochondrial disorders, Lafora disease and coeliac disease[143] should be considered (for details, see Chapter 15).[1]

Differentiating ICOE-G from PS

The differentiation here is straightforward and statistically validated.[1] The seizures of ICOE-G are purely occipital and as such start and often end only with occipital lobe symptomatology. Further, seizures are mainly brief, frequent and diurnal. Rarely, seizures may be longer and also occur in sleep, but these are also fundamentally different to the rolandic epilepsy or the autonomic seizures and autonomic status epilepticus of PS (Table 12.2). Exceptionally, ictal vomiting may occur in ICOE-G but this follows the appearance of visual symptomatology, as occurs with reflex photosensitive occipital seizures, and the same patient usually has frequent brief occipital seizures. Conversely, visual symptoms in PS, when present, are not the sole manifestation of a seizure or stereotypical; only exceptionally (1%) are they reported at seizure onset.[9,84,90] From the EEG standpoint, the occipital spikes that characterise ICOE-G are also common in PS, but these often occur with extra-occipital spikes and with shifting locations in sequential EEG (Figure 12.4). Further, ictal EEG is markedly different between these syndromes (Figure 12.6). Some reported difficulties in differentiating ICOE-G from PS[144] may arise when emphasis is unduly placed on individual symptoms that may overlap, rather than on a comprehensive synthetic analysis of their quality, chronological sequence and other clustering features in the respective electro-clinical phenotypes, which is the basis for precise differential diagnosis in clinical practice. If any other diagnostic approach is followed, then even non-epileptic disorders such as migraine with aura could be deemed as overlapping with ICOE-G (visual hallucinations and headache), PS (lengthy duration and vomiting) or both (age, family history of epilepsies). It may be because of these limitations and the retrospective character of their study that Taylor et al. (2008)[144] found that only one of their 16 patients was typical in all respects of PS and that ICOE-G was as frequent as PS, which contrasts with all previous prospective studies cited in this chapter. Such a discrepancy may indicate that PS is still unrecognised even by epileptologists and that the study does not represent the vast majority of typical PS. Further, the commonly quoted argument that PS is not essentially different from ICOE-G, "considering that the younger the children are, the less likely they are to describe visual symptoms," is not tenable: (i) more than two-thirds of children with PS are older than 4 years and therefore able to describe their visual experiences and (ii) there is no difference in seizure presentation between younger and older children with PS. A few patients with either PS or rolandic epilepsy may later develop purely occipital seizures as of ICOE-G. These cases are easy to diagnose and indicate the intimate links of these disorders within the framework of BCSSS (page 365).

Prognosis

The prognosis of ICOE-G is unclear, although available data indicate that remission occurs in 50–60% of patients within 2–4 years of onset. Seizures show a dramatically good response to carbamazepine in more than 90% of patients. However, 40–50% of patients may continue to have visual seizures and infrequent secondarily GTCSs, particularly if they have not been appropriately treated with carbamazepine. Rarely, atypical evolutions to epilepsy with continuous spikes and waves during slow-wave sleep and cognitive deterioration have been reported.[145] Also rarely, children with ICOE-G may manifest with typical absence seizures, which usually appear after the onset of visual seizures.[146]

Although no significant differences were found in basic neurophysiological functions between patients with ICOE-G and control groups, patients' performance scores for attention, memory and intellectual functioning were lower.[147]

Management

In contrast to other phenotypes of the BCSSS, patients with ICOE-G often suffer from frequent seizures and therefore medical treatment, mainly with carbamazepine, is likely to be mandatory.[1,131] Secondarily GTCSs are probably unavoidable without medication.

A slow reduction in the dose of medication 2 or 3 years after the last visual or other minor or major seizure should be advised, but if visual seizures reappear, treatment should be restored. See details in the section on Management (page 368).

Other phenotypes of BCSSS[1]

There are well-documented reports of children suffering from benign childhood focal seizures with clinico-EEG manifestations that cannot be classified as typical cases of rolandic epilepsy, PS or ICOE-G. Their existence verifies the unified concept of BCSSS. They may represent atypical presentations of the recognised syndromes within the BCSSS.

Benign childhood seizures with affective symptoms

Benign childhood epilepsy with affective symptoms[29,148] is a rare clinical phenotype of the BCSSS with features common in both PS (behavioural and autonomic symptoms) and rolandic epilepsy (arrest of speech and hypersalivation).

Demographic data

Onset is between 2 and 9 years of age. Both sexes are equally affected. Prevalence may be very low.

Clinical manifestations

Seizures manifest with terror and screaming, autonomic disturbances (pallor, sweating, abdominal pain, salivation), chewing and other automatisms, mild impairment of consciousness and arrest of speech.

The predominant seizure symptom is sudden fear or terror:

> This terror was expressed by the child starting to scream, to yell or to call his mother; he clung to her or to anyone nearby or went to a corner of the room hiding his face in his hands. His terrorised expression was sometimes associated with either chewing or swallowing movements, distressed laughter, arrest of speech with glottal noises, moans and salivation, or some kind of autonomic manifestation, such as pallor, sweating or abdominal pain, that the child expressed by bringing his hands onto his abdomen and saying 'It hurts me, it hurts me'. These phenomena were associated with changes in awareness (loss of contact) that did not amount to complete unconsciousness.[148]

The seizures are brief, lasting between 1 and 2 min, with a maximum duration of 10 min.

Half the children have frequent (several times a day) seizures from the onset of the disease, which may occur with the same semiology, whether awake or asleep. Some children may have brief and infrequent nocturnal rolandic seizures at the same time as the affective attacks. Generalised seizures do not occur.

Aetiology

This is probably a rare phenotype of BCSSS or may be atypical presentations of PS and rolandic epilepsy.

A fifth of patients have febrile seizures, and a family history of undefined types of epilepsy are common (36%).

Diagnostic procedures

All tests, apart from the EEG, are normal.

Electroencephalography[29,148]

The inter-ictal EEG shows high-amplitude functional spikes located around the fronto- and parieto-temporal electrodes. These are exaggerated by sleep and may be associated with generalised discharges.

Ictal EEG discharges are localised to the frontotemporal, centrotemporal or parietal areas, or may be diffuse. They are stereotypical in each individual patient.

Prognosis

Remission occurs within 1 or 2 years of onset. At the active stage of the disease, behavioural problems may be prominent, but subside with the seizures. The response to treatment is excellent.

Management

In the active phase of the disease and because of the frequent seizures, anti-epileptic medication, mainly carbamazepine, may be needed.

Benign childhood epilepsy with parietal spikes and frequent ESESs

Benign childhood epilepsy with parietal spikes and frequent ESESs[40,45,149] may be another phenotype of BCSSS. Defining features are EEG spikes in parietal regions, which are often elicited by tactile stimulation. However, ESESs (see page 342)[1,40–42,45,46,90] are not specific for any syndrome because they also occur in 10–20% of children with rolandic seizures (Figure 12.1),[45] in a few patients with PS[1,90] and in children with no seizures.[150]

Clinically, patients suffer from versive seizures of the head and body, often without impairment of consciousness. These are mainly diurnal and infrequent. Multiple daily seizures and focal status epilepticus are exceptional.

Remission usually occurs within 1 year of seizure onset, but EEG abnormalities may persist for longer.

Benign childhood focal seizures associated with frontal or midline spikes

Benign childhood focal seizures associated with frontal[1,151,152] or midline spikes[1,153] have been described and long follow-up reports have confirmed a benign course, although no systematic studies have been published. However, it should be remembered that EEG spike foci of various locations are also seen in rolandic epilepsy and more commonly in PS. Midline spikes are more common in children than in adults and they are not specific for any type of epilepsy.[154,155] Of six children with at least one EEG having only midline spikes, five had normal development with febrile seizures (one case), rolandic epilepsy (one case), PS (one case), a single complex focal occipital seizure (one case) or brief seizures with loss of consciousness only (one case). The only symptomatic case had generalised convulsions.[155]

Benign infantile focal epilepsy with midline spikes and waves during sleep

Benign infantile focal epilepsy with midline spikes and waves during sleep (or benign focal epilepsy in infants with central and vertex spikes and waves

during sleep) has been recently described as a new BCSSS.[156–159] In terms of age, this is borderline between benign infantile seizures of Watanabe-Vigevano syndrome (page 365) and BCSSS. Age at onset is in the first 3 years of life and both sexes are equally affected. Infants are normal and all tests other than the EEG are normal. Seizures consist mainly of staring, motion arrest, facial cyanosis, loss of consciousness and stiffening of the arms. Clonic convulsions and automatisms are rare. Duration of seizures is from 1 to 5 min. Seizures are mainly diurnal (but may also occur during sleep), they may occur in clusters and are generally infrequent (one to three seizures per year). There is a strong family history of undefined types of epileptic seizures, with benign epilepsies prevailing.

Inter-ictal EEG abnormalities are seen only in NREM sleep and consist of small, mostly singular, midline spikes and waves.

The prognosis is excellent, with remission of seizures, normal development and normalisation of the EEG before the age of 4.

Benign childhood seizure susceptibility syndrome: A unified concept

Benign childhood focal seizures with focal EEG sharp–slow-wave complexes are probably a group of syndromes of one nosological continuum.[1,20,36,90] They share common clinical and EEG characteristics. Seizures are infrequent, usually nocturnal and remit within 1–3 years of onset. Brief or prolonged seizures, even status epilepticus, may be the only clinical event in the patient's lifetime. Ictal autonomic manifestations, such as hypersalivation, emesis, headache and ictal syncope, which are unusual in other epileptic syndromes or in adults, are frequent and may occasionally appear in isolation. The clinical and EEG characteristics of one syndrome may evolve into another or a child may simultaneously develop features of another form of benign childhood focal seizures.

Febrile seizures are common. Neurological and intellectual states are normal, but some children may experience mild and reversible neuropsychological problems during the active stage of the disorder. Brain imaging is normal. There are usually severe EEG abnormalities of spikes, which are disproportionate to the frequency of seizures. Epileptogenic foci, irrespective of their location, manifest as abundant, high-amplitude, sharp–slow-wave complexes which occur mainly in clusters. They are often bilateral, independent or synchronous, frequently combined with foci from other cortical areas or brief generalised discharges, and are exaggerated in sleep stages I–IV. A normal EEG is rare and should prompt a sleep EEG study. Similar EEG features, which resolve with age, are found in normal school-age children (Table 12.1) and 1% of children who have had an EEG for reasons other than seizures.

There is no justification for suggesting that all these syndromes differ merely because an 'epileptogenic' focus is a little anterior or posterior, or lateral or medial to the centrotemporal regions. A unified concept of benign childhood focal seizures is also suggested by the frequency of more than one type of benign childhood focal seizures in an affected child, siblings or both.

In all probability, all these conditions are linked together by a common, genetically determined, mild and reversible, functional derangement of the maturational process of the brain.[1,36] This derangement is often clinically silent and presents in more than 90% with EEG sharp and slow waves that are age related. The remaining minority have infrequent focal seizures with symptoms that are localisation and age related and dependent. A few of these children, with or without seizures, could also possibly have minor and fully reversible neuropsychological symptoms that are rarely clinically overt and can be detected

only by formal neuropsychological testing. Finally, there may be a very small number of patients (<1%) in whom this derangement of brain maturation may be further derailed to a more aggressive condition with seizures, neuropsychological manifestations and EEG abnormalities of various combinations and various degrees of severity, such as atypical benign focal epilepsy of childhood, Landau–Kleffner syndrome and epilepsy with continuous spike-and-slow-wave during sleep (see Chapter 10).

My overall impression and appeal is that benign childhood focal seizures, and their clinical and EEG manifestations and evolutions, need appropriate prospective studies, such as those performed for febrile seizures.

Febrile seizures and BCSSS

One of the most interesting aspects of benign childhood seizures is their striking age-related sequence. Benign neonatal and infantile seizures, febrile seizures, rolandic epilepsy, PS and other clinical phenotypes of BCSSS are specific to children and do not occur in adults. That children are particularly susceptible to seizures is well documented.

There are three main periods of age-related childhood susceptibility to benign seizures (Figure 12.10):

1. Febrile, mainly *generalised*, convulsions first appear in early childhood at a peak age of around 18–22 months.

Diagrammatic age-related presentation of febrile, rolandic and Panayiotopoulos syndromes

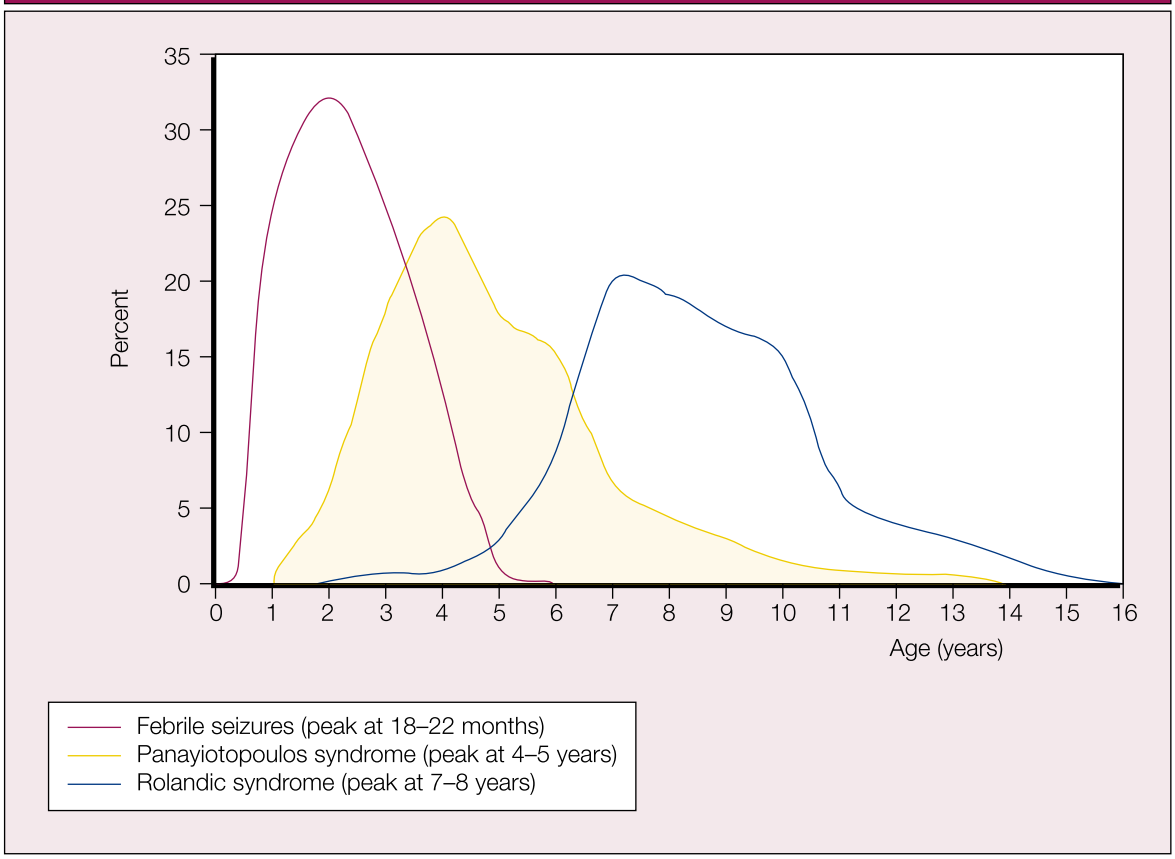

Figure 12.10 *Reproduced with permission from Panayiotopoulos (2002).*[90]

2. PS covers the intermediate period, occurring at a peak of 4 or 5 years, and presents with mainly autonomic seizures.
3. Rolandic *focal* seizures occur in late childhood at a peak age of 7–8 years.

It is probably beneficial to analyse this further, as it is likely to aid our understanding of the disordered age-related maturational processes:

- In the first or early period (febrile seizures), the brain is vulnerable to seizures that are triggered by fever and mainly present with convulsions that are commonly generalised.
- The second or intermediate period (PS) consists of spontaneous seizures that are often prolonged for hours and present principally with autonomic and mainly emetic symptoms.
- The third or late period (rolandic seizures) consists of spontaneous focal sensorimotor seizures.

These three periods of clinical seizure susceptibility also have peculiar EEG accompaniments. The EEG is almost normal in the first period of febrile seizures, shows mainly posterior and multifocal spikes in the intermediate period of PS, and rolandic spikes in the late period of rolandic seizures.

All these indicate that the brain in early childhood has a low threshold to generalised convulsions provoked by fever, with a relatively silent EEG spike capacity. Subsequently, the autonomic system, and in particular the emetic centres, become vulnerable, the seizure discharges may be self-sustained and the cortex exhibits a diffuse multifocal epileptogenicity, which is unequally distributed and mainly affects the posterior regions. Finally, in the third period of late childhood, brain epileptogenicity shrinks to around the rolandic regions to produce the distinctive clinical and EEG manifestations of the rolandic syndrome.

These are incontrovertible facts about the developing brain that have not yet been explored, and we should also consider the neonatal and early infantile periods, because they have their own peculiarities, as indicated by the benign neonatal seizures that occur during the first few days of life, and the benign infantile focal seizures of Watanabe–Vigevano syndrome.

This point is exemplified by reports of children with neonatal seizures who later developed rolandic syndrome[160] or PS.[91] Maihara, *et al*[160] described a family with benign familial neonatal seizures in which two siblings later developed rolandic seizures and EEG CTSs. Lada, *et al*[91] reported an otherwise normal boy who first had benign neonatal seizures, and then two febrile seizures at the age of 18 months and 3 years. This was followed by a nocturnal autonomic seizure of PS with ictal vomiting and deviation of the eyes at 6 years of age; the EEG showed occipital paroxysms. I have also described a boy who, at 8 weeks, had three focal seizures of right-sided convulsions involving the face and upper limbs (benign infantile seizures of the Watanabe–Vigevano syndrome). Subsequent EEGs were normal and treatment was stopped at the age of 10 months. He was well until the age of 7 years when he started having rolandic seizures and later developed epilepsy with continuous spike-and-wave during sleep (Figures 9.1 and 10.12). The brain MRI was normal (case 17.2 of Panayiotopoulos[1]).

Benign (isolated) focal seizures of adolescence

Benign (isolated) focal seizures of adolescence[161–168] constitute an idiopathic, short-lived and transient period of seizure susceptibility during the second decade of life. The seizures are single or occur in a cluster of up to five seizures over 36 hours, never to occur again.[168]

Considerations on classification

Benign (isolated) focal seizures of adolescence may be considered among ‘conditions with epileptic

seizures that do not require a diagnosis of epilepsy'.[2] They are not an ILAE-recognised syndrome.

Demographic data

The seizures start and end within the second decade of life with a peak onset at 13–15 years, and a 71.2% male preponderance. They may account for between 7.5%[169] and 22%[164,168] of patients who have simple focal seizures in the second decade of life. Around 200 cases have been described.[162,164,165,170,171]

Clinical manifestations

The syndrome manifests with a single seizure or a cluster of two to five focal seizures. There are no epileptic events before or after this limited seizure period, which lasts for no more than 36 hours. The physical and mental states of patients are normal.

Motor seizures, usually without jacksonian marching, and somatosensory seizures are the most common types. Visual, vertiginous and autonomic symptoms are reported in a fifth of cases. Temporal lobe seizures almost never occur, and most of the seizures are diurnal (87%).

The teenager is fully aware and can give a reliable account of the onset of the clinical manifestations (simple focal seizures) in the majority of episodes (88%). However, consciousness rarely remains intact throughout the whole event; the seizures usually evolve to impaired cognition and/or secondarily GTCSs, which occur in half the cases.

Diagnostic procedures

Laboratory tests and brain imaging are normal. The EEG may show some minor, non-specific abnormalities with no spikes or focal slowing. In a recent report, nine of 37 cases had functional spikes,[165] which is incompatible with this syndrome; these patients probably suffered from benign childhood focal seizures as described earlier.

Differential diagnosis

These patients are difficult to diagnose, because there are no specific features at onset to differentiate them from others with similar clinical manifestations, but with different aetiologies, such as symptomatic or cryptogenic focal epilepsies. My practice is to investigate all adolescents with onset of focal seizures using MRI and EEGs, which, if normal, would make the diagnosis of benign focal seizures of adolescence more likely. A definitive diagnosis cannot be made until the patient has been free of seizures for 1–5 years.[162,164]

Prognosis and management

The prognosis is excellent and no drug treatment is required because only one or a cluster of two to five focal seizures (which cannot be predicted) occur within 36 hours.

Management of benign childhood focal seizures

Short- and long-term treatment strategies of benign childhood focal seizures are empirical.[20] Current practice parameter guidelines for febrile seizures,[172,173] if appropriately modified, may be the basis for similar guidelines in benign childhood focal seizures.[20,90] Based on the risks and benefits of the effective therapies, continuous anti-epileptic medication is not recommended for children who have had only one or brief seizures. Most clinicians treat recurrent seizures with carbamazepine, but in exceptional cases this may worsen seizures. Lengthy convulsive seizures are a medical emergency; rectal or buccal benzodiazepam

is prescribed for home administration. Recurrent and lengthy seizures create anxiety in parents and patients and, as such, appropriate education and emotional support should be provided.

Acute management of a child with prolonged seizures

Control of the seizure is paramount. On the rare occasions that the child is febrile, treatment of any fever and the underlying illness is also important.

Autonomic status epilepticus needs thorough evaluation for proper diagnosis and assessment of the neurological/autonomic state of the child. Aggressive treatment should be avoided because of the risk of iatrogenic complications, including cardiorespiratory arrest.[8,10]

Long-lasting convulsive seizures (>10 min) or convulsive status epilepticus (>30 min to hours), although rare, constitute a genuine paediatric emergency that demands appropriate and vigorous treatment (see treatment of status epilepticusin Chapter 3). Benzodiazepines, in intravenous, rectal or buccal preparations, are commonly used to terminate status epilepticus.

Early parental intervention is more effective than late emergency treatment.

Prophylactic AED treatment of benign childhood focal seizures

Continuous AED treatment is not usually recommended. Although there are effective therapies that could prevent the occurrence of additional seizures, the potential adverse effects of such therapy are not commensurate with the benefit. The great majority of children with benign focal seizures do not need AED treatment even if they have lengthy seizures or more than two recurrences. The risks are small and the potential side effects of drugs appear to outweigh the benefits.

In patients with recurrent seizures and/or when parental anxiety associated with seizures is severe, small doses of AEDs may be effective in preventing a recurrence. There is no convincing evidence, however, that any therapy will alleviate the possibility of recurrences. In deciding management for a child with benign childhood focal seizures, the following should be considered:

- Most children have an excellent prognosis: about 10–30% of patients may have only a single seizure, and seizures may be infrequent (usually 2–10) in 60–70%. However, 10–20% of patients may have frequent seizures, which are sometimes resistant to treatment.
- Remission of benign childhood focal seizures is expected in all patients by the age of 15, or 16 years at the latest.
- The possibility of future epilepsy is a most unlikely event and probably not higher than that in the general population.
- There is no evidence that the long-term prognosis is worse in untreated children, although they may not be protected against seizure recurrences.
- Some children become frightened, even by simple focal seizures, and some parents are unable to cope with the possibility of another fit despite firm reassurances.
- Persistence and frequency of EEG functional spikes do not predict clinical severity, frequency or degree of liability to recurrent seizures.

Continuous prophylaxis consists of daily monotherapy using any AED that has proven efficacy in focal seizures and minimal adverse effects in children. The 2006 ILAE treatment guidelines found that 'no AED had level A or level B efficacy and effectiveness evidence as initial monotherapy' in rolandic epilepsy.[174] Of older AED most authorities prefer carbamazepine in USA[175] and valproate in Europe,[176] though these may have equivalent efficacy with phenobarbital, phenytoin and clonazepam;[17,84] carbamazepine may exaggerate seizures in a minority of children with BCSSS including PS[177] and valproate is associated with significant ADRs. Recently, sulthiame (available only in a few countries) has been revived as an excellent drug for the treatment of rolandic epilepsy with EEG normalisation[178–180] but this may be associated with cognitive abnormalities.[181] Recommended newer

AED include levetiracetam,[76–78,182,183] oxcarbazepine[77] and gabapentin.[184] Lamotrigine is also used[175] though this drug have been associated in a few reports with seizure exacerbation and cognitive deterioration in rolandic epilepsy.[79–81,185]

Stopping medication

Strategies of withdrawing medication differ among experts, although all agree that there is no need to continue medication 1–3 years after the last seizure and certainly not after age 14 when most benign childhood focal seizures remit, or age 16, when they are practically non-existent. My practice is to start the gradual withdrawal of medication 2 years after the last seizure, making sure that the child does not have any minor seizures.

However, I do not adhere to fixed rules and may continue medication until age 13–15 years depending on the severity, frequency and age at onset of seizures. Thus, in a child with frequent, severe and difficult-to-control fits in early childhood, I would not stop medication if the child had a seizure-free period of 2 or 3 years by age 7. Conversely, for a child who had three or four nocturnal seizures at age 11 and 12, I would slowly discontinue medication after a 2-year seizure-free period. I advise very slow withdrawal, reducing the dose in monthly steps until complete discontinuation. I follow this procedure because I expect that any possible seizure recurrence during the process of very slow drug withdrawal would manifest with mild, brief and simple focal seizures with no secondarily GTCSs. In the case of phenobarbital and benzodiazepines, slow withdrawal of medication is mandatory to avoid risking withdrawal seizures.

Parental attitude and education

By Thalia Valeta

Benign childhood focal seizures, like febrile convulsions,[186] despite their excellent prognosis, are usually a dramatic experience for those parents who are young and inexperienced and often think that their child is dead or dying.[187]

In my study of parental attitude and reaction in benign childhood focal seizures and particularly PS,[187] the most common fears and expressions were:

> I thought he/she was dying, choking, asphyxiated, electrocuted, never to come around again.
>
> I thought he had a stroke.
>
> I was terrified, petrified.
>
> The doctor told me that because the seizure was longer than half an hour this may affect his brain and that time will tell.
>
> We sleep with our daughter in between us on a large bed, and we keep an eye on her as she enters and exits sleep.

The following are the most dominant points emerging from that study:[187]

- *Uncertainty of what this event was:* Most parents felt uncertain about what had happened and that they were not given sufficient information or reassurance; some were told that the child had not had a seizure. Initially, some children were diagnosed as having encephalitis, atypical migraine, fainting, gastroenteritis or motion sickness. Some parents of children with recurrent seizures found the correct diagnosis through their own research on the internet and in medical literature.
- *Anxiety about what caused the event:* This was often associated with a feeling of guilt – of parental acts directly associated with the event (child relatively unattended, preceding parental arguments, child involved in leisure activity that may have caused the attack), heredity or with previous events in the child's development (birth, trauma, illness, family history of illness).
- *The effect of the seizure in the child's development:* 'Is this going to affect his or her brain?' The majority of parents were reassured that one brief seizure would not affect the child's development. However, some parents of children with lengthy seizures were left with the impression that because the seizure was prolonged, it may have had some

adverse effect on the child and that only 'time will tell'.

- *Lack of advice regarding relapses:* No specific advice was provided about the possibility of relapses and what the parents should do if such a seizure recurred.

These results indicate that there is a need for supportive family management, education and specific instructions about emergency procedures for possible subsequent seizures. Demonstrations of first aid practices for seizures are necessary. Parents of young children should be given general information about benign childhood focal seizures and, in particular, PS, in which seizures may last for many hours, and which is compounded by physicians' uncertainty over diagnoses, management and prognosis. Parents who have watched their child during a fit need specific information and psychological support to overcome anxiety and panic. Anxiety may result in overprotection, which interferes with parent–child separation and independence.[187,188]

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Idiopathic generalised epilepsies

The idiopathic generalised epilepsies (IGEs) constitute nearly a third of all epilepsies.[1] They are genetically determined and affect otherwise healthy people of both sexes and all races.[2] IGEs manifest with typical absences, myoclonic jerks and generalised tonic–clonic seizures (GTCSs), alone or in varying combinations and severity (see Chapter 2 for details of seizures).[3] Seizure-precipitating factors and photosensitivity are common.[4] Most seizures occur on awakening, particularly after sleep deprivation. Absence status epilepticus is frequent (see Chapter 3 for details).[5] Syndromes of IGE usually start in childhood or adolescence, but some have an adult onset.[6,7] They are generally life-long, although a few are age-related.

The diagnosis of IGE is usually easy, although IGEs are frequently misdiagnosed as non-epileptic or as other focal and symptomatic epileptic disorders.[8,9] The EEG is the most sensitive test in the diagnosis and confirmation of IGE.[10] The EEG shows generalised polyspike–wave discharges (GPSWD) and/or generalised spike–wave discharges (GSWD), either ictally or inter-ictally. These discharges are frequently precipitated by hyperventilation, sleep deprivation and intermittent photic stimulation (IPS). Inconspicuous clinical manifestations become apparent on video-EEG and with breath counting during hyperventilation. The EEG is unlikely to be normal in untreated patients. In suspected cases with a normal, routine awake EEG, an EEG during sleep and awakening should be obtained. Molecular genetic analyses have led to important breakthroughs in the identification of candidate genes and loci; genetic heterogeneity is common.[2]

Treatment of IGEs with older[11] and newer[12] antiepileptic drugs (AEDs) is demanding. There are two main reasons for this. First, some AEDs of benefit in focal epilepsies are contraindicated in the IGEs.[13] Second, efficacy of AEDs differs even within seizures of IGEs. IGEs usually respond well to appropriate AEDs, but treatment is often life-long. Advice regarding circadian distribution, lifestyle and seizure precipitants is as important as drug treatment.[14] Avoidance of precipitating factors and adherence to long-term medication is essential to avoid seizures. Children and women with IGEs merit special concern and management. The fact that nearly half of patients with IGEs are currently taking 'ill-advised AED' medication[15,16] is a grave problem that needs to be addressed.[17] Misdiagnosis and inappropriate AED treatment are confounding factors accounting for avoidable intractability, morbidity and sometimes mortality.

The IGEs have been extensively reviewed in a recent expert multi-authored supplement of *Epilepsia*,[18] including a thorough historical account by the outgoing President of the ILAE, Peter Wolf.[19]

Considerations on classification

The classification of IGE is controversial. There are two schools of thought with diversely opposing views:

1. IGE is one disease.
2. IGE comprises many distinct syndromes.

In practical terms the view that 'IGE is one disease' would be an overall easy clinical diagnostic approach,

but this would discourage diagnostic precision. The view that 'IGE comprises many distinct syndromes' would be more demanding diagnostically, sometimes requiring exhaustive clinical and video-EEG data, but this is often a price that we have to pay as physicians in pursuing accurate diagnosis, which is the golden rule in medicine. This view also (1) satisfies 'maximum practical application to differential diagnosis', which is a main reason for reorganising the classification of epileptic syndromes, and (2) takes advantage of 'significant advances in our understanding' of IGEs, which constitute a third of 'epilepsy'.

Along these lines there is no justification for the proposed unification of 'IGEs with onset in adolescence'.[20] The major conceptual problem in this proposition is that it takes 'age at onset-adolescence' as the most significant, almost defining factor, which is at variance with the definition of a syndrome.[21] Furthermore, the same IGE syndrome may start in childhood, adolescence and occasionally adult life.[21]

On the surface, syndromes of IGE may look alike if their clinico-EEG manifestations are not properly analysed. For example, juvenile myoclonic epilepsy (JME) and juvenile absence epilepsy (JAE) both manifest with absences, myoclonic jerks and GTCSs. However, severe absences are the main and the most disturbing seizure type in JAE; myoclonic jerks may not occur or may be randomly distributed. Conversely, myoclonic jerks on awakening are the defining symptom of JME; absences are mild and occur in only a third of patients. In addition, video-EEG studies have documented that the clinico-EEG features of typical absence seizures (TAS) are syndrome-related.[22,23] Unifying all TAS as a single type is of no benefit to any cause.

In genetic terms, animal studies have documented numerous syndromes of IGEs[24] and this is likely to also be the case in humans,[23] where new genetic technologies are rapidly identifying specific genes responsible for IGEs.

Syndromes of IGE recognised by the ILAE

The following are IGEs as listed in the new ILAE classification scheme[25] in accordance with the age at onset (Table 5.2):

- benign myoclonic epilepsy in infancy (see Chapter 9)
- epilepsy with febrile seizures plus (EFS+; see Chapter 9)
- epilepsy with myoclonic–astatic seizures (EM-AS)
- epilepsy with myoclonic absences (MAE)
- childhood absence epilepsy (CAE)
- IGEs with variable phenotypes
  - juvenile absence epilepsy (JAE)
  - juvenile myoclonic epilepsy (JME)
  - epilepsy with GTCSs only

Video-EEG documentation of many patients with these syndromes can be found in the companion CD of references.[23,26]

Epilepsy with myoclonic–astatic seizures

Synonym: EM-AS, Doose syndrome.

EM-AS[23,27–36] is considered as an IGE in the new ILAE diagnostic scheme.[25] The diagnosis of this syndrome requires careful application of inclusion and exclusion criteria (Table 13.1). Its characteristic symptom, myoclonic–astatic seizures, is shared by many other childhood syndromes, particularly epileptic encephalopathies.

Diagnostic criteria for idiopathic EM-AS[29,30]

Inclusion criteria

- Normal development prior to the onset of seizures and normal MRI
- Onset of myoclonic, myoclonic–atonic or atonic seizures between 7 months and 6 years of age
- Normal background EEG with 2–3 Hz GPSWD without focal spike discharges

Exclusion criteria

- Dravet syndrome, Lennox–Gastaut syndrome, myoclonic epilepsy in infancy or other epileptic syndromes manifesting with myoclonic–atonic seizures
- Tonic seizures

Table 13.1

Considerations on classification

The new ILAE Task Force considers EM-AS as an IGE,[25] a view which is similar to that of Doose:[29]

> EM-AS belongs to the epilepsies with primarily generalised seizures and thus stands in one line with absence epilepsies, JME, as well as the infantile and juvenile idiopathic epilepsy with GTCS. Like these types of epilepsy, EM-AS is polygenically determined with little non-genetic variability. The disease is characterised by the following criteria: genetic predisposition (high incidence of seizures and/or genetic EEG patterns in relatives); mostly normal development and no neurological deficits before onset; primarily generalised myoclonic, astatic or myoclonic–astatic seizures, short absences and mostly GTCSs; no tonic seizures or tonic drop attacks during daytime (except for some rare cases with a most unfavourable course); generalised EEG patterns (spikes and waves, photosensitivity, 4–7 Hz rhythms), no multifocal EEG-abnormalities (but often pseudofoci).
>
> Doose (1992)[29] on EM-AS

This contrasts markedly with the previous classification of 1989 where EM-AS was listed as a 'cryptogenic/symptomatic' generalised epilepsy in the same group of disorders as that of the Lennox–Gastaut syndrome.[21]

The problem may reflect a lack of specific diagnostic criteria and undefined boundaries of certain epileptic syndromes and particularly the epileptic encephalopathies, which may manifest with myoclonic–astatic seizures. This particularly refers to Dravet syndrome, Lennox–Gastaut syndrome and atypical benign partial epilepsy of childhood. Cases of benign and severe myoclonic epilepsy in infants may have been included in EM-AS.[29] Other myoclonic epilepsies with brief seizures reported as intermediate cases between EM-AS and Lennox–Gastaut syndrome probably prove this point.[37]

However, it is generally accepted that some children with myoclonic–astatic seizures are otherwise normal with no discernible causes other than a strong genetic epileptic background and these probably represent the genuine, idiopathic syndrome of EM-AS (of Doose syndrome to distinguish them from symptomatic or cryptogenic epilepsies with myoclonic–astatic seizures). Kaminska, *et al.* (1999)[38] found evidence that EM-AS is distinct from Lennox–Gastaut syndrome, 'and the distinction appears from the first year of the disorder'.

Another important point to remember is that this syndrome mainly manifests with myoclonic–atonic seizures and these are not synonymous with myoclonic–astatic seizures (see Chapter 2, page 49).

Demographic data

Prevalence may be about 1% to 2% of all childhood epilepsies; two-thirds are boys. Onset is between 7 months and 6 years (peak 2–4 years).

Clinical manifestations

EM-AS is characterised by myoclonic–astatic seizures that often occur together with atonic, myoclonic and absence seizures; myoclonic–astatic status epilepticus is common.

Children are normal prior to the onset of seizures. In two-thirds, febrile and afebrile GTCSs appear first, several months prior to the onset of myoclonic–astatic seizures.

Myoclonic–astatic (in fact, myoclonic–atonic) seizures are the defining symptoms (100% of the cases).[29] These manifest with symmetrical myoclonic jerks immediately followed by loss of muscle tone (post-myoclonic atonia; Figure 13.1).

In addition, atonic and absence seizures occur frequently, sometimes many times per day in the active period of the disease.

Atonic seizures of sudden, brief and severe loss of postural tone may involve the whole body or only the head. Attacks are brief, 1–4 s and frequent. Generalised loss of postural tone causes a lightning-like fall. The patient collapses on the floor irresistibly. In brief and milder attacks there is only head nodding or bending of the knees.

Myoclonic jerks precede or less often intersperse with the atonic manifestations (Figure 13.1).

Absence seizures alone without clinical symptoms, other than impairment of consciousness, are exceptional. However, more than half of the cases have brief absence seizures often together with myoclonic jerks, facial myoclonias and atonic manifestations.

Tonic seizures are an exclusion criterion.

Non-convulsive status epilepticus (myoclonic–atonic status epilepticus) lasting for hours or even days (Figure 13.2) is common, affecting a third of patients. This manifests with varying degrees of usually severe cognitive impairment or cloudiness of consciousness interspersed with repetitive myoclonic and atonic fits. Facial myoclonus of eyelids and mouth may be continuous, together with irregular jerks of the limbs and atonic seizures of head nodding or falls. Myoclonic–atonic status epilepticus may occur several times during a period of 1 or 2 years.

Boy aged 6 with myoclonic–astatic epilepsy

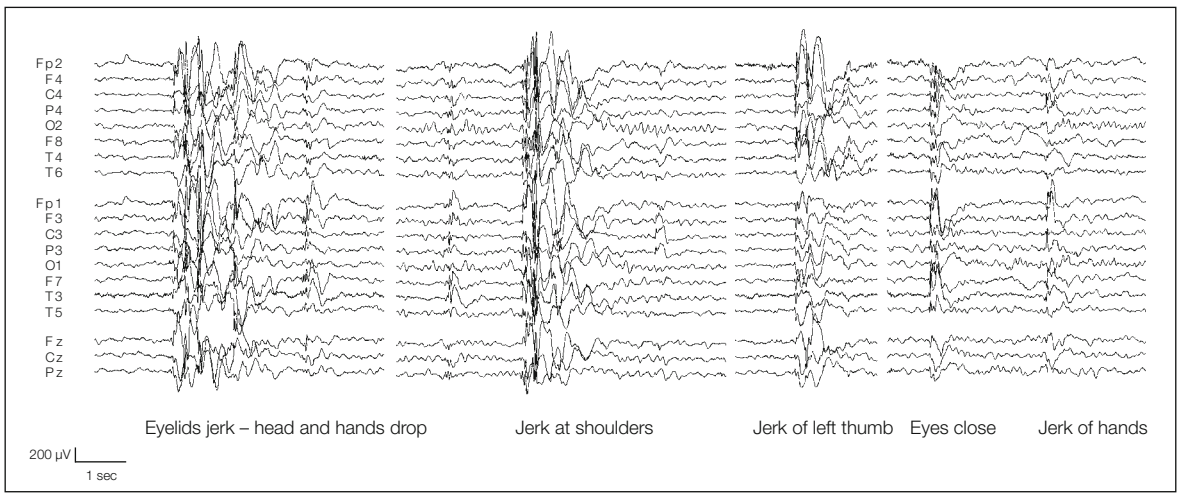

Figure 13.1 Samples from video-EEG of a 6-year-old normal boy with EM-AS. The background activity was normal but there were frequent (at least every 10 s) 3–6 Hz GPSWD with anterior maximum. They were brief for 1–4 s. These were frequently associated with single jerks of mainly the shoulders but also, on other occasions, of the thumb or eyelids. The jerks occurred simultaneously with the first or the second polyspike–wave complex of the discharges. Some jerks were followed by atonic attacks. The EEG also showed brief (<0.5 s) abortive 1.5 Hz GPSWD with anterior maximum and an alternating but not consistent side emphasis. There were no clinical manifestations. The paroxysmal discharges occurred with eyes opened and closed, spontaneously and during overbreathing. IPS did not evoke photoparoxysmal responses.

Boy aged 8 in myoclonic–astatic status epilepticus

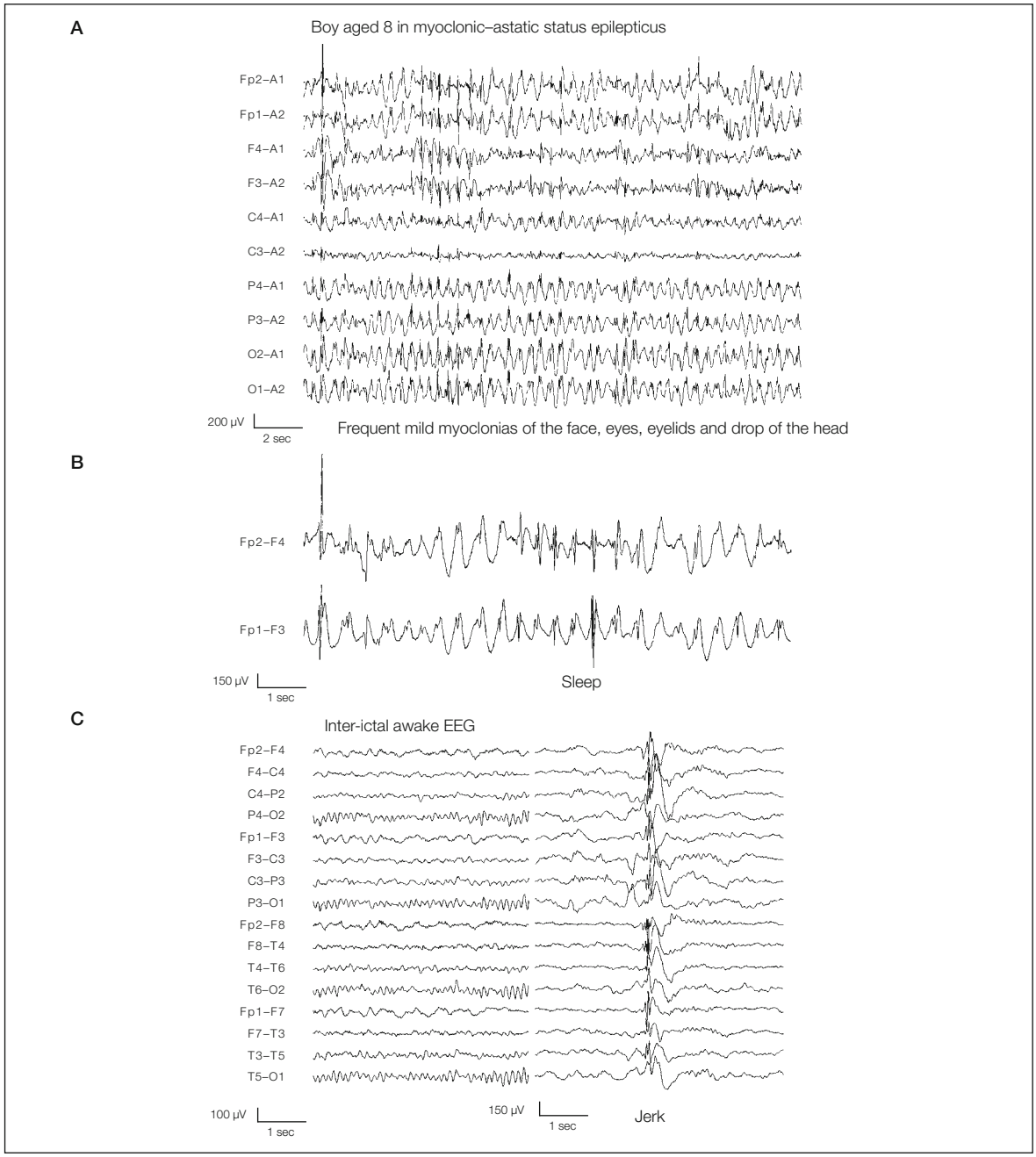

Figure 13.2 Samples of video-EEG of a boy in myoclonic–astatic status epilepticus. (**A**) The EEG showed electrical status epilepticus during wakefulness and sleep. This consisted of nearly continuous 2.5–3 Hz GPSWD. This pattern occasionally alternated with relatively normal background activity lasting <30 s. The main clinical manifestations were frequent facial subtle myoclonias (eyelid fluttering, upwards deviation of the eyes with spontaneous eye opening associated with fast eyelid fluttering, subtle facial twitches) and a few massive myoclonic jerks occasionally with some atonic components. Clinically, there was no apparent impairment of consciousness. (**B**) Details of the EEG shown in (**A**) (note calibration: higher sensitivity and faster speed). (**C**) The video-EEG 1 month later was normal during wakefulness with a few myoclonic jerks only during sleep.

Aetiology

EM-AS may be genetically determined in a multifactorial polygenic fashion with variable penetrance.[27,29,34] A third of patients have familial seizure disorders and mainly IGEs.[27,29,34] Of significant interest are the clinical and molecular studies of EFS+, where myoclonic–atonic seizures are common (see page 265).[31] EFS+ has strong genetic links with Dravet syndrome (see page 266). However, mutations in the SCN1A gene are rarely found in patients with EM–AS.[31,38]

Diagnostic procedures

By definition all tests other than EEG are normal.

Electroencephalography

Inter-ictal EEG may be normal at the stage of febrile or afebrile GTCSs. Rhythmic theta activity in the parasagittal regions may be the only significant abnormality. Subsequently, when myoclonic–atonic seizures appear, there are frequent clusters of 2 or 3 Hz GPSWD interrupted by high-amplitude slow waves in cases with predominant atonic or myoclonic–atonic seizures. In children with predominantly myoclonic seizures, paroxysms of irregular spikes or polyspike–wave complexes prevail.

The *ictal EEG* of myoclonic and atonic seizures manifests with discharges of irregular spike–wave or polyspike–wave complexes at a frequency of 2.5–3 Hz or more (Figures 13.1 and 13.2). Atonia is usually concurrent with the slow wave of a single or polyspike–wave complex, and the intensity of the atonia is proportional to the amplitude of the slow wave. Drop attacks are associated with diffuse electromyography (EMG) paucity indicating their true atonic nature.[30] The myoclonus of EM-AS appears to be a primarily generalised epileptic phenomenon, which differs from that of Lennox–Gastaut syndrome,[40] which originates from the frontal cortex spreading to contralateral and ipsilateral cortical areas.

In myoclonic–atonic status epilepticus, the EEG shows continuous or discontinuous and repetitive 2–3 Hz GPSWD (Figure 13.2).

Differential diagnosis

Differential diagnosis of EM-AS is mainly between benign myoclonic epilepsy in infancy, Dravet syndrome, Lennox–Gastaut syndrome and late-onset West syndrome. In general, children with EM-AS are normal prior to the development of seizures, have a strong family history of IGE, and the background EEG and brain imaging are normal.

Diagnostic tips

The diagnosis of EM-AS is probably secured if myoclonic–atonic seizures start in a previously normal child with pre-existing febrile or afebrile GTCSs and familial seizure disorders (see, however, EFS+).[31]

Differential diagnostic problems from Lennox–Gastaut syndrome probably reflect ill-defined inclusion and exclusion criteria.

Progressive myoclonic epilepsies, such as myoclonic epilepsy with ragged red fibres, Lafora and Unverricht disease, may initially imitate EM-AS. However, their associated relevant neurological abnormalities and, often, their relentless progression and deterioration will establish the diagnosis (see Chapter 17).

Atypical benign partial epilepsy of childhood (see Chapter 10) may also imitate EM-AS, because of repeated falls, absences and diffuse slow-spike–wave activity mainly in the sleep EEG. The main differentiating point is that these children also have nocturnal focal seizures similar to the rolandic seizures that are often the presenting symptom. Also, the EEG shows centrotemporal and other functional spikes in various locations.

Atypical evolutions of rolandic epilepsy[41,42] *and Panayiotopoulos syndrome*[43,44] may present with similar features as EM-AS, but these follow the typical presentations of these syndromes (see Chapter 12). A similar, but reversible, clinico-EEG condition may be induced by carbamazepine,[45] oxcarbazepine[46] and lamotrigine[47] in a few children with rolandic seizures or Panayiotopoulos syndrome.[48] This possibility should be considered in children with benign focal

seizures and dramatic deterioration after treatment with these AEDs.

Children with 'epilepsy with continuous spike-and-wave during sleep' (see Chapter 10) may also have drop attacks due to atypical absences or negative myoclonus.

Non-epileptic myoclonus may rarely raise a diagnostic problem with EM-AS.

Prognosis

Prognosis is unclear, probably because of different inclusion and exclusion criteria. Half of patients achieve a seizure-free state and normal or near-normal development. These may correspond to the idiopathic form of EM-AS (of Doose syndrome). Spontaneous remission with normal development has been observed in a few untreated cases but these may belong to myoclonic epilepsy in infancy. The others, probably belonging to symptomatic or cryptogenic cases or other syndromes continue with seizures, severe impairment of cognitive functions and behavioural abnormalities. Ataxia, poor motor function, dysarthria and poor language development may emerge.

Management

Drug therapy is dictated by the type of seizure. Valproate, which is effective in myoclonic jerks, atonic seizures and absences, is the most efficacious of the AEDs. Add-on small doses of lamotrigine have a beneficial pharmacodynamic interaction with valproate. Topiramate reduces the frequency of atonic seizures[49] and levetiracetam may be an effective therapeutic option.[12,50]

In resistant cases, ketogenic diet, alone[51] or followed by adrenocorticotrophic hormone (ACTH) and ethosuximide, have been found to be highly beneficial.[52] Benzodiazepines, acetazolamide, sulthiame and even bromides are also used.

Carbamazepine, phenytoin and vigabatrin are contraindicated (Table 13.7).

In myoclonic–atonic status epilepticus, intravenous benzodiazepines are often efficacious, but may, rarely, precipitate tonic status epilepticus.

Childhood absence epilepsy

CAE[23,53,54] is the prototype IGE of typical absence seizures (TAS).[55] It is genetically determined, age related and affects otherwise normal children. Table 13.2 lists inclusion and exclusion criteria.

Considerations on classification

The ILAE Commission of 1989[21] defines CAE by age at onset and the frequency of absences:

> CAE (pyknolepsy) occurs in children of school age (peak manifestation age 6–7 years), with a strong genetic predisposition in otherwise normal children. It appears more frequently in girls than in boys. It is characterised by very frequent (several to many per day) absences. The EEG reveals bilateral, synchronous symmetrical spike–waves, usually 3 Hz, on a normal background activity. During adolescence, GTCSs often develop. Otherwise, absences may remit or more rarely, persist as the only seizure type.[21]

The new ILAE reports initially classified CAE as an IGE,[25] but later simply listed it among other syndromes of childhood (Table 5.2).[56]

The ILAE definition[21] is very broad and requires revision.[55] Otherwise, any type of frequent absence seizures occurring in childhood would be erroneously equated with CAE. Because of this ambiguity, the epidemiology, genetics, age at onset, clinical manifestations, other types of seizure,

Inclusion and exclusion criteria for CAE

Inclusion criteria for CAE

- Age at onset between 4 and 10 years and a peak at 5–7 years
- Normal neurological state and development
- Brief (4–20 s, exceptionally longer) and frequent (tens per day) absence seizures with abrupt and severe impairment (loss) of consciousness. Automatisms are frequent but have no significance in the diagnosis
- EEG ictal generalised discharges of high-amplitude spike and double or maximum triple spike and slow-wave complexes. They are rhythmic at around 3 Hz with a gradual and regular slowdown from the initial to the terminal phase of the discharge. Their duration varies from 4 to 20 s (exceptionally longer)

Exclusion criteria for CAE

The following may be incompatible with CAE:

- Other types of seizure, such as GTCSs, or myoclonic jerks prior to or during the active stage of absences
- Eyelid myoclonia, perioral myoclonia, rhythmic massive limb jerking, and single or arrhythmic myoclonic jerks of the head, trunk or limbs. However, mild myoclonic elements of the eyes, eyebrows and eyelids may be featured – particularly in the first 3 s of the absence seizure
- Mild or no impairment of consciousness during the 3 Hz discharges
- Brief EEG 3 Hz spike–wave paroxysms of <4 s, polyspikes (more than three) or ictal discharge fragmentations
- Visual (photic) and other sensory precipitation of clinical seizures

Table 13.2 *Reproduced from Loiseau and Panayiotopoulos.*[54]

long-term prognosis and the treatment of CAE that are reviewed in this chapter may not accurately reflect the syndrome of CAE. It is also because of this ambiguity that some authors: (1) have divided patients with childhood-onset absence seizures into 'sub-syndromes', including those who remit, those who persist into adolescence and develop GTCSs, and those who develop both GTCSs and myoclonic seizures during adolescence;[57] and (2) consider that CAE 'evolves' into JAE or JME.[58]

The inclusion and exclusion criteria of Table 13.2 proposed by Loiseau and Panayiotopoulos[54] for CAE should not be taken as an extreme position. They do not differ significantly from the ILAE (1989)[21] criteria of CAE with:

- age at onset in childhood
- very frequent (several to many per day) absences, presumably with severe impairment of consciousness
- ictal EEG with bilateral, synchronous and symmetrical 3 Hz GSWD, on a normal background activity (that presumably excludes fragmented, asymmetrical and asynchronous 3–5 Hz GSWD with intra-discharge variations)
- GTCSs accepted only if they develop later in adolescence.

Also, the ILAE Commission (1989),[21] by accepting 'epilepsy with myoclonic absences' as a separate syndrome, differentiates myoclonic absences from typical absences of CAE. It is along this line that eyelid myoclonia (which is a predominantly myoclonic and less of an absence syndrome) is counted as an exclusion criterion. Whether, perioral myoclonia or single violent jerks during the ictus of an absence seizure is an exclusion criterion may be debatable. However, their presence indicates a worse prognosis (see relevant syndromes). The same applies to polyspikes (more than three spikes per wave), which

also indicate a bad prognosis,[57,59] or the coexistence of myoclonic jerks or GTCSs.[22]

Furthermore, by accepting 'typical absence seizures consistently provoked by specific stimuli' as a specific type of reflex seizures, the ILAE Commission (1989)[21] indicates that these may be a separate group from CAE.

A recent report on CAE[60] well reflects the misunderstanding surrounding this syndrome (Table 13.3). It is used here as an example to emphasise the points made in this chapter and for the differentiation of IGEs with absence seizures in general:[55]

- The report defines TAS 'as a clinical change associated with generalised spike-and-slow-wave activity or multiple-spike-and-slow-wave activity with a frequency of >2.5Hz at onset'. Whether this clinical change always involved impairment of consciousness is not stated. Impairment of consciousness (absence) is a prerequisite of any definition of TAS. This may be associated with other clinical symptoms (myoclonic, atonic, clonic, autonomic), but these do not constitute TAS without clinically detectable impairment of consciousness.
- The diagnostic criteria for CAE applied in the report are clearly different, not only from those in Table 13.2, but also from the 1989 ILAE definition;[21] the age range was lowered to include children as young as 2 or 3 years old and the seizure frequency was broadened to include 'daily' absences, but not 'several per day' (i.e. pyknolepsy).
- No follow-up is provided despite the original presentation of the patients between 1992 and

Electroclinical features of a heterogeneous group of children thought to have CAE[60]

Electroclinical features*	No. of patients	Epileptic syndromes that these features are more likely to manifest	Exclusion criterion of CAE?
A. Duration of seizure <4 s	21	JME, EMA	Yes
B. Age of child <4 years	7	EMA, PMA, MAE	Probably yes (exceptional)
C. No severe impairment of consciousness during seizure	16	All other IGEs with absences but CAE and JAE	Yes
D. Myoclonic features in seizures except mild in eyes, eyebrows and eyelids	12	MAE, PMA, EMA	Yes if severe and consistent during the absence†
E. Photic induction of seizures	8	EMA, IGE with photosensitivity	Yes if this is a consistent provocation of clinical seizures
F. More than three spikes per wave	13	JME, EMA	Probably yes if consistent in the whole duration of the discharge†
G. Disorganised discharges	25	JME, PMA, EMA	Yes if consistent in the whole duration of the discharge†

Table 13.3 *The electroclinical features listed were used by Sadleir, *et al*[60] to define CAE. †Onset of absences (first 1 or 2 s) used by the authors for the measurement of the frequency of spike–wave discharges is usually unreliable to make this and other assessments because of variable clinical and EEG manifestations that do not persist in the remainder of the ictal discharge (Figure 13.3).[22] The same patient may have different onsets of consecutive absences even within the same EEG. Myoclonic jerks, disorganised discharges, more than three spikes per spike–wave complex and fast or slow spike–wave can all occur in the first second of absence seizures in CAE. In accordance with well-documented video-EEG studies, JME is likely to have features A, C, F and G; epilepsy with myoclonic absences (MAE) or perioral myoclonia with absences (PMA) certainly have D; and eyelid myoclonia with absences (EMA) has A–G.

1997. It is to be expected that most of them will now be in remission (as for 'true' CAE) or will have developed the full features of other IGEs and conditions with absences starting in childhood, as suggested in Table 13.3.[55]

Demographic data

Onset is between 4 and 10 years of age (peak at 5–7 years). Two-thirds are girls. Prevalence is about 10% and annual incidence rate is approximately 7/100,000 of children with epileptic seizures younger than 15 or 16 years of age.

Clinical manifestations

CAE manifests with the most classical example of TAS.[55,61] Absences are severe and frequent, with tens or hundreds per day (hence the term pyknolepsy).[62] They are of abrupt onset and abrupt termination (Figure 13.3). Their duration varies from 4 to 20 s, although most of them last around 10 s. Clinically, the hallmark of the absence is abrupt, brief and severe impairment of consciousness with unresponsiveness and interruption of the ongoing voluntary activity, which is not restored during the ictus. The eyes spontaneously open, overbreathing, speech and other voluntary activity stops within the first 3 s from the onset of the ictal electrical discharge. Automatisms occur in two-thirds of the seizures but are not stereotyped. The eyes stare or move slowly. Mild myoclonic elements of the eyes, eyebrows and eyelids may feature in CAE in the first 1–3 s of the absence. However, more severe and sustained myoclonic jerks of facial muscles may indicate other IGEs with absences.

The attack ends as abruptly as it has commenced, with sudden resumption of the pre-absence activity as if it had not been interrupted. TAS are nearly invariably provoked by hyperventilation.

Other seizures are not compatible with CAE. The only exception is febrile convulsions prior to the onset of absences and solitary or infrequent GTCSs long after the onset of TAS (usually in adolescence after absences have remitted).

Aetiology

Although CAE is genetically determined, the precise mode of inheritance and the genes involved remain largely unidentified.[2,63] In monozygotic twins, 84% had 3 Hz GSWD and only 75% of pairs had clinical absence seizures. These events occurred 16 times more often than in dizygotic twins.[64]

Recently, loci at various chromosomes (1p, 8q24, 5q31.1 and 19p13.2) have been identified in families with absences of childhood onset (not necessarily equated with CAE). Furthermore, current evidence suggests that mutations in genes encoding GABA receptors[65] or brain-expressed voltage-dependent calcium channels[66,67] may underlie CAE.

Acquired factors may play a facilitating role.

Diagnostic procedures

In typical cases, only EEG is needed.

Electroencephalography

Inter-ictal EEG in CAE has normal background, with frequent rhythmic posterior delta activity, which may be a good prognostic sign.[68] Focal spikes are common.[45,69]

Diagnostic tips

TAS of CAE are easy to diagnose and reproduce by hyperventilation

Any child with sudden, brief and transient cessation of physical and mental activity should be tested clinically for absences with the hyperventilation test and the events should be video-recorded. See blue box on page 56.

Ictal discharges consist of 3 Hz GSWD. Spikes are single, double or occasionally triple in the spike and slow-wave complexes (Figure 13.3).[22] The GSWD are rhythmic at around 3 Hz (2.5–4 Hz), with a gradual and regular slow down of the frequency by 0.5–1 Hz from the initial to the terminal phase of the discharge. The opening phase of the discharge, 1 or 2 s from the onset, is usually fast and unreliable for these measurements. There are no marked variations in the relation of spike to slow wave, no fluctuations

in the intradischarge frequency and certainly no fragmentations of the ictal discharges (Figure 13.3).

Differential diagnosis

CAE should be the easiest type of epileptic syndrome to diagnose because seizures have abrupt onset and termination, have daily frequency and are nearly invariably provoked by hyperventilation. A child suspected of typical absences should be asked to perform the hyperventilation test as this will provoke an absence in as many as 90% of those who suffer from it.

CAE is not synonymous with any type of absence seizures starting in childhood. Therefore, other epilepsy syndromes with absence seizures that may be life-long and have a worse prognosis should be meticulously differentiated from CAE.

Diagnosis should improve with heightened awareness and video-EEG studies. Exclusion criteria for CAE are significant (Tables 13.2 and 13.3).

Video-EEG of an 8-year-old boy with classical CAE

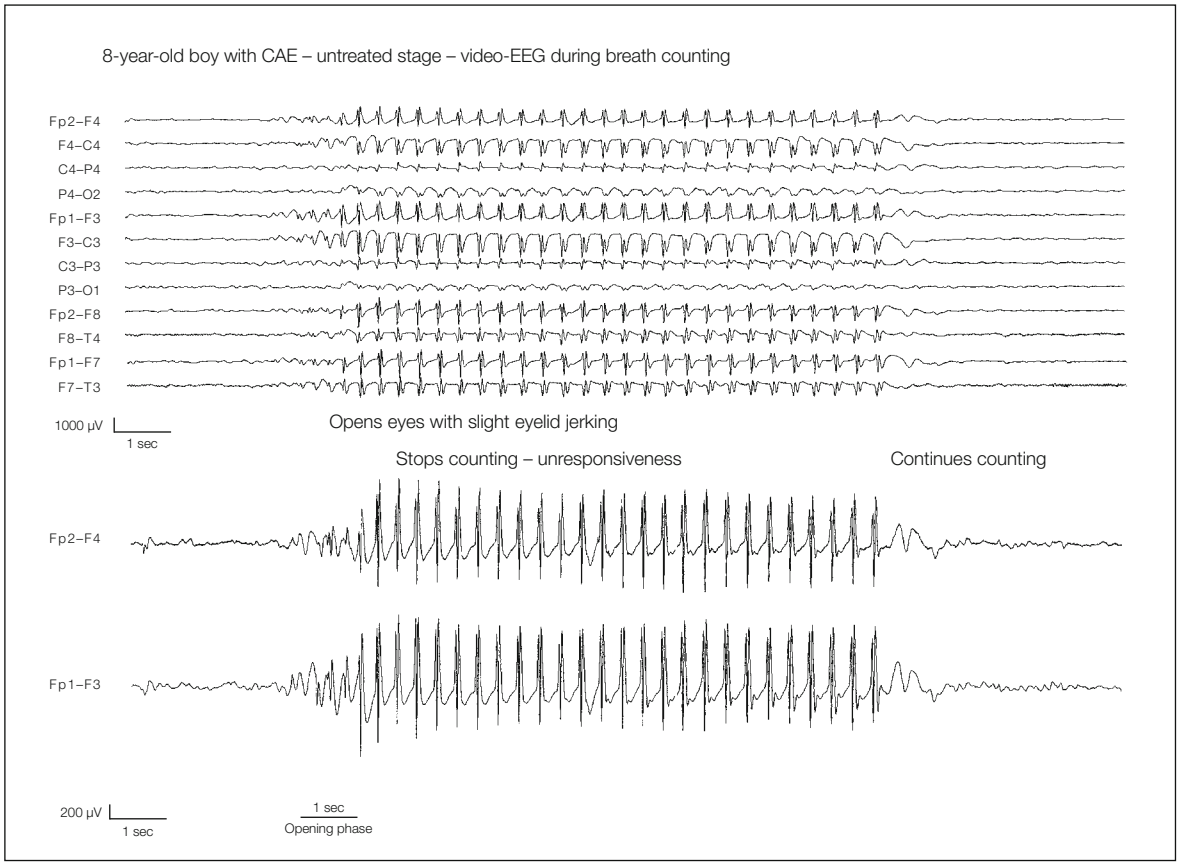

Figure 13.3 He was referred for an EEG because of 'blanks and day dreaming'. The diagnosis had been overlooked despite frequent absences for 2 years, which also interfered with his scholastic performance. The illustrated seizure had all the characteristic features of typical absences in CAE. Initially there was some brief eyelid flickering in the opening phase of the GSWD followed by opening of the eyes, eyes and head deviating upwards and to the right, and simultaneous cessation of breath counting. He remained unresponsive during the rest of the GSWD. Counting was restored immediately after the end of the GSWD. Note, the fast and asymmetrical onset of the GSWD in the opening phase during the first second. Subsequently, the GSWD was entirely rhythmical and regular with abrupt termination to clinical and EEG normality.

Automatisms have no significance in the diagnosis. They should not be taken as evidence of complex focal seizures, which require entirely different management (Table 2.7).

Prognosis

> For myself I shall be well satisfied if I have made it appear probable to you that there does exist a form of epilepsy in children which is distinguishable by its clinical features and in which the prognosis is always good.
>
> Adie (1924)[62] on pyknolepsy (CAE)

By applying strict criteria for diagnosis, the prognosis of CAE is excellent,[54,61,70] as Adie had found.[55] Remission occurs before the age of 12 years. Less than 10% of the patients may develop infrequent or solitary GTCSs in adolescence or adult life. It is exceptional for patients to continue having absence seizures in their adult life.

Poor social adjustment of patients with CAE has been reported.[61] A more recent report[71] found that of 69 children diagnosed but not necessarily suffering from genuine CAE, 25% of had subtle cognitive deficits, 43% linguistic difficulties, 61% a psychiatric diagnosis, particularly attention deficit hyperactivity disorder and anxiety disorders, and 30% clinically relevant attention and somatic complaints, followed by social and thought problems. Duration of illness, seizure frequency, and AED treatment were related to the severity of the cognitive, linguistic, and psychiatric comorbidities.[71] The same authors in another report found that brain MRI showed significantly smaller grey matter volumes of the left orbital frontal gyrus as well as both left and right temporal lobes compared to children without epilepsy.[72] Male gender and an earlier age of diagnosis may be associated with the need for two medications for seizure control in CAE.[73]

Management[54,74,75]

Monotherapy with either valproate or ethosuximide controls absences in 80% of patients.[75] Another option is lamotrigine monotherapy, although this is less effective with around half of patients becoming seizure free.[75–77]

If monotherapy fails or unacceptable adverse reactions appear, the used drug should be replaced by another. Adding small doses of lamotrigine to valproate may be the best combination in resistant cases.

There are anecdotal reports that children may not respond to syrup of valproate despite adequate levels, but seizures stop if this is replaced with tablets of valproate.[75] Sometimes seizures stop only with maximum tolerated doses of valproate. It is my experience that once seizure cessation has been achieved, valproate may be safely reduced to more moderate doses without relapses.[75]

Contraindicated drugs, either because they are ineffective or make seizures worse, are carbamazepine, gabapentin, oxcarbazepine, phenytoin, phenobarbital, pregabalin, tiagabine and vigabatrin.

Withdrawing anti-epileptic medication: in the pure form of CAE, drug therapy can be gradually withdrawn (over 3–6 months) after 2 or 3 years free of seizures.

Epilepsy with myoclonic absences

Epilepsy with myoclonic absences (MAE)[78–82] is a rare IGE syndrome of childhood that demands scrupulous exclusion of other forms of symptomatic and cryptogenic cases manifesting with the same seizure (myoclonic absences).

Considerations on classification

Myoclonic absences (the seizures) may feature either in normal or neurologically and mentally

abnormal children.[61,80–82] MAE was previously categorised among the 'cryptogenic or symptomatic generalised epilepsies and syndromes'.[21] The new ILAE diagnostic scheme considers only the idiopathic form (Table 5.2),[25] which probably represents less than a third of the whole spectrum of epileptic disorders manifesting with myoclonic absences. The others are symptomatic or probably symptomatic cases.[21]

Demographic data

Onset varies from the first months of life to the early teens (peak 7 years). Boys predominate. MAE is very rare. I have seen only three cases over a period of 15 years out of nearly 200 patients with video-EEG-recorded TAS.[22,23]

Clinical manifestations

The myoclonic absences are the defining symptom of MAE (Figure 13.4). These manifest with impairment of consciousness, which varies from mild to severe, and rhythmic myoclonic jerks, mainly of the shoulders, arms and legs, with a concomitant tonic contraction. Eyelid twitching is practically absent but perioral myoclonias are frequent. The jerks and the tonic contraction may be unilateral or asymmetrical and head/body unilateral deviation may be a constant feature in some patients. The tonic contraction mainly affects shoulder and deltoid muscles that may cause elevation of the arms. The duration of the absences varies from 8 to 60 s. Myoclonic absences occur many times per day.

Absence status epilepticus is rare.

Other seizures, such as GTCSs or atonic fits, occur in two-thirds of patients, often predicting an unfavourable prognosis (these are probably symptomatic cases).

Aetiology

Myoclonic absences (the seizures, not the syndrome) are due to idiopathic, cryptogenic or symptomatic causes including chromosomal abnormalities.[83] A third are idiopathic and only these belong to this syndrome.

Diagnostic procedures

By definition, in MAE all other tests but EEG should be normal. Brain MRI and chromosomal testing[83] are needed for the detection of symptomatic cases.

Electroencephalography

Background EEG is usually normal at onset but may deteriorate or be abnormal in symptomatic cases. In half of cases, inter-ictal EEG shows brief, generalised, focal or multifocal spike and slow wave.

Ictal EEG shows rhythmic 3 Hz GPSWD even in those with unilateral or asymmetrical clinical manifestations (Figure 13.4). Polygraphic studies have revealed that each myoclonic jerk coincides with the spike component of the discharge.[80,82]

Differential diagnosis

The differential diagnosis of MAE from other syndromes with absences is easy because of the characteristic type of myoclonic absences. The difficulty is between idiopathic and symptomatic/cryptogenic cases that manifest with the same seizure type (myoclonic absences). Symptomatic cases often have an abnormal neurological state, abnormal background EEG and abnormal brain MRI. Chromosomal abnormalities are common.[83] Additionally, absences with rhythmic myoclonic jerking but less than 2.5 Hz GPSWD and other characteristics of atypical absences may occur in epileptic encephalopathies,[84,85] and these may account for some of the cases with chromosomal abnormalities.[83]

Prognosis

Nearly half of children with MAE have impaired cognitive functioning prior to the onset of absences, but these are probably symptomatic cases. However, half of those who were normal prior to the onset of absences develop cognitive and behavioural impairment. This may mean a deteriorating effect of the EEG discharges on cognition.

Management

Myoclonic absences are often resistant to treatment. Half of patients (probably the symptomatic ones) continue having seizures in adult life, developing

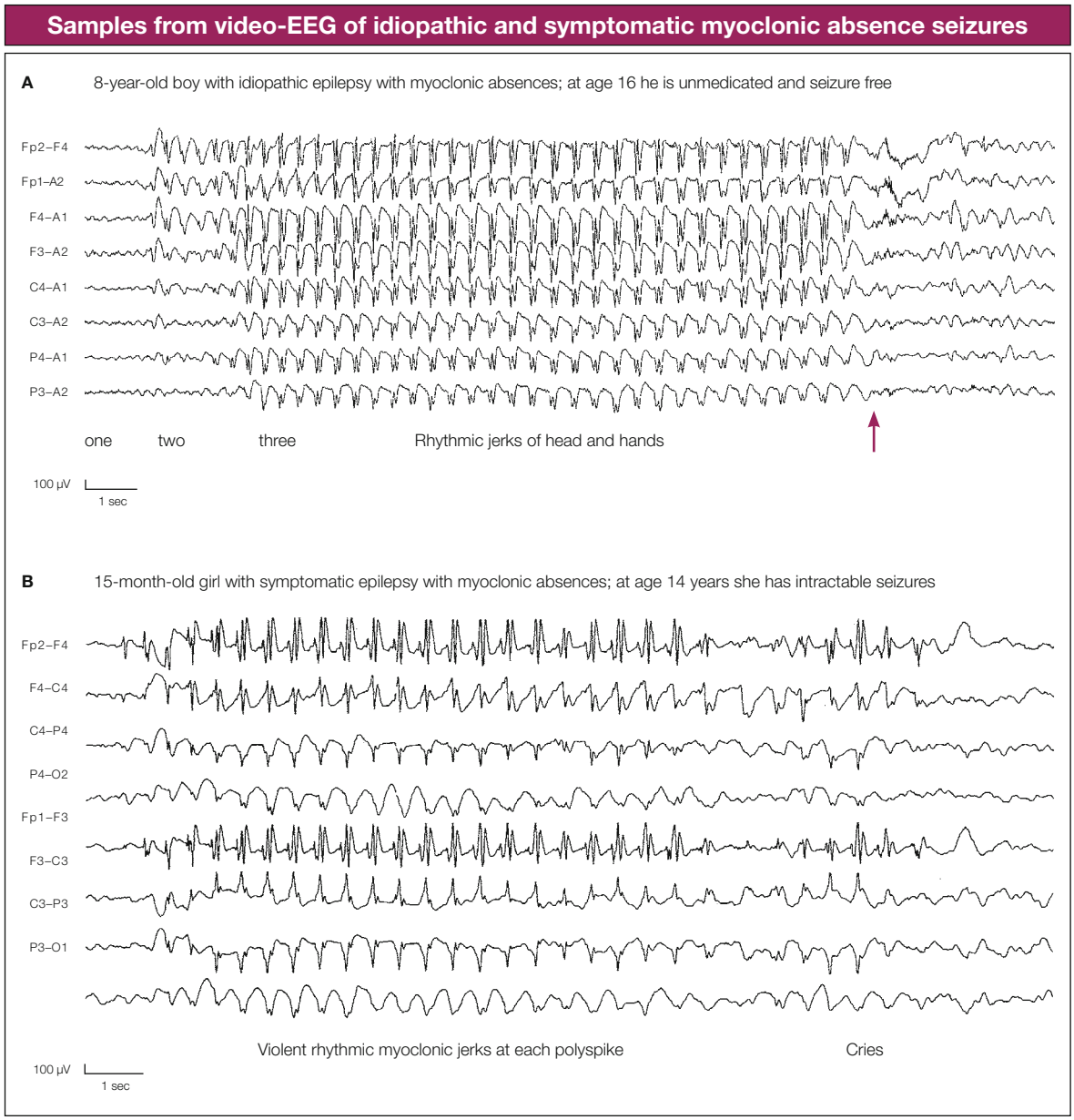

Figure 13.4 (**A**) A video-EEG of a normal boy aged 8 years with myoclonic absences from age 6. The illustrated absence occurred during hyperventilation with breath counting (annotated) and it was terminated with somatosensory stimuli by tapping his shoulder (red arrow). Myoclonic absences were frequent, hundreds per day, and manifested with rhythmic myoclonic jerks and unresponsiveness. Valproate failed to achieve control, but absences ceased completely when ethosuximide was added to valproate at age 8. Medication was withdrawn at age 11. No further seizures occurred in the next 8 years of follow-up and he is academically successful. (**B**) Girl aged 15 months with myoclonic absences due to birth anoxia. Typical absence seizures started at 15 months of age. These were many per day, lasted for 8–10 s and were characterised by synchronous and bilateral myoclonic jerks of limbs and head with apparent loss of consciousness. Subsequently, she developed frequent, mainly nocturnal GTCSs, while myoclonic absences continued. These were intractable to any appropriate medication. At age 14 years she has significant learning difficulties, spastic paraparesis and numerous epileptic seizures. See video-EEG of these cases in the companion CD of *The Epilepsies: Seizures, Syndromes and Management*.[23]

features of other types of epilepsy such as Lennox–Gastaut syndrome or JME.

Early control of absences may prevent subsequent cognitive deterioration and secure normal development. Treatment frequently requires high doses of valproate often combined with ethosuximide or small doses of lamotrigine. Clonazepam and acetazolamide may be used in polytherapy.

Juvenile absence epilepsy

Juvenile absence epilepsy (JAE) is an IGE syndrome[21,25,86] mainly manifesting with severe TAS. Nearly all patients (80%) also suffer from GTCSs and a fifth from sporadic myoclonic jerks.[22,23,87,88]

Considerations on classification

The ILAE Task Force has not yet reached definite conclusions regarding the definition of JAE, although there is a tendency to consider JAE as part of a broader syndrome of IGE in adolescence.[20,25]

The 1989 ILAE classification broadly defined JAE by frequency of absences (less frequent than of CAE) and age at onset (around puberty).[21] These are insufficient criteria for the categorisation of any syndrome.[74] Thus, epidemiology, genetics, age at onset, clinical manifestations, other types of seizure, long-term prognosis and treatment may not accurately reflect the syndrome of JAE. JAE can be accurately defined on a cluster of video-EEG-studied clinical and EEG manifestations (Table 13.4).[22,86]

Main inclusion and exclusion criteria for JAE

Inclusion criteria for JAE

- Unequivocal clinical evidence of absence seizures with severe impairment of consciousness. Nearly all patients may have GTCSs. A fifth have myoclonic jerks, but these are mild and do not show the circadian distribution of JME
- Documentation of ictal 3–4 Hz GPSWD, >4 s, that are associated with severe impairment of consciousness and often with automatisms. Normal EEG in treated patients are common

Exclusion criteria for JAE

The following may be incompatible with JAE

Clinical exclusion criteria:

- Absences with marked eyelid or perioral myoclonus or marked single or rhythmic limb and trunk myoclonic jerks
- Absences with exclusively mild or clinically undetectable impairment of consciousness
- Consistent visual, photosensitive and other sensory precipitation of clinical absences is probably against the diagnosis of JAE. However, on the EEG, intermittent photic stimulation often facilitates generalised discharges and absences

EEG exclusion criteria:

- Irregular, arrhythmic GPSWD with marked variations of the intradischarge frequency
- Significant variations between the spike/polyspike and slow wave relations in GPSWD
- Predominantly brief discharges (<4 s)

Table 13.4

Demographic data

Peak age at onset is 9–13 years (70% of patients) but range is from 5 to 20 years.[86,88] Myoclonic jerks and GTCSs usually begin 1–10 years after the onset of absences. Rarely, GTCSs may precede the onset of absences.[86,87] Both sexes are equally affected. Exact prevalence of JAE is not known because of variable criteria. In adults older than 20 years, prevalence of JAE may be around 2% or 3% of all epilepsies and around 8–10% of IGE.[89,90]

Clinical manifestations

Frequent and severe typical absences are the characteristic and defining seizures of JAE (Figure 13.5). The usual frequency of absences is approximately one to ten per day but this may be much higher for some patients.[86–88] Nearly all patients also develop GTCSs and a fifth of them also suffer from mild myoclonic jerks.

Typical absences are severe and frequent, often daily, and very similar to those of CAE, although they may be milder. The hallmark of the absence is abrupt, brief and severe impairment of consciousness with total or partial unresponsiveness. Mild or inconspicuous impairment of consciousness is not compatible with JAE. The ongoing voluntary activity usually stops at onset but may be partly restored during the ictus. Automatisms are frequent, usually occurring 6–10 s after the onset of the EEG discharge (Figure 13.6). In JAE, mild myoclonic elements of the eyelids are common during the absence. However, more severe and sustained myoclonic jerks of facial muscles may indicate another IGE with absences. Severe eyelid or perioral myoclonus, rhythmic limb jerking and single or arrhythmic myoclonic jerks of the head, trunk or limbs during the absence ictus are probably incompatible with JAE.

Duration of the absences varies from 4 to 30 s but it is usually long (about 16 s).

GTCSs are probably unavoidable in untreated patients. GTCSs occur in 80% of patients, mainly after awakening, although nocturnal or diurnal GTCSs may also be experienced.[86–89,91,92] GTCSs are usually infrequent but they may also become severe and intractable.

Myoclonic jerks occurring in 15–25% of the patients are infrequent, mild and of random distribution. They usually occur in the afternoon hours when the patient is tired, rather than in the morning after awakening.[86,93]

Absence status epilepticus is truly generalised non-convulsive (without any type of jerks or convulsions) and occurs in a fifth of patients.[94]

Seizure-precipitating factors

Mental and psychological arousal is the main precipitating factor for typical absences. Conversely, sleep deprivation, fatigue, alcohol, excitement and lights, alone or usually in combination, are the main precipitating factors for GTCSs.

Some authors reported that 8% of JAE patients suffered from photosensitivity clinically or on EEG.[87] However, clinical photosensitivity, which is a consistent provocation of seizures (absences, GTCSs or jerks), may be incompatible with JAE. These patients may belong to other IGEs.[86] EEG photosensitivity that is facilitation of absences by IPS may not be uncommon.

Aetiology

JAE is determined by genetic factors but its mode of transmission and relation to other forms of IGE, particularly CAE and JME, has not yet been established; a single Mendelian mode appears to be unlikely.

There is an increased incidence of epileptic disorders in families of patients with JAE and there are reports of monozygotic twins with JAE.[22,88,95] A proband with JAE was found in three of 37 families selected because at least three members were affected by IGE in one or more generations.[96] However, only one sibling also had JAE, while other members mainly had GTCSs.[96]

JAE may be linked to chromosome 8,[97] 21,[98] 18[99] and probably 5.[99] Heterogeneity may be common. Autopsy[100] and MRI studies[101] found microdysgenesis and other cerebral microstructural changes in patients with JAE.

Diagnostic procedures

All but EEG tests are normal.

Electroencephalography

The EEG in untreated patients is abnormal with absences easily elicited by hyperventilation (Figure

13.5). The background inter-ictal EEG is normal. Focal epileptiform abnormalities and abortive asymmetrical bursts of spikes/polyspikes are common.

The ictal EEG shows 3–4 Hz GPSWD. The frequency at the initial phase of the discharge is usually fast (3–5 Hz). There is a gradual and smooth decline in frequency from the initial to the terminal phase. The discharge is regular, with well-formed spikes and polyspikes, which retain a constant relation with the slow waves (Figure 13.5).

Differential diagnosis

In general, and particularly in adults, absences are often misdiagnosed as complex focal seizures, although their differentiation is easy (Table 2.7).[102]

The differentiation of JAE from other IGEs with absences may be more difficult without appropriate video-EEG evaluation.[22,86] In children, it is often difficult to distinguish between CAE and JAE, because their features overlap and manifestations are similar. In JAE absences often start at a later age, usually they are less frequent and impairment of cognition is less severe.[22] Automatisms are equally prominent in both. Limb myoclonic jerks (not during the absences) and/or GTCSs in the presence of severe absences, indicate JAE.

JAE is distinctly different from Jeavons syndrome of very brief seizures marked with rapid eyelid myoclonia (Chapter 16), perioral myoclonia with absences (PMA) of rhythmic perioral myoclonia during the absence, and MAE of rhythmic myoclonic jerks.

In adolescents, the differential diagnosis should not be difficult between JAE and JME (Table 13.5). Severe absences are the major problem in JAE; myoclonic jerks are the main seizure type in JME. Absences in JME are mild and often inconspicuous.

Prognosis

JAE is a life-long disorder although seizures can be controlled in 70–80% of patients. However, there is a tendency for the absences to become less severe in terms of impairment of cognition, duration and frequency with age and particularly after the fourth decade of life. GTCSs are usually infrequent, often

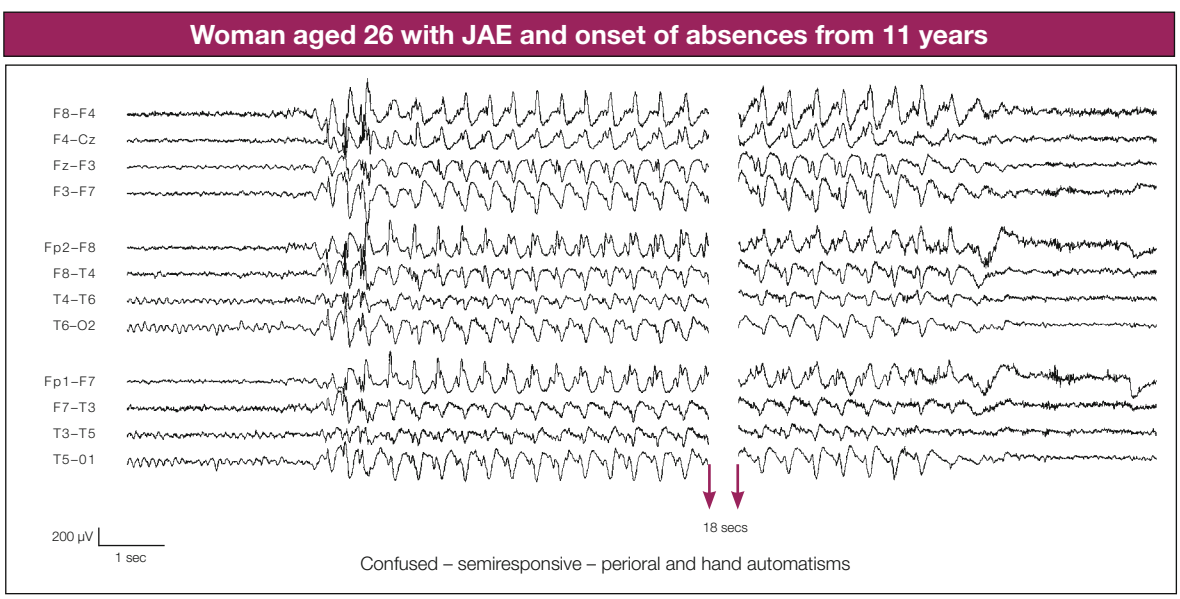

Figure 13.5 From video-EEG of a 26-year-old normal woman. She started having frequent (tens per day) typical absence seizures with severe impairment of consciousness at age 11 years. At age 14 years she had her first GTCS. Since then, long absences of 20–30 s continue daily. Also she has three to five GTCSs every year, mainly in the morning after awakening. These are preceded by clusters of absences. Occasionally, she also has random, infrequent and mild limb myoclonic jerks, which started at age 20. Treatment with various appropriate anti-absence drugs resulted in minor improvement, but compliance varies.

Key differences between JME and JAE

	JME	JAE
Main type of seizures	Myoclonic jerks	Typical absences
Circadian distribution	Mainly on awakening	Any time during the day
Typical absences	Mild and often imperceptible; they occur in a third of patients	Defining seizure type; they are very severe and occur in all patients
Myoclonic jerks	Defining seizure type; they occur in all patients and mainly on awakening	Mild; they occur in a fifth of patients and are random
GTCS	They mainly occur after a series of myoclonic jerks on awakening	They mainly occur independently or less commonly after a series of absence seizures
EEG	Brief (1–3 s) 3–6 Hz GPSWD, which are usually asymptomatic	Lengthy (8–30 s) 3–4 Hz GPSWD, which are usually associated with severe impairment of consciousness

Table 13.5

precipitated by sleep deprivation, fatigue and alcohol consumption. Myoclonic jerks, if present, are not troublesome for the patient. A fifth of the patients have frequent and sometimes intractable absences and GTCSs, and this figure may be higher if appropriate treatment is not initiated at early stages of JAE.

Management

The treatment of IGE is detailed from page 411. In JAE, the consensus is that, because of the frequent combination of absences and GTCSs, the drug of choice is valproate, which controls all seizure types in 70–80% of the JAE patients. Lamotrigine, which controls absence seizures and GTCSs in around 50–60% of patients, is probably another good monotherapy option in cases, for example in women, where valproate is unsuitable.

If monotherapy with valproate is partially effective, add-on treatment with small doses of lamotrigine (particularly if GTCS is the problem) or ethosuximide (particularly if absences persist) may further improve or control the situation.

Control of absences is usually (90%) associated with good control of GTCSs and it is adversely affected by the frequency and the duration of GTCSs before starting valproate treatment.

Levetiracetam is formally indicated for GTCS and myoclonic jerks of IGEs as documented with RCTs.[103,104] Recent evidence suggests that levetiracetam is also effective in absences seizures of IGEs including juvenile absence epilepsy.[105–108]

The role of other newer drugs such as topiramate and zonisamide has not been properly evaluated.

Patients should be warned regarding precipitating factors of GTCS.

Treatment may be life-long because attempts to withdraw medication nearly invariably leads to relapses, even after many years free of seizures.

Juvenile myoclonic epilepsy

Synonym: JME, Janz syndrome.

This syndrome is one of the most important IGEs that is genetically determined.[109–113] The frequent errors in its diagnosis and management are avoidable.

Demographic data

The triad of absences, jerks and GTCSs shows a characteristic age-related onset. Absences, when a feature, begin between the ages of 5 and 16 years.

Myoclonic jerks follow 1–9 years later, usually about the age of 14 or 15 years. GTCSs normally appear a few months later than the myoclonic jerks, although they can occasionally appear earlier. Both sexes are equally affected. Prevalence is 8–10% among adult and adolescent patients with epilepsies.[1,23,112]

Clinical manifestations

JME is characterised by:

- myoclonic jerks on awakening
- GTCSs in nearly all patients
- typical absences in more than a third of the patients.

> Lots of blanks and jerks; then I had a grand mal... I usually have fits when rushing after getting up; usually does not happen later in the day.[109]

Myoclonic jerks occurring after awakening are the most prominent and characteristic seizure type (see also Chapter 2).[11,112,114–117] They are shock-like, irregular and arrhythmic clonic movements of proximal and distal muscles mainly of the upper extremities. They are often inconspicuous, restricted to the fingers, making the patient prone to drop things or look clumsy. They may be violent enough to cause falls. A fifth of patients describe their jerks as unilateral, but video-EEG shows that the jerks affect both sides (Figure 13.6).[115,117]

Some patients (<10%) with mild forms of JME never develop GTCSs.[112]

Typical absence seizures: A third of patients have typical absences, which are brief with subtle impairment of consciousness (Figures 13.7 and 13.8). They are different from the absence seizures of CAE or JAE.[22,114,118]

Absences appearing before the age of 10 years may be more severe. They become less frequent and severe with age.[22,114,118]

A tenth of patients do not perceive absences, despite GPSWD lasting for more than 3 s.[112,118] However, on video-EEG with breath counting during hyperventilation, such EEG discharges often manifest with mild impairment of cognition, eyelid flickering or both (Figures 13.7 and 13.8).[75]

GTCSs usually follow the onset of myoclonic jerks.[111,112,114–116,119]

Myoclonic jerks, usually in clusters and often with an accelerating frequency and severity may precede a GTCS, a so-called clonic–tonic–clonic generalised seizure.[115]

Woman aged 33 with JME and erroneous treatment with carbamazepine

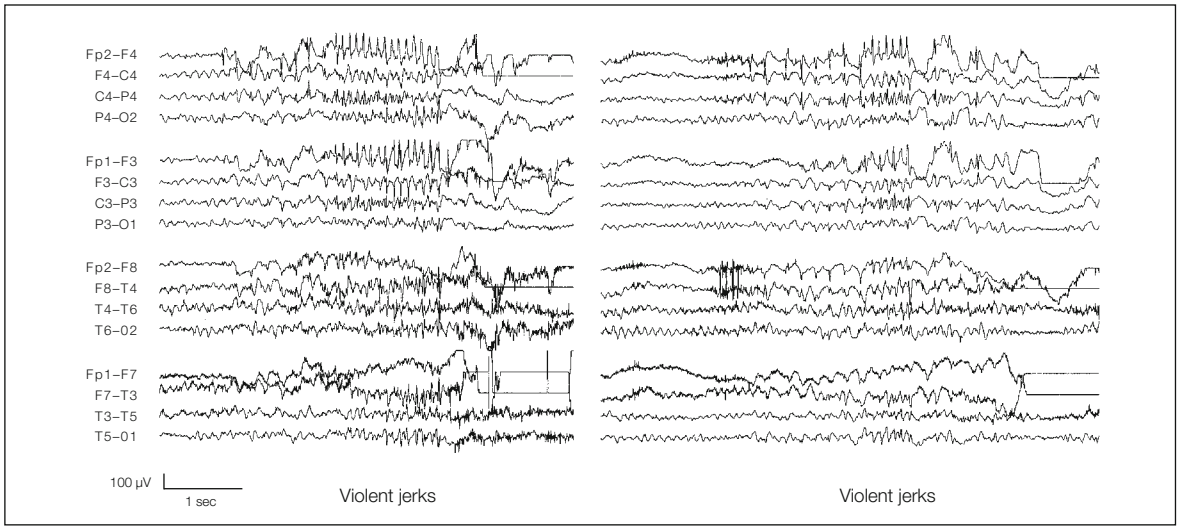

Figure 13.6 Samples from the video-EEG of a woman with JME but on erroneous AED treatment with carbamazepine. Violent myoclonic jerks occur with generalised polyspike discharges (see also Figure 13.9 of the same patient).

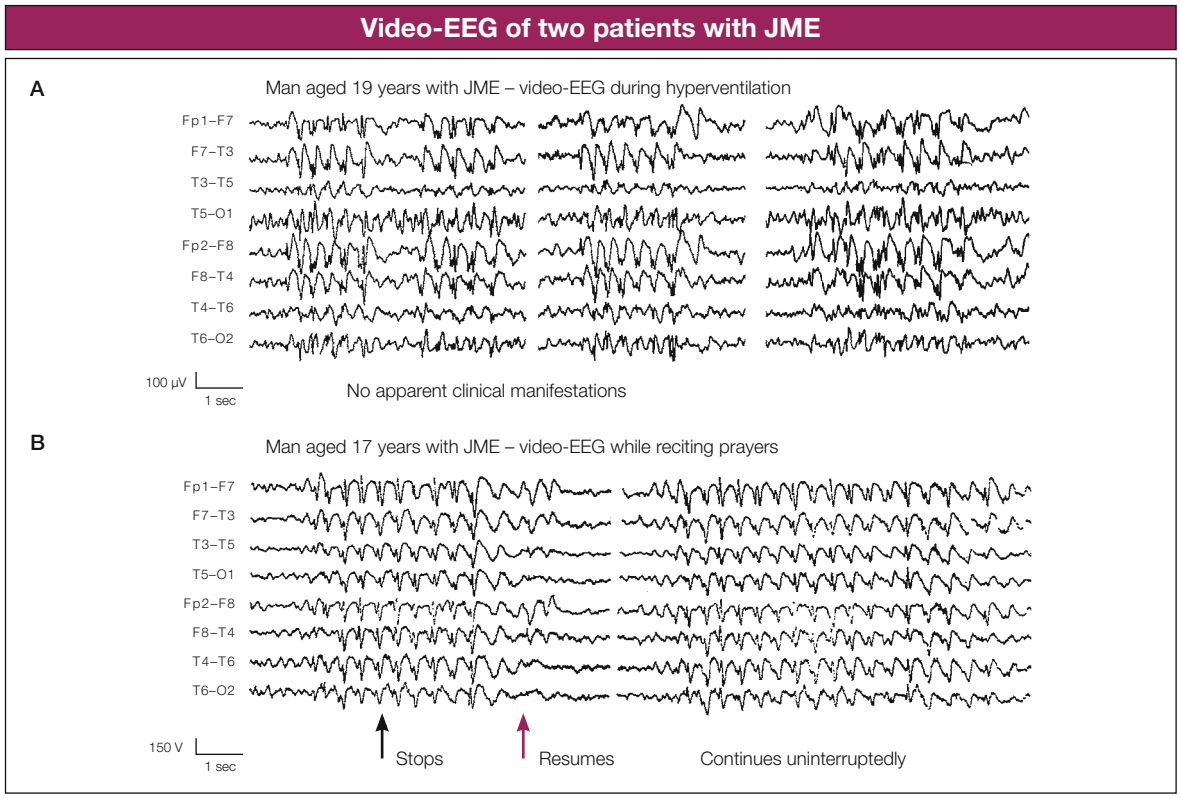

Figure 13.7 (**A**) GPSWD are not associated with apparent clinical manifestations (but these may have been revealed if breath counting was performed during hyperventilation). (**B**) GPSWD are associated with mild impairment of cognition. *Modified with permission from Panayiotopoulos,* et al *(1989).*[22]

Status epilepticus: Myoclonic status epilepticus is probably more common than appreciated.[112,120] This almost invariably starts on awakening, often precipitated by sleep deprivation, or missing medication. Consciousness may not be impaired, although in some patients absences are often interspersed with myoclonic jerks (Figure 13.9).

Pure absence status epilepticus[94] is very rare. Generalised tonic–clonic status epilepticus is infrequent. For further details on status epilepticus, see Chapter 3.

Circadian distribution: Seizures, principally myoclonic jerks, occur within 30 min to 1 hour of awakening. Myoclonic jerks rarely occur at other times unless the patient is tired. GTCSs occur mainly on awakening preceded by clusters of myoclonic jerks, but may also be purely nocturnal or random. Absence seizures rarely show a circadian predilection.

Seizure-precipitating factors

Sleep deprivation and fatigue, particularly after excessive alcohol intake, are the most powerful precipitants of jerks and GTCSs in JME.

> Sleep deprivation means a late night followed by a brief sleep suddenly interrupted by either compulsory early awakening in order to go to work or on a trip. An unscheduled telephone call early next morning may frequently have disastrous effects.

Photosensitivity is confirmed with EEG in more than 30% of patients but this may be of no clinical significance. Probably less than a tenth of patients have seizures induced by photic stimulation in daily life (Figure 13.8).

Other common and prominent seizure-precipitating factors include mental stress and emotions, in particular excitement, concentration, mental

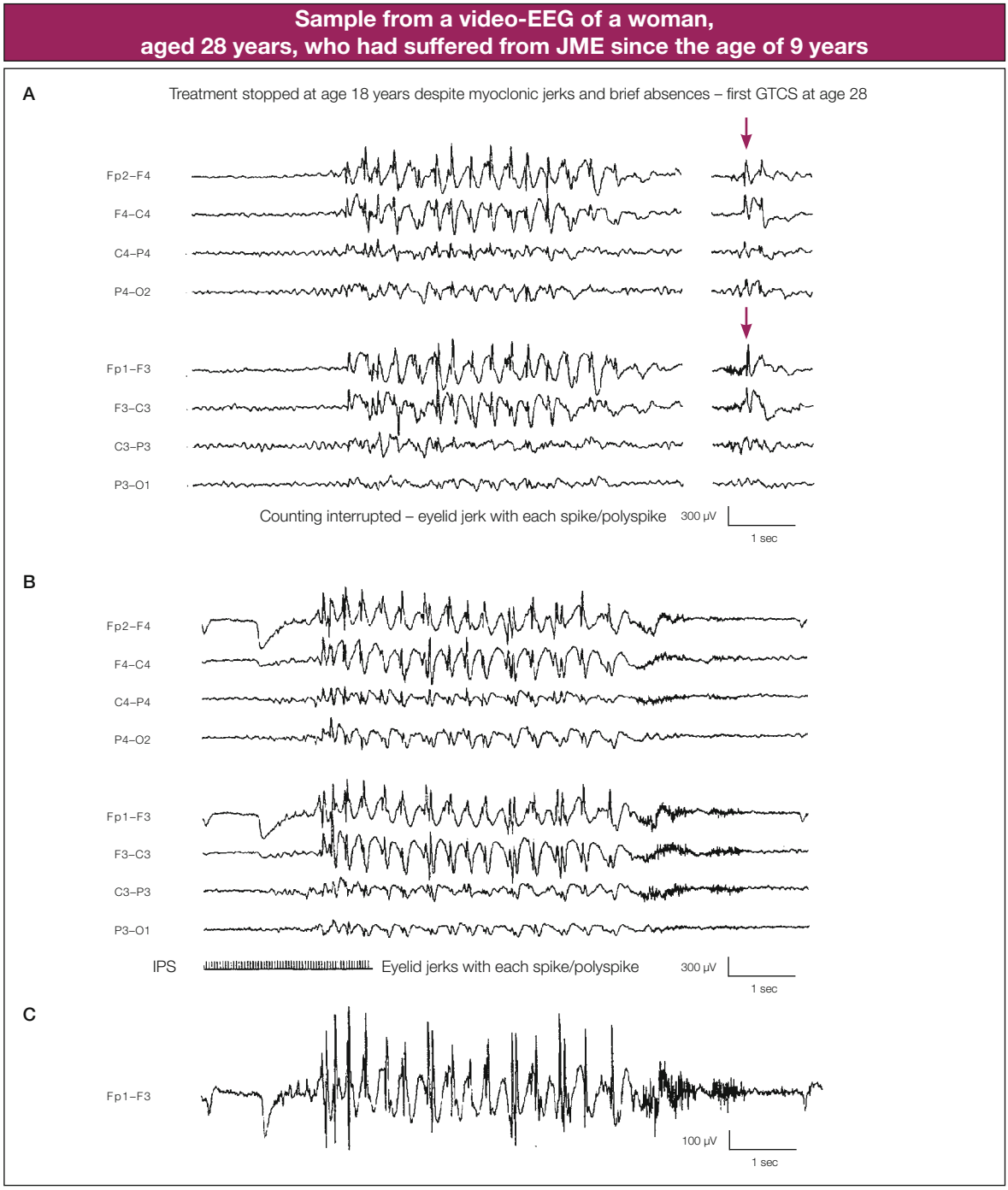

Figure 13.8 This woman was referred for a routine EEG because she had experienced 'probable IGE-absences from age 9 until age 18 years. Myoclonus as a teenager when sleep deprived. Recently suffered her first ever GTCS following sleep deprivation. No absence or myoclonus for 10 years. Treatment with valproate was withdrawn at age 18 years.' The video-EEG documented that she still had brief absences, which manifest with mild impairment of cognition and eyelid jerks. These were spontaneous, or induced by (**A**) hyperventilation and (**B**) intermittent photic stimulation. Note the polyspike–wave of the discharges and the irregular intradischarge frequency (**C**). Also note the bifrontal spike-slow wave discharges (**A**, red arrows).

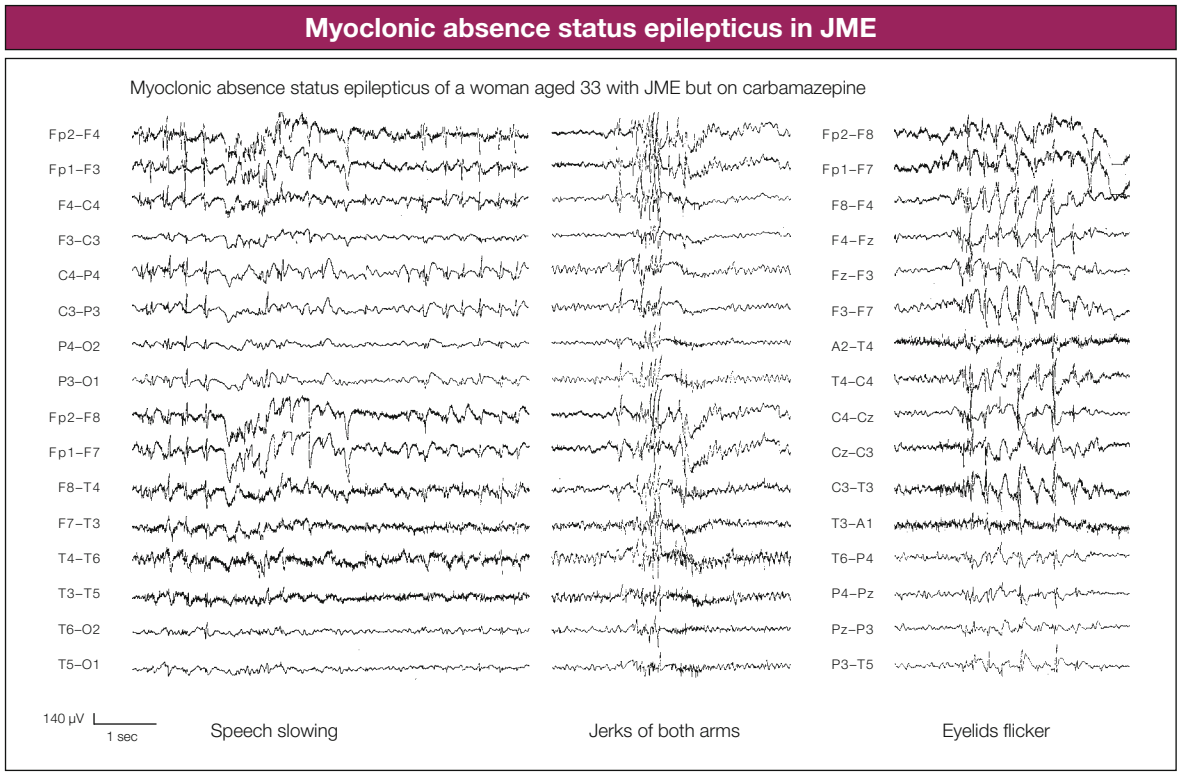

Figure 13.9 Video-EEG of a woman with classical JME, but on carbamazepine at the time of this recording (see also Figure 13.6 from the same patient). The patient was mildly confused with continuous jerking of the hands (middle) and, rarely, the eyelids. The ictal EEG consisted of repetitive and discontinuous frequent GPSWD interrupted by brief intervals of relative normality. Each GPSWD consisted of varying numbers of polyspikes/spikes–wave in various combinations and morphologies.

and psychological arousal, failed expectations or frustration.

Personality, behavioural, cognitive and psychological aberrations have been frequently reported in patients with JME.[114,121–124]

Aetiology

JME is a genetically determined syndrome.[2,111,119,125] Around 50–60% of families of probands with JME report seizures in first- or second-degree relatives.[119,126] Inheritance is probably complex.[127–129] The proposed models of inheritance include polygenic with a lower manifestation threshold for females, autosomal dominant with variable penetrance, a two-locus model with a dominant gene on chromosome 6p and an as-yet-unknown recessive gene, or the possibility that different genotypes with different modes of inheritance underlie the phenotype.[130]

Families with autosomal[125] or dominant[125,127] mendelian inheritance have been described, but these may be rare.

Molecular studies favour a susceptibility locus for JME in chromosome 6p11–12 (*EJM1*)[129] or 15q14 (*EJM2*).[131,132] A gene, *C6orf33*, in the *EJM1* region has been identified.[133] An association of JME with an HLA-DR allele[134,135] was not replicated.[136]

Genetic heterogeneity of JME is a possible explanation for such discordant observations.

It has been hypothesised that JME is a frontal lobe variant of a multi-regional, thalamocortical network epilepsy rather than a generalised epilepsy syndrome.[137]

Diagnostic procedures

All tests except EEG are normal. Using new MRI technologies, abnormalities involving mesio-frontal cortical structures have been reported in some patients with JME.[123,138]

Electroencephalography

The EEG in untreated patients is usually abnormal, with 3–6 Hz GPSWD, and with intradischarge fragmentations and unstable intradischarge frequency (Figures 13.7 and 13.8). A third of the patients show photoparoxysmal responses. A third may also have focal EEG abnormalities of single spikes, spike–wave complexes or slow waves.[22]

A normal EEG in a patient suspected of having JME should prompt an EEG during sleep and awakening.

The typical EEG discharge of a myoclonic jerk is a generalised burst of polyspikes of 0.5–2 s duration (Figures 2.9 and 13.6).

The ictal discharges of absences in JME are distinctly different from those in CAE and JAE.[22,118] They consist of spike/double/treble or polyspikes usually preceding or superimposed on the slow waves (Figures 13.7–13.9). Polyspikes consist of up to eight to ten spikes with a characteristic 'worm-like' or compressed capital W appearance ('Ws'). The number and amplitude of spikes shows considerable inter- and intradischarge variation. The intradischarge frequency of the GPSWD varies from 2 to 10 Hz, with a mean of 3–5 Hz. The frequency is often higher in the first second from onset. Fragmentations of the discharge are common and characteristic. Ws and fragmentation of discharges are observed in all patients, but vary quantitatively between patients and between discharges (Figures 13.7 and 13.8).

Brief discharges are far more common than long ones, and most of the discharges last for 1–4 s.

Differential diagnosis

JME is a typical example of a frequently misdiagnosed common epileptic syndrome resulting in avoidable morbidity.[139,140] Failure to diagnose JME is a serious medical error because JME defies all aspects of general advice regarding 'epilepsy'. Diagnosis should improve with heightened medical awareness. Physicians should be ever alert to the possibility of JME.

The rate of misdiagnosis of JME is as high as 90%.[139,140] Factors responsible include lack of familiarity with JME, failure to elicit a history of myoclonic jerks, misinterpretation of absences as complex focal seizures, misinterpretation of jerks as focal motor seizures, and high prevalence of focal EEG abnormalities.

JME is easy to diagnose because of a characteristic clustering of myoclonic and other generalised seizures of IGEs, circadian distribution, precipitating factors and EEG manifestations. Patients are otherwise normal and there is no mental or physical deterioration if properly diagnosed and treated.

Diagnostic tips

GTCSs, usually preceded by myoclonic jerks, are nearly pathognomonic of JME if they occur in the morning after:

- a party to celebrate, for example, a birthday, the end of school term or New Year's eve
- waking up early in the morning to travel for vacations, particularly after a late night
- replacement of valproate with carbamazepine in women wishing to start a family
- withdrawal of appropriate medication after many seizure-free years.

Of other IGEs, JAE may be more difficult to differentiate because this syndrome may also manifest with similar clinical and EEG manifestations. The main differentiating factor is that absences with severe impairment of consciousness, not the myoclonic jerks, are the main seizure type in JAE (Table 13.5). Myoclonic jerks, if they occur, are mild and random often lacking the circadian distribution of JME.

Another formidable situation is when JME starts with absences in childhood prior to the development of myoclonic jerks. There are no prospective video-EEG studies of these patients. Retrospectively

examining EEG and clinical manifestations of these patients, I am of the opinion that their absences are distinct from CAE or JAE in that they are usually shorter and milder, and ictal EEG often contains GPSWD. Certainly, this situation is not CAE progressing to JME as some authors reported.[141] It is JME starting with absences prior to the development of myoclonic jerks.

Diagnostic tips

Revealing myoclonic jerks is an essential part of diagnosing JME

Elicitation of the characteristic history of myoclonic jerks is something of an art. It is often necessary to physically demonstrate mild myoclonic jerks of the fingers and hands, and to inquire about morning clumsiness and tremors.[142] Questions like 'do you spill your morning tea?' and 'do you drop things in the morning?', together with a simultaneous demonstration of how myoclonic jerks produce this effect, may be answered positively by patients who denied experiencing myoclonic jerks on direct questioning. Further elaboration is required to confirm that clumsiness was due to genuine myoclonic jerks. If the patient reports normal hypnagogic jactitations, it is reassuring that the concept of myoclonic jerks has been understood. Diagnostic yield may be improved by emphasising the close relationship between jerks and fatigue, alcohol and sleep deprivation. Some patients do not report their jerks, erroneously assuming that this is a self-inflicted normal phenomenon related to excess of alcohol and lack of sleep.

Prognosis

All seizures are probably life-long, although improving after the fourth decade of life.[143] JME may vary in severity from mild myoclonic jerks to frequent and severe falls and GTCSs if not appropriately diagnosed and treated.

Seizures are generally well controlled with appropriate medication in up to 90% of patients.[109,112,115,144] Patients with all three types of seizure are more likely to be resistant to treatment.[145]

Management

Advice regarding life-style, avoidance of precipitating factors and long-term medication is essential for a patient with an incontrovertible diagnosis of JME. Avoidance of alcohol indulgence and compensating for sleep deprivation is mandatory. Some patients with mild forms of JME have GTCSs or myoclonic jerks only after excessively violating these factors.

Pharmacological treatment

All formal current recommendations discourage or practically prohibit the use of valproate in women of childbearing age but provide no documented alternatives for their treatment in JME, where valproate has been the first line AED for the last 30 years.

Converging evidence from multiple and independent sources indicate that levetiracetam is the first choice AED in the treatment in at least women with JME.

Valproate is the most effective AED in the treatment of JME, but is humbled by serious adverse reactions in women and has not been yet compared with levetiracetam in face to face RCTs. However, it may still be considered as first line AED therapy in men with JME.

Levetiracetam is the likely candidate to replace valproate in the treatment of JME:

a. In non¬control independent studies, 62–67% of patients with intractable JME, including those that have failed with valproate, became seizure free with levetiracetam monotherapy or polytherapy. This high rate of response to levetiracetam has been confirmed in recent more systematic studies of monotherapy[146] or conversion to monotherapy from polytherapy (including valproate failures).[147]
b. Levetiracetam is the first and only newer AED licensed for the treatment of myoclonic seizures in JME (adjunctive therapy in adults and adolescents) because of its efficacy and safety tested in RCT.[148]
c. It appears to have a favourable profile in women and pregnancy (see Chapter 7, page 208).
d. It has high and sustained efficacy, fast action, good safety profile, and lack of clinically meaningful interactions with other drugs.[12,149]

Lamotrigine is widely used in JME because:

(a) It was the first of the newer AEDs that appeared to be effective in JME, but this was mainly in combination with valproate; its promyoclonic effect as monotherapy became apparent much later[150,151]

(b) It was promoted as the only alternative to valproate in women; its interactions with hormonal contraception and pregnancy that may lead to seizure deterioration or toxicity, as well as the uncertainties surrounding its teratogenic potential, only recently have been reported (see chapter 7 page 208).[152–156]

Considering all this new information, compounded with the high rate of idiosyncratic ADRs, necessity for slow titration and drug-to-drug interactions, lamotrigine monotherapy in JME patients is questionable.

Clonazepam administered in small doses (0.5–2 mg at night) is probably the most effective treatment for myoclonic jerks. However, clonazepam alone may not suppress GTCSs.[112,157] Furthermore, clonazepam may deprive patients of the warning of an impending GTCS provided by the myoclonic jerks.[112,157] In mild JME with myoclonic jerks only, clonazepam alone may be recommended.

When cost is of concern, *phenobarbital* is the best option. It is effective in about 60% of patients.

Topiramate and *zonisamide* are by far second options, particularly in women.

Contraindicated drugs include vigabatrin, tiagabine, gabapentin, pregabalin, phenytoin, oxcarbazepine and carbamazepine. Carbamazepine is not effective in jerks and absences but it is possibly effective on GTCSs of IGEs.

See details of the treatment of IGEs on page 411.

Prevention of GTCSs and termination of myoclonic and absence status epilepticus

It is important to remember that patients with JME often experience myoclonic jerks or myoclonic-absence status epilepticus long before terminating to a GTCS. This can be prevented by home administration of an appropriate benzodiazepine preparation, as detailed in Chapter 3.

Duration of AED treatment and withdrawal of medication

Life-long treatment with proper AEDs is usually considered necessary in patients with JME. Withdrawal of appropriate medication results in relapses, even in patients who have been seizure free for many years with an appropriate AED.[112] In mild forms of JME, it may be safe to reduce the dose of medication slowly over months or years, especially after the fourth decade of life.[143] Persistence or recrudescence of myoclonic jerks necessitates continuation of medication.

Epilepsy with GTCS only

GTCSs are a common feature in IGEs and occur predominantly on awakening (see Chapter 2). Overall, GTCSs are reported to occur on awakening (17–53% of patients), diffusely whilst awake (23–36%), during sleep (27–44%) or randomly (13–26%).[158] It is undetermined what proportion of these patients also has other generalised seizures (jerks or absences).

GTCSs are the most severe forms of epileptic seizures, while absences and myoclonic jerks may be mild and sometimes inconspicuous to the patient and imperceptible to the observer.[159,160] They are often detected only by meticulous history taking and video-EEG. A patient with a first GTCS has often suffered from minor seizures (absences, myoclonic jerks or both), sometimes many years prior to the GTCS.

Considerations on classification

IGE with GTCS was only considered a syndrome in the new ILAE diagnostic scheme,[20,25] and incorporated

'epilepsy with GTCS on awakening (EGTCSA)' previously recognised as a separate syndrome.[21]

In the previous edition of this book, it was emphasised that 'IGE with GTCS only' has not been precisely defined by the ILAE Task Force.[25] Its name implies that it includes only those patients with GTCSs alone (ie, without absences and/or jerks) and that these may occur at any time. However, it is more likely that it is a broader category (rather than a syndrome) of 'IGE with *predominantly* GTCS' (also including patients with mild absences, myoclonic jerks or both).

The new ILAE report[56] has now revised its position and specifies the following:

> Epilepsy with GTCS only is not a syndrome, and the Core Group was unable to agree on any syndrome with this feature: the consistent diurnal pattern of seizures in some patients needs further investigation. Whether epilepsy with GTCS on awakening exists as a distinct entity is unclear.

A genetically determined syndrome of 'intractable childhood epilepsy with GTCS' (see Chapter 10, page 285) is probably unrelated to the 'epilepsy with GTCS only' covered in this chapter.

Demographic data

Age at onset varies from 6 to 47 years with a peak at 16 or 17 years; 80% have their first GTCS in the second decade of life. Men (55%) slightly predominate over women, probably because of differences in alcohol exposure and sleep habits. The prevalence of IGE with GTCS only is unknown. In my studies with strict criteria (GTCS only)[23] this may be very small (0.9% of IGEs), but others have given a prevalence of 13–15% among IGEs.[161,162]

Clinical manifestations

By definition all patients suffer from GTCSs but this syndrome has not been examined in its entirety. Only EGTCSA has been extensively studied[163–165] and is presented in this chapter.

Patients suffer from GTCSs, which occur within 1 or 2 hours after awakening from either nocturnal or diurnal sleep. The seizure may occur while the patient is still in bed or having his breakfast or upon arriving at work. Seizures may also occur during relaxation or leisure.[158,163,164]

Janz described patients with EGTCSA as unreliable, unstable and prone to neglect.[164,165] The sleep patterns of EGTCSA patients are particularly unstable and modifiable by external factors (eg, AEDs), and the patients may suffer from chronic sleep deficit.[158,163,164]

Seizure-precipitating factors

Sleep deprivation, fatigue and excessive alcohol consumption are the main seizure precipitants. Shift work, changes in sleep habits, particularly during holidays and celebrations, predispose to GTCSs on awakening. A quarter of patients are reported to show photosensitivity on EEG.[158]

Aetiology

There is a high incidence of epileptic disorders in families,[158,164] and a link to the *EJM1* locus has been reported.[166] Conversely, adolescent-onset idiopathic GTCS epilepsy with GTCS at any time, whilst awake was not linked to the *EJM1* locus.[166] Severe IGE of infancy with GTCS is often related to mutations of the *SCN1A* gene.

Diagnostic procedures

By definition all tests other than EEG are normal.

Electroencephalography

EEG shows GPSWD in half of patients with pure EGTCSA (Figure 13.10) and 70% of those with additional absences or myoclonic jerks preceding GTCSs.

A normal routine EEG should prompt a video-EEG performed on sleep and on awakening. Myoclonic jerks or, more frequently, brief absences will often be revealed. Focal EEG abnormalities in the absence of generalised discharges are rare. Photoparoxysmal responses are reported in 17% of females and 9% of males with EGTCSA.[158]

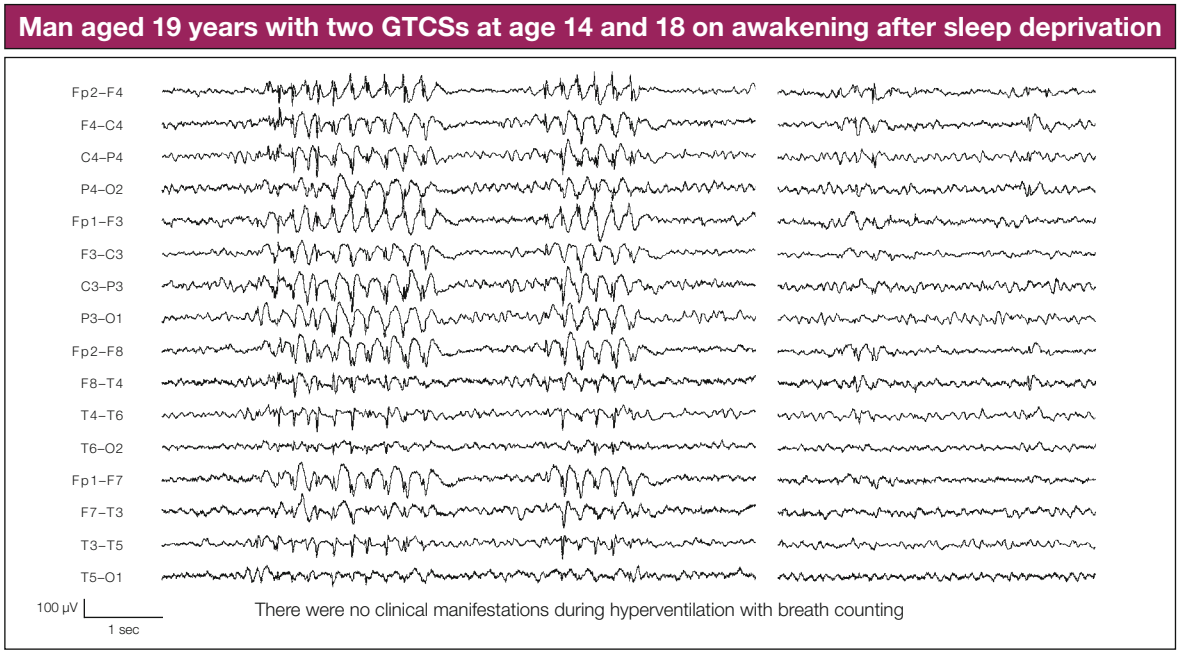

Figure 13.10 Asymptomatic GPSWD on video-EEG of a 19-year-old university student who had two GTCSs at age 14 and 18. They both occurred half an hour after awakening from a brief sleep during exam periods. There was no clinical history of any other types of seizure and there were no other symptoms preceding either of the GTCSs. Note that the discharges may start from right or left. Also note focal spikes at various locations.

Differential diagnosis

The differential diagnosis is mainly from patients with other IGEs, which share with EGTCSA the same propensity to seizures after awakening and the same precipitating factors. JME and JAE are examples of IGE syndromes, which may cause diagnostic difficulties. Rarely, secondarily GTCSs of focal epilepsies may also consistently occur on awakening.

Prognosis

As in all other types of IGE with onset in the mid-teens, EGTCSA is probably a life-long disease with a high (83%) incidence of relapse on withdrawal of treatment.[158,163] Characteristically, the intervals between seizures become shorter with time, the precipitating factors less obvious, and GTCSs may become more random (diurnal and nocturnal), as a result of either the evolution of the disease or drug-induced modifications.

Management

Patients should be warned of the common seizure precipitants – sleep deprivation with early awaking and alcohol consumption – and when possible should avoid occupational night shifts. Patients, after adjusting their life styles, may become seizure free. Drug treatment is the same as for IGE with GTCSs (see page 411).

Other probable syndromes of IGE to consider

> Implicitly, one must be prepared to split before one can lump. Thus we must always be on guard against unwittingly lumping because we are unaware of certain characteristics on which we should have split.
>
> Berg and Blackstone (2003)[167]

Probable syndromes of IGE that are not officially recognised by the ILAE are:[7,23,168]

- IGE with absences of early childhood
- perioral mycoclonia with absences
- IGE with phantom absences
- monogenic IGE syndromes
- Jeavons syndrome (eyelid myoclonia with absences), which is described with the reflex epilepsies (Chapter 16).

"Absence status epilepsy" has been recently proposed as a new IGE syndrome based on 11 adult patients in whom recurrent, unprovoked, typical absence status epilepticus was the main clinical feature.[169] Most patients also had infrequent GTCS or absence seizures (including phantom absences) which sometimes appeared many years before the onset of absence status epilepticus. Thus, these patients probably represent heterogeneous syndromes such as IGE with phantom absences, IGE with GTCS or other IGEs with absence status epilepticus, which were often the result of prior inappropriate AED treatment.

Video-EEG documentation of most of the syndromes described in this section can be found in the CD companion to references 23 and 26. Their diagnosis in clinical practice is significant at least for genetic and prognostic reasons.

IGE with absences of early childhood[91,170–173]

Typical absences starting from early childhood (a few months to 5 years of age) are not a specific expression of a distinct syndrome. This may be the first manifestation of MAE, perioral or eyelid myoclonia with absences, EM-AS, CAE or more severe forms of generalised epilepsies. By excluding all these, it is realistic to propose that there is a syndrome of IGE that starts in early childhood primarily manifesting with absences, often combined with GTCSs and possibly with myoclonic jerks.

Doose,[171,172] having studied 140 cases with onset of absences in early childhood rightly concluded that 'this is an heterogeneous subgroup within IGE. There is a distinct overlap with early childhood epilepsy with GTCS and myoclonic–astatic epilepsy on the one side and with CAE on the other. Thus it should not be regarded as a special syndrome.'[171,172] I am in complete agreement with this statement. Age at onset of absence seizures alone, cannot define an epileptic syndrome. However, with improved diagnostic skills, applying inclusion (eg, including absences and GTCSs) and exclusion criteria (eg, excluding CAE, EM-AS, MAE, PMA and possibly symptomatic cases) it appears there there is such an idiopathic generalised epilepsy that we have to define more precisely.

Based on currently available data, this is an IGE (occurring in otherwise normal children) with the following features:

- absences are markedly different from CAE; clinically they are less severe and less frequent
- GTCSs are common (two-thirds) and often the first seizure type
- myoclonic jerks and myoclonic–astatic seizures occur in 40%
- absence status epilepticus is common and may lead to cognitive impairment
- boys are more likely to suffer GTCSs than girls

- ictal EEG 3 or 4 Hz GPSWD is very irregular and termination is not abrupt but often fades with slow spike–wave
- background EEG shows a moderate excess of slow waves
- long-term prognosis is worse than in CAE
- strong family history of IGE and GPSWD in EEG of unaffected members, particularly mothers.

Perioral myoclonia with absences[174,175]

Typical absences with motor symptoms of perioral myoclonia is a non-specific symptom. However, this often combines with a clustering of other clinical and EEG features suggestive of an interesting syndrome of PMA within the IGEs.

Considerations on classification

PMA has been recognised neither as a seizure type nor as a syndrome by the ILAE.[21,25] That absences with perioral myoclonia is a discrete seizure type has been unequivocally documented with video-EEG recordings.[23,174,176–179] The symptom of perioral myoclonia may also rarely occur in absence seizures of other IGEs and, as such, perioral myoclonia alone cannot be taken as sole evidence of the syndrome of PMA. However, there is often a non-fortuitous clustering of other symptoms indicating that these absences may often constitute the main symptom of a syndrome within the broad spectrum of IGE, which we proposed to call PMA. Other manifestations of this syndrome include: GTCSs, which often start early prior to or together with the absences; frequent occurrence of absence status epilepticus; resistance to treatment; and persistence in adult life.[174,175]

Demographic data

Onset varies from 2 to 13 years (median 10 years). Girls are far more frequently affected than boys. The prevalence of PMA is small in children (<1% with typical absences) but, because it fails to remit, it is higher in adults (9.3%) with TAS.

Clinical manifestations

TAS with perioral myoclonia are the defining symptom. The characteristic feature is perioral myoclonia, which consists of rhythmic contractions of the orbicularis oris muscle that cause protrusion of the lips, contractions of the depressor anguli oris resulting in twitching of the corners of the mouth or, rarely, more widespread involvement, including the muscles of mastication producing jaw jerking (Figure 13.11). Impairment of consciousness varies from severe to mild. Most patients are usually aware of the perioral myoclonia. Duration is usually brief, lasting a mean of 4 s (range 2–9 s). Absences of perioral myoclonia may be very frequent, occurring many times per day, 1–2 per week, or they are rare.

All patients suffer GTCSs, which often start before or soon after the onset of clinically apparent absences. Exceptionally, GTCSs may start many years after the onset of absences. GTCSs are usually infrequent (range once per lifetime to 12 per year) and are often heralded by clusters of absences or absence status epilepticus.

Absence status epilepticus is very common in PMA (57%) and frequently ends with a GTCS (Figure 13.11). It is more common than in any other syndromes of IGE with typical absences.[94] Perioral myoclonia may be more apparent than impairment of consciousness or *vice versa*.

Aetiology

Half of patients have first-degree relatives (mainly siblings) with IGE and absences.[174,180]

Diagnostic procedures

All tests are normal except EEG.

Electroencephalography

Inter-ictal EEG frequently shows (1) abortive bursts or brief <1 s of 4–7 Hz GPSWD – these

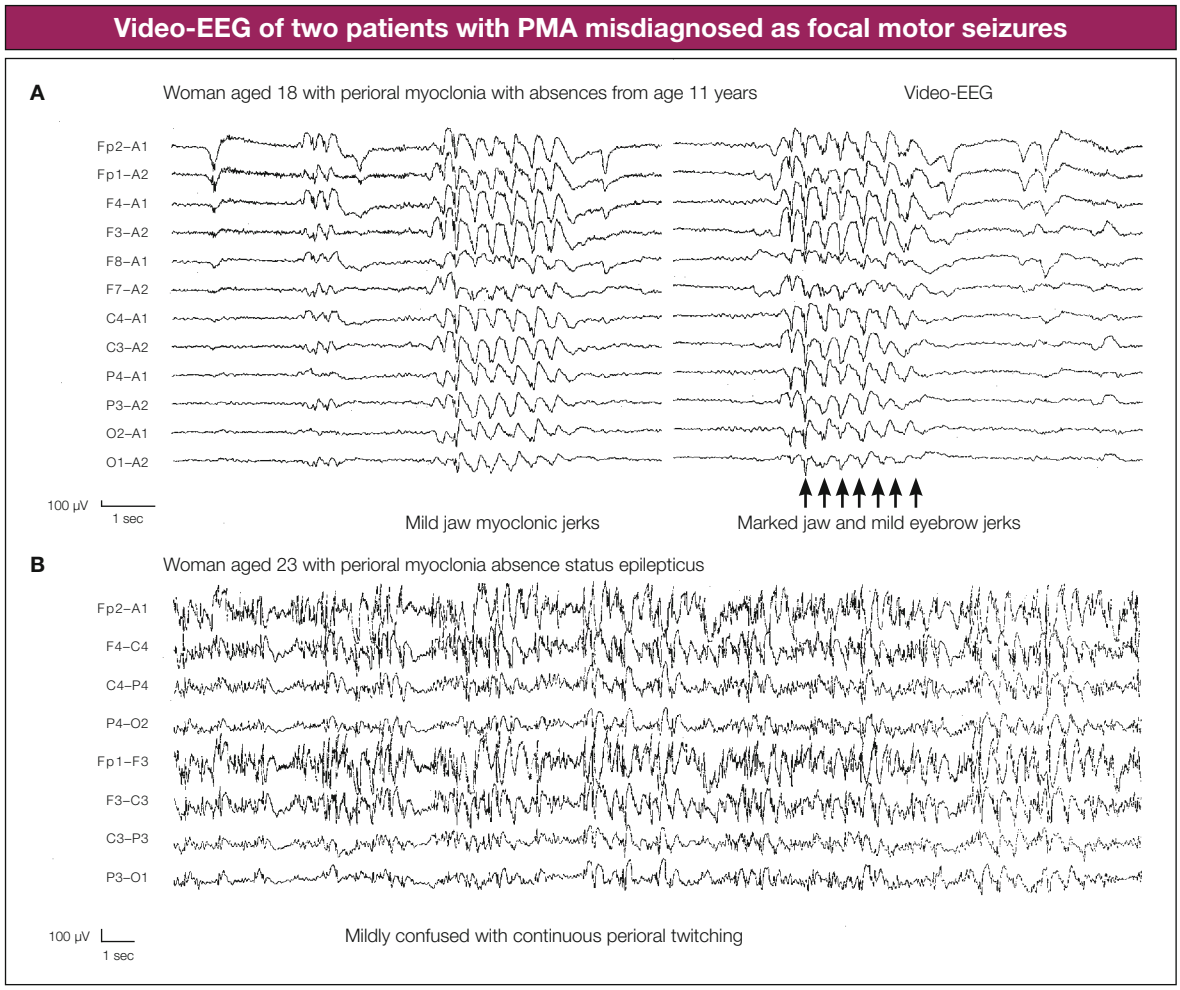

Figure 13.11 (**A**) From video-EEG recording of a woman with perioral myoclonia with absences (case 6 in Panayiotopoulos, *et al*[174]). She was referred because of 'focal motor seizures and secondarily GTCS'. She had onset of GTCSs and absences at age 11 years. Seizures continued despite treatment with appropriate AED combinations such as valproate, ethosuximide, clonazepam, lamotrigine and acetazolamide. Absences were frequent, often in daily clusters and consisted of brief, about 5 s, moderate impairment of consciousness with violent rhythmic jerking of the jaw. GTCSs occurred between one and ten times per year, usually after awakening, preceded by clusters of absences with the jaw myoclonus spreading to limb jerks prior to generalised convulsions. She was more concerned about the absences because they interfered with her daily life 'everyone notices the jerks of my jaw' and less with the GTCSs, which usually occurred at home. The initial misdiagnosis of 'focal motor seizures' was because the jaw jerking was described by her mother as unilateral. (**B**) From the EEG of a 23-year-old woman while in perioral myoclonia absence status epilepticus (case 2 in Panayiotopoulos[174]). She was mildly confused with continuous perioral twitching. This ended with a GTCS. Initial presentation at age 11 years was with GTCS. Absences with perioral myoclonia were noted at the same time and were diagnosed as focal motor seizures.

are usually asymmetrical and may give the impression of a localised focus; and (2) focal abnormalities, including single spikes, spike–wave complexes and theta waves with variable side emphasis.

The ictal EEG consists of 3–4 Hz GPSWD with frequent intradischarge irregularities in terms of numbers of spike in the spike–wave complex, fluctuations in spike amplitude and the occurrence of fragmentations.

There is no photosensitivity.

Diagnostic tips

Useful clinical indicators in favour of PMA and against CAE, JAE or other forms of IGE:

- onset of GTCSs before or at the same age as typical absences
- relatively brief duration of absences with perioral myoclonia
- frequent occurrence of absence status epilepticus.

Differential diagnosis

Patients with PMA are frequently erroneously diagnosed as having focal motor seizures, because of (1) the prominent motor features of the absences which are often reported and sometimes recorded as unilateral; and (2) inter-ictal focal EEG abnormalities. However, this error is unlikely to happen if the EEG is properly obtained and interpreted. Also, patients with focal motor seizures are unlikely to suffer status epilepticus, which is common in PMA.

The main differential diagnosis is from CAE, JAE or IGE with phantom absences depending on the age at onset. Video-EEG invariably reveals perioral myoclonia that sometimes may be subtle, particularly in treated patients.

Prognosis

Absences and GTCSs may be resistant to medication, unremitting and possibly life-long.

Management

Treatment is with valproate alone or combined with ethosuximide, small doses of lamotrigine or clonazepam.

Absence status epilepticus, for which most patients are aware, should be terminated with immediate self-administered medication of oral midazolam or rectal benzodiazepines (see Chapter 3, page 83).

IGE with phantom absences[159]

Phantom absences are typical absence seizures (see page 51) with the mildest form of impairment of consciousness.[159]

IGE with phantom absences[159,160] is characterised by a triad of:

1. phantom absences
2. GTCSs, which are commonly the first overt clinical manifestations, usually starting in adulthood and are infrequent
3. absence status epilepticus, which occurs in half of the patients.

Considerations on classification

Phantom absences are mild absence seizures, causing only inconspicuous impairment of cognition. Although not classical, they fulfil the ILAE criteria of TAS with GPSWD of more than 2.5 Hz.[55,159]

Phantom absences have not been considered in any previous ILEA classification,[21,25] but this may now change. The recent ILAE report[26] makes the following reference:

> Phantom absences are likely to be a result of brain maturation.

Furthermore, there is reasonable evidence to support that phantom absences are not only a discrete seizure but may also constitute the main symptom of a syndrome within the broad spectrum of IGE. There is non-fortuitous clustering of other symptoms such as GTCSs of usually late onset, frequent occurrence of absence status epilepticus and persistence into adult life.[159] That these patients have IGE is beyond any doubt as they all are of normal intelligence and physical state, high-resolution MRI is normal, the EEG shows GPSWD and the seizures are generalised.

The syndrome of IGE with phantom absences has not been recognised by the ILAE.[21,25] Accordingly, these cases are probably categorised among undefined IGE or other syndromes of IGE.

Demographic data

The first overt clinical manifestations of GTCSs appear in adult life, although absences may have started much earlier. Men and women are equally affected. Prevalence has been estimated at 15% among IGE with typical absences, 10% of IGE and 3% of 410 consecutive patients older than 16 years with epileptic seizures.[159] Genton[181] reported that, among 253 consecutive cases of IGE, 32 (15.4%) patients had rare GTCSs with GPSWD in the inter-ictal EEG.

Clinical manifestations

This syndrome manifests with phantom absences, GTCSs and, often, ASE.

Phantom absences denote TAS, which are so mild that they are inconspicuous to the patient and imperceptible to the observer.[159] They are disclosed by video-EEG recording and breath counting during hyperventilation. The absences manifest with interruption, delays or errors of counting and occasionally with eyelid blinking. Ictal EEG shows brief (usually 3 or 4 s), 3–4 Hz GPSWD (Figure 3.1 and 13.12). Phantom absences may be more common than appreciated in patients with IGE (particularly adults) but are often unrecognised.

GTCSs are usually the first overt clinical manifestation.[159] These are of late onset, infrequent and without consistent circadian distribution or specific precipitating factors.

Absence status epilepticus: Half of patients suffer from absence status epilepticus, which often lasts for many hours alone or prior to a GTCS (Figure 3.1). This manifests with cognitive impairment, which is usually of mild or moderate severity. The patient communicates poorly, is slow, feels strange and confused, makes errors at work, looks depressed but does not become unresponsive. More commonly than usually appreciated are experiential, mental and sensational symptoms. The

Video-EEGs in two patients suffering from IGE with phantom absences

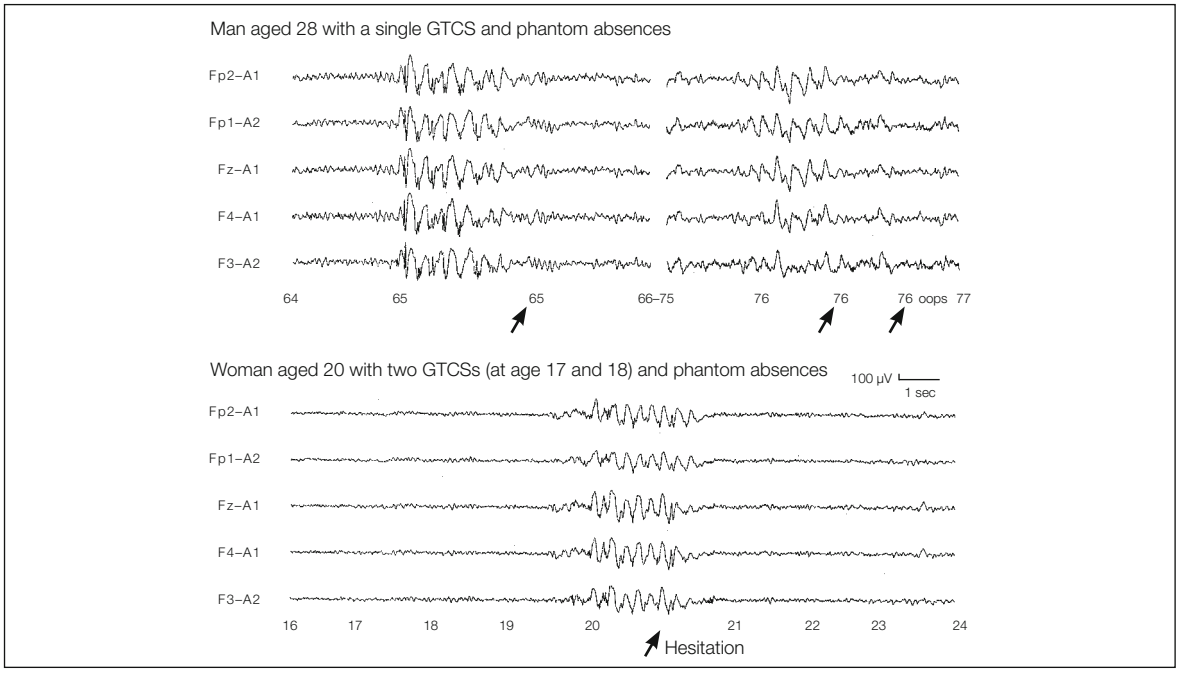

Figure 13.12 The numbers denote the actual breath counting during hyperventilation. Note that errors, when they occur (arrows), are only related to these brief discharges. Errors consist of hesitation in pronouncing the next consecutive number, repetitions and erroneous counting sequence. These absences are impossible to detect without breath counting and video-EEG.

patient is often aware of the impeding GTCS and tries to find a safe place to have it. There may be some post-ictal recollection of the events (see also Chapter 3).

Aetiology

IGE with phantom absences is probably genetically determined.[159]

Diagnostic procedures

All tests are normal except the EEG.

Electroencephalography

The background activity is normal but half of patients have EEG focal paroxysmal abnormalities consisting of short transient localised slow, sharp waves or spikes or both, occurring either independently or in association with the generalised discharges.[159,182] EEG photosensitivity is exceptional.

Ictal EEG consists of 3–4 Hz GPSWD with occasional fragmentations (Figures 3.1 and 13.12). They are typically brief (2–4 s) lasting usually no more than 5 s. Mild cognitive impairment manifested by hesitation, discontinuation and errors in breath counting is the only clinical ictal symptom during the generalised discharges. A few patients may also have mild ictal eyelid fluttering.[159,182] Hyperventilation is a major provocative factor.

During absence status epilepticus, the EEG shows continuous 3 Hz GPSWD (particularly adults) (Figure 3.1).

Differential diagnosis

The diagnostic and management errors involved in adult patients with IGE and TAS have been well reported.[102,159] The magnitude of the problem is worse in IGE with phantom absences, in which the absences are very mild, absence status epilepticus is misdiagnosed as non-epileptic events or temporal lobe epilepsy, and GTCSs are of late onset. This is compounded by frequent EEG focal abnormalities and the current practice of most EEG departments not to appropriately test cognition during brief GPSWD.[55]

The main features to consider in IGE with phantom absences are:

- the first overt unprovoked GTCS appears in adult life
- absence status epilepticus
- differentiation from other syndromes of IGE.

It is essential to take a careful clinical history and to interpret symptoms correctly, which may be suggestive of typical absences and absence status epilepticus.

> A history of altered consciousness preceding GTCSs should not be taken as evidence of complex focal seizures, depression or an unspecified seizure prodrome. Absence status epilepticus is more likely.

Other forms of the so-called 'adult-onset IGE' may be otherwise typical examples of JME, JAE or other IGE syndromes that start or become clinically identifiable after the age of 20 years.[183,184] Some of the patients described may suffer from IGE with phantom absences.

IGE with phantom absences is also different from IGE with GTCS. In IGE with GTCS, phantom absences do not occur, GTCSs tend to occur on awakening and episodes of absence status affect half as many patients than of IGE with phantom absences. There is no evidence for a maturational influence on the duration of GSW in either syndrome.[160]

Prognosis

IGE with phantom absences may be a life-long propensity to seizures that is of undetermined onset and remission. Patients are of normal intelligence, which does not show any signs of deterioration. In addition, phantom absences, although frequent, do not appear to affect daily activity.

Management

There are many questions to answer in deciding whether patients with phantom absences need treatment. All patients of IGE with phantom absences had a normal life without medication until their first GTCS, probably many years after the onset of frequent daily mild absence seizures. We do not know how many people in the general population with the same problem will never develop GTCSs or absence status epilepticus. However, for those that will eventually have GTCSs, treatment may be needed. Drugs of choice are those of IGE with absence seizures; these include valproate and lamotrigine.

Autosomal dominant cortical tremor, myoclonus and epilepsy

IGE syndromes with Mendelian (monogenic) inheritance have been described in the past decade. Of those with autosomal dominant inheritance, 'autosomal dominant cortical tremor, myoclonus and epilepsy' (ADCME) is the more common.[185–188] Familial infantile myoclonic epilepsy is of autosomal recessive inheritance.[189,190]

ADCME is a term used recently to include a number of familial autosomal disorders manifesting with cortical tremor, myoclonus and epilepsy, such as benign familial adult myoclonic epilepsy, familial adult myoclonic epilepsy, familial essential myoclonus and epilepsy, familial cortical tremor and epilepsy, and autosomal dominant cortical myoclonus and epilepsy. It has been described mainly in Japanese and Italian families. They all have a similar phenotype and the condition may be a single relatively benign non-progressive autosomal dominant IGE syndrome with high penetrance and genetic heterogeneity.[185,186,191] Its categorisation by some authors[192] among progressive myoclonus epilepsy is questionable (see Chapter 17).

Epidemiology

Age at onset of cortical tremor and myoclonus varies from 11 to 50 years. ADCME is probably the most common of all autosomal IGE syndromes.

Aetiology

ADCME, as the name suggests, is of autosomal dominant inheritance with high penetrance and genetic heterogeneity. The genes for ADCME have been mapped to 8q24 in Japanese[193,194] and 2p11.1-q12.2 in European families.[185,186,195] Conversely, none of these loci were found in a large French family with ADCME linked to chromosone 16pl3.[188]

Clinical manifestations

Adult-onset cortical tremor and myoclonus are the defining symptoms. Cortical tremor looks like fine shivering of the fingers and hands intensified by posture, fine movement, and emotional and physical stress. The majority of patients also suffer from cortical myoclonus manifesting with distal, arrhythmic and erratic jerks of mainly the hands and fingers. These are also exaggerated by posture, fine movement, and emotional and physical stress. Most patients (80%) also have infrequent GTCSs in periods of worsening myoclonus. GTCSs are usually precipitated by sleep deprivation and photic stimulation. Rarely, in some families, additional complex focal seizures may occur. Mental and neurological states are usually normal. Families with members having concurrent migraine or blindness have been reported.

Diagnostic procedures

The EEG shows generalised polyspikes and waves and photoparoxysmal responses. Photomyogenic responses may also be present. Somatosensory and visually evoked potentials are of very high amplitude. Consistent with cortical myoclonus, long-loop C-reflexes are enhanced and cortical spikes precede the rhythmic jerk on jerk–locked EEG back-averaging.[186] Surface EMG shows irregular, arrhythmic or semirhythmic EMG bursts at around 10 Hz. These EMG bursts last about 50 ms and are usually synchronous between agonist and antagonist muscles, without the regular agonist/antagonist alternation of the essential tremor.[185,186]

Prognosis

ADCME is a non-progressive disorder. Epileptic seizures are usually infrequent, but cortical tremor and myoclonus may sometimes be severe. Occasionally, mental decline is reported in old age.

Differential diagnosis

Cortical tremor may be misinterpreted as essential tremor from which it is clinically and electrophysiologically different.

Management

This is with AEDs that have anti-myoclonic activity, such as valproate, phenobarbital, clonazepam and levetiracetam.[7,185,186,196] Piracetam in high doses is often beneficial for the cortical tremor. Lamotrigine, gabapentin, tiagabine and pregabalin, because of pro-myoclonic action, are contraindicated.

Genetic counselling, as with the autosomal dominant disorders (see Chapter 14), is part of the management.

AED treatment of IGEs[11,12,17,23]

IGEs demand different treatment strategies from the focal epilepsies.[11,12,17,23] Ignoring this fact results in avoidable intractability, morbidity and sometimes mortality. Nearly half of patients with IGEs are treated with inappropriate AEDs. Practising physicians have a colossal task in not only properly diagnosing IGE, but also in deciding which of the many older and newer AEDs are the most suitable (Tables 7.12 and 13.6) and which are contraindicated (Table 13.7) for the seizures and preferably the syndromes of IGEs.

The management of women with IGEs at childbearing age has been significantly affected by the revelations of valproate adverse reactions and its practical exclusion in this specified group of patients. What are the alternatives?

Important clinical facts to remember are:

- GTCSs are the more likely cause of referral. The first task of the physician is to properly diagnose whether these are of generalised onset (primarily GTCSs) or of focal-onset (secondarily GTCSs), which have different responses to AED treatment. Table 13.8 lists AEDs licensed for the prophylactic treatment of primarily GTCSs in the USA or Europe or both. AEDs licensed and recommended for secondarily GTCSs are listed in Chapter 15.
- Absences and myoclonic jerks are other types of seizure in IGEs that should be detected. These may often occur long before the first GTCS and/or may be the main seizures, as for example with absences of CAE and JAE, and the myoclonic jerks of JME.
- Photosensitivity is a common precipitating or facilitating factor of seizures occurring in a third of patients with IGEs.

Important established documentation to remember is that:

(A) Many AEDs licensed for the treatment of focal epilepsies are contraindicated in IGEs (Table 13.7).

- tiagabine and vigabatrin are major pro-absence agents
- carbamazepine, oxcarbazepine and phenytoin exacerbate absences and myoclonic jerks
- gabapentin and pregabalin are ineffective in all types of idiopathic epileptic seizures and may exacerbate some of them, particularly myoclonic jerks.

(B) A drug efficacious in one type of generalised seizure may be ineffective or exaggerate another type of generalised seizure. Even among the AEDs licensed for the treatment of primarily GTCSs (Table 13.8):

- carbamazepine, oxcarbazepine and phenytoin exacerbate absences and myoclonic jerks
- clonazepam is the best choice of drug for myoclonic jerks, but is ineffective in primarily GTCSs
- lamotrigine is effective in primarily GTCSs and absences, but may exacerbate myoclonic jerks.[150,151,200,201]

(C) A drug efficacious in 'generalised' seizures of childhood epileptic encephalopathies may be ineffective or exaggerate IGEs:

- vigabatrin is the drug of first choice in the treatment of West syndrome, but its use is contraindicated in IGE.

(D) A drug found to be efficacious in secondarily GTCSs, may be ineffective in primarily GTCSs or deleterious in IGEs:

Efficacy and safety of primary AEDs used in the treatment of IGEs, the triad of their seizures and photosensitivity

AED	Myoclonic jerks	GTCSs	Absences	Photo-sensitivity	Serious ADRs*	Titration	Drug–drug interactions†
Valproate	Very effective	Very effective	Very effective	Very effective	Yes	Optional (2–4 weeks)	Many
Levetiracetam	Very effective	Very effective	Effective	Very effective	No	Optional (1–2 weeks)§	Insignificant‡
Lamotrigine	Exaggerates in 50%	Very effective	Very effective	Probably effective	Yes	Mandatory (6–8 weeks)	Many
Topiramate	Probably effective	Very effective	Probably effective	Undetermined	Yes	Mandatory (6–8 weeks)	Many
Clonazepam	Very effective	Ineffective	Weakly effective	Weakly effective	No	Mandatory (3–4 weeks)	Insignificant
Ethosuximide	Effective (negative myoclonus)	Ineffective	Very effective	Ineffective	Yes	Mandatory (3–4 weeks)	Insignificant
Zonisamide	Effective	Effective	Weakly effective	Ineffective	Yes	Mandatory (4–5 weeks)	Many
Phenobarbital	Effective	Very effective	Ineffective	Ineffective	Yes	Mandatory (6–8 weeks)	Many

Table 13.6 *See Chapter 7 and references 197,198; †see Pharmacopoeia and reference 199. ‡Enzyme inducers may decrease its plasma levels by 20–30%. §Sometimes the first dose is therapeutic.

AED contraindicated in the treatment of IGEs*

- Carbamazepine, oxcarbazepine and phenytoin (though they may control primarily GTCS if added to first-line drugs)
- Gabapentin (ineffective in primarily GTCS and may exacerbate absences and myoclonic jerks)
- Pregabalin (strongly pro-myoclonic)
- Tiagabine and vigabatrin (strongly pro-absence drugs with a high incidence of induced absence status epilepticus)

*Contraindicated is any AED that either makes seizures worse or is ineffective because (1) it averts beneficial AED treatment or (2) it exposes the patient to unnecessary ADRs (some of which may be life threatening) with no benefit to the illness

Table 13.7

- gabapentin and pregabalin are AEDs licenced for 'the treatment of focal and secondarily GTCSs', are ineffective in primarily GTCSs and may aggravate other types of IGE seizures, particularly myoclonic jerks
- tiagabine, an AED licensed for the treatment of focal and secondarily GTCSs, is a potent pro-absence agent that induces absence seizures and provokes absence status epilepticus, often ending with GTCSs in IGE.

AEDs licensed (FDA, EMEA or both) for the prophylactic treatment of primarily GTCSs	
AEDs licensed for primarily GTCSs (sole or adjunctive)	**Other types of seizure**
Carbamazepine	Exaggerates absences and myoclonic jerks
Clonazepam	Also licensed for absences and myoclonic jerks but may exaggerate GTCSs in JME
Lamotrigine	Also licensed for absences but exaggerates myoclonic jerks
Levetiracetam	Also licensed for myoclonic jerks
Phenobarbital	Also licensed for myoclonic jerks but exaggerates absences
Phenytoin	Exaggerates absences and myoclonic jerks
Primidone	Also licensed for myoclonic jerks but exaggerates absences
Topiramate	Not licensed for absences or myoclonic jerks
Valproate	Also licensed for absences and myoclonic jerks

Table 13.8

(E) In patients with primarily GTCSs, an AED that abolishes another type of seizure (i.e. absences or myoclonic jerks) does not necessarily reduce the frequency of primarily GTCSs. This contrasts with secondarily GTCSs, where AEDs that abolish focal seizures also eradicate secondarily GTCSs:

- ethosuximide is a first option AED for absence seizures and negative myoclonus but is ineffective in GTCSs
- clonazepam is the most effective anti-myoclonic AED, but its effect in absences is weak and may aggrevate GTCSs.

(F) IGEs are often easily treatable, which means that a small dose of an appropriate AED is as good as a large dose.[202]

- no difference in the control of various types of JME could be demonstrated between 1000 mg and 2000 mg of valproate.[203]

Treatment of newly diagnosed IGEs

The treatment of newly diagnosed patients with IGEs should follow the same general principles detailed in Chapter 7. Diagnosis should first establish that the patient has genuine epileptic seizures and then:

- ensure that this is IGE and not focal epilepsy
- define the types of seizure that the patient suffers in order of severity and risk to the patient
- define, if possible, the IGE syndrome.

In choosing the first AED to be recommended from Table 13.6, efficacy and adverse reactions have to be carefully balanced, because treatment is often life-long. Therefore, also consider long-term effects such as:

- adverse drug reactions (ADRs) on growth and development of children
- hormonal changes and ADRs on the reproductive life of a woman, including teratogenicity.

The management and AED treatment specific to each syndrome of IGE can be found in the description of the epileptic syndromes of this chapter.

IGEs: RCTs and evidence-based recommendations

There is an especially alarming lack of well-designed, properly conducted RCTs for patients with generalised seizures/epilepsies and for children in general.[205]

In the 2006 ILAE authoritative evidence-based review and analysis of the efficacy and effectiveness of AEDs as initial monotherapy for epileptic seizures,[205] no AED reached the high level A (AED established as efficacious or effective) or B (probably efficacious or effective) required for an AED to 'be considered for initial monotherapy – first-line monotherapy' in:

- adults and children with GTCSs
- children with absence seizures
- juvenile myoclonic epilepsy.

Myoclonic seizures or other IGEs could not even be assessed.

Clinical note

Do all primarily GTCSs of different syndromes have the same responsiveness?[12]

- It is postulated, but not proven, that primarily GTCSs of idiopathic epilepsies are all equally responsive to the various AEDs.[12] This is probable for primarily GTCSs of IGEs. However, primarily GTCSs of febrile seizures are mainly responsive to phenobarbital and valproate, but not to carbamazepine and phenytoin.
- It is likely, but not proven, that primarily GTCSs of symptomatic epilepsies do not have the same responsiveness as the primarily GTCSs of IGEs.

Knowing the answer to these questions may have a significant impact in the interpretation of certain RCTs and particularly those that have studied the effect of an AED in so-called primarily GTCSs in mixed populations of IGEs and symptomatic generalised epilepsies; e.g. in an RCT evaluating topiramate for primarily GTCS, almost half (41%) of patients had tonic seizures (24%), atypical absences (8%) and drop attacks (9%), none of which are types of seizure accepted in IGEs.204 Furthermore, to emphasise the diagnostic problems in these studies, one patient included in the topiramate analysis group was diagnosed as having Lennox–Gastaut syndrome based on information obtained after study completion.[204]

In a recent class 3 RCT involving patients with IGE,[206] valproate was significantly better than both lamotrigine (hazard ratio [HR] 1.55; 95% confidence interval [CI], 1.07–2.24) and topiramate (HR 1.89; 95% CI, 1.32–2.70) for time to treatment failure. For time to 12-month remission, valproate was significantly better than lamotrigine (HR 0.68; 95% CI, 0.53–0.89), but there was no significant difference between valproate and topiramate. Levetiracetam has not been assessed.

In addition to other methodological problems (see pages 190–193), this RCT did not study the effects of the AEDs on the different seizure types of IGE (absences, myoclonic jerks or GTCSs) or IGE syndromes. This contradicts the aforementioned principles of AED therapy of IGEs, which are in agreement with the authors' statement: 'an overall analysis, ignoring epilepsy type, might lead to an erroneous conclusion that a new drug is not inferior to a standard'.[206] In addition, like in all other RCTs, 'misclassification of patients' epilepsy type'[207] and 'questionable selection of patients'[208] may have confounded the results of RCTs examining the effect of AEDs in IGE, particularly on primarily GTCSs.

For the levels of evidence supporting the recommendations proposed in this section, see Chapter 7.

Older AEDs in IGEs[11,23]

Of the older AEDs effective in the treatment of IGEs the position is as follows (the AEDs are listed in order of efficacy in primarily GTCSs).

Valproate has superior efficacy in all seizures and syndromes of IGEs. Valproate monotherapy controls absence seizures and myoclonic jerks in about 75% and GTCSs in 70% of patients with IGE. Valproate is the first-choice AED in IGEs for men. However, valproate is undesirable in women because of its teratogenic effects and its tendency to cause weight gain and polycystic ovary syndrome (see Principles of therapy in women with epilepsy; Chapter 7). The risk for major congenital malformations (MCMs) with valproate monotherapy is three to five times higher than the background rate. This is higher with increasing doses of valproate, and it is double or more in combination with other AEDs, particularly with lamotrigine (10%).[209,210]

Phenobarbital is the preferred drug for the treatment of primarily GTCSs and JME when cost is of concern. It worsens absences.

Phenytoin is effective in primarily GTCSs. It worsens absences and possibly myoclonic jerks.

Carbamazepine is effective in primarily GTCSs, but aggravates absences and myoclonic jerks.

Clonazepam, even in small doses of 0.5–1 mg, is probably the most potent antimyoclonic drug with some anti-absence effect; it is ineffective in primarily GTCSs or, by suppressing myoclonic jerks, deprive patients of the warning symptoms of an impeding GTCS.[157]

Clobazam has not been evaluated in primarily GTCSs of IGE, but it may be effective in some cases. Clobazam is a very useful AED in focal epilepsies and secondarily GTCSs. However, in IGE, I have found clobazam to be far inferior to clonazepam in controlling myoclonic jerks, and may have only a very weak effect on absences.

Acetazolamide has been used for treating primarily GTCSs in cases resistant to conventional treatment, although its use may induce nephrolithiasis.[211]

Ethosuximide is a potent anti-absence AED controlling 70% of absences in monotherapy. It may improve myoclonic seizures (particularly negative epileptic myoclonus), but is ineffective in GTCSs.

Newer AEDs useful in IGEs

Of the newer AEDs, only levetiracetam, lamotrigine, topiramate and zonisamide (in order of efficacy) appear to be effective agents in IGEs. All others – vigabatrin, tiagabine, gabapentin, pregabalin and oxcarbazepine – are contraindicated in IGEs.

Levetiracetam, because of its efficacy in primarily GTCSs,[103] myoclonic jerks[104] and photosensitivity and its safer ADR profile, appears to be the most probable substitute for valproate in at least JME and women.[146–148,212]

Of significant importance in the treatment of women with IGEs are the reported results of the UK Pregnancy Registry (see Table 7.15).[214]

Lamotrigine is effective in primarily GTCSs[215] and absence seizures,[205] whereas it aggravates myoclonic jerks.[151] It has important pharmacodynamic interactions with valproate. Problems with lamotrigine include: a high incidence of idiosyncratic reactions that are more prominent in children and can occasionally be fatal; marked interactions with pregnancy[153,155,216] and hormonal contraception;[217] and possible teratogenicity (see Principles of therapy in women with epilepsy, Chapter 7).[156,210]

Topiramate[218] is another broad-spectrum AED that is effective in primarily GTCSs[205] and myoclonic jerks, with some weak action on absence seizures.[219] In the IGEs, including JME, it appears to be less effective than valproate but more effective than lamotrigine.[206] Topiramate is unlikely to achieve monotherapy status in the long-term treatment of IGEs, mainly because of its many ADRs and its relatively inferior efficacy in IGEs compared with valproate and levetiracetam. More recently, concerns have also been raised about possible teratogenic effects (page 208) in women with epilepsy and that in animal experiments topiramate may damage the retina, similar to vigabatrin.[220]

Zonisamide is also a broad-spectrum AED, but its role in IGE is largely uncertain.[221] It probably has a weak beneficial effect in primarily GTCSs, absences and jerks, although a few patients may have an excellent response.[222] ADRs may be particularly troublesome in children (see page 612).

Monotherapy with one of the AEDs listed in Table 13.6 is unlikely to fail if it is appropriately evaluated and chosen for the particular IGE syndrome and individual patient. Monotherapy should not be abandoned before making sure that the maximum tolerated dose has been achieved.

Management of patients with difficult to treat IGEs

IGEs have a better prognosis, and a more favourable response to, appropriate AEDs than symptomatic and focal epilepsies: 'most patients with IGE are easily controlled with appropriate medication, refractory patients are rare'.[223] Prevalence of intractable IGE may be in the order of 10–30% and this is mostly due to delayed or inappropriate treatment.[224]

Management of patients with difficult to treat IGEs, providing that they truly suffer from epileptic seizures, should follow the same principles as detailed in Chapter 7:

- Based on clinical and EEG evidence, establish the type or types of seizures (absences, myoclonic

jerks and GTCSs alone or in combination), and make sure that these are primarily and not secondarily generalised. Previous EEGs, particularly in untreated stages, are invaluable.
- Establish precipitating factors and circadian distribution as well as their effect regarding intractability.
- List in chronological order all AEDs previously used, and in what doses and combinations. Establish which drugs were beneficial and which made the situation worse.
- Consider thoroughly the current situation regarding: (1) seizures – which are the more predominant and more disturbing; and (2) AEDs – which are definitely or possibly effective, ineffective or contraindicated with respect to seizures and adverse reactions.
- Consider thoroughly all the above, including sex, age and compliance, in making a definite plan of which AEDs with adverse effects (seizure efficacy and patient tolerability) should be withdrawn and which of the indicated AEDs should be increased in dosage or added to the scheme.
- Of the newer AEDs, those which are likely to be effective as monotherapy are also the most likely to be suitable in polytherapy. The order of priority as determined by efficacy, safety, drug–drug interactions and other parameters are levetiracetam, lamotrigine, topiramate and zonisamide. All other newer AEDs – gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin – are contraindicated.

Drug withdrawal

In CAE, treatment may be slowly withdrawn 1–3 years after controlling all absences. All other syndromes of the IGEs are probably life-long and confront the usual textbook advice of withdrawal of medication after 2 or 3 years from the last seizure because relapses are probably unavoidable. However, if seizures are mild and infrequent, drug withdrawal may be attempted. This should be in small decrements, probably over years, warning the patient that re-appearance of even minor seizures such as absences or myoclonic jerks mandates continuation of treatment. EEG confirmation of the seizure-free state is needed during the withdrawal period.

Useful reminder

Small doses of the added AED are sometimes very effective.

In cases with persistent myoclonic jerks, clonazepam in a single small dose (0.5–2 mg) prior to sleep may have a dramatic beneficial effect.[75]

In men on valproate, adding small doses of lamotrigine (25–50 mg) is very effective because of pharmacodynamic interactions between these drugs.

Management of status epilepticus in IGEs

IGEs have a high prevalence of absence status epilepticus, which often goes undetected or is misdiagnosed as a prodrome or focal non-convulsive status epilepticus (which is less common than absence status epilepticus).[225] Conversely, generalised tonic–clonic status epilepticus is less common in IGEs than other epilepsies.

The management of status epilepticus is detailed in Chapter 3.

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fourteen

Familial (autosomal dominant) focal epilepsies

In the past two decades, significant progress in molecular and statistical genetics has led to breakthroughs in the mapping and identification of gene variants of genetic diseases that follow Mendelian patterns of inheritance in humans. Of more than 500 genetic loci associated with Mendelian genetic diseases that have been mapped to specific chromosomal locations, almost 100 gene variants have been cloned on the basis of their position. The cloning and sequencing of these gene variants has helped elucidate the function and cellular biology of their gene products.

Similar advances have been made in identifying the genetic and molecular basis of: [1–7]

(a) many diseases that are frequently associated with epileptic seizures such as metabolic, storage, and mitochondrial disorders and symptomatic epilepsies of malformation of cortical development. Direct molecular diagnosis is now possible in several of these inherited diseases, such as Lafora disease (see chapter 17).

(b) various syndromes of focal and generalised epilepsies (as detailed in the description of each of them in this book). Most of these have a polygenic complex inheritance due to multiple susceptibility genes; a number of genes may each make a subtle contribution to the disease and genes may determine how a person reacts to environmental factors contributing to the disease. However, a few are monogenic Mendelian (single gene) epileptic syndromes and have been successfully identified, mainly by Berkovic and his team.[1,4,7,8] Identification of the various forms of familial focal epilepsy is difficult, particularly in small families in which there are insufficient numbers of individuals to identify a specific pattern. Berkovic et al.[8] have recently provided clinical guidelines for this task, "which will eventually be supplanted by specific molecular diagnosis".

Recommended websites on genetics

Definitions, glossary and details on genetics can be found through appropriate websites, of which the most important are those provided by the National Human Genome Research Institute (www.nhgri.nih.gov), the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov), the Online Mendelian Inheritance in Man (OMIM; www.ncbi.nlm.nih.gov/omim), the Human Genome Organisation (HUGO) Gene Nomenclature Committee (www.gene.ucl.ac.uk/nomenclature/index.html) and Swiss-Prot (www.expasy.org/sprot).

The GeneTests website (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests) is a publicly funded medical genetics information resource available at no charge, which provides current, authoritative information on genetic testing and its use in diagnosis, management and genetic counselling, with an illustrative glossary. This is now hosted at the National Center for Biotechnology Information.

Familial (autosomal dominant) focal epilepsies are monogenic forms of epilepsy identified in large but rare families, with an epileptic trait segregating in the absence of environmental factors. In these families, phenotypes are determined by mutations

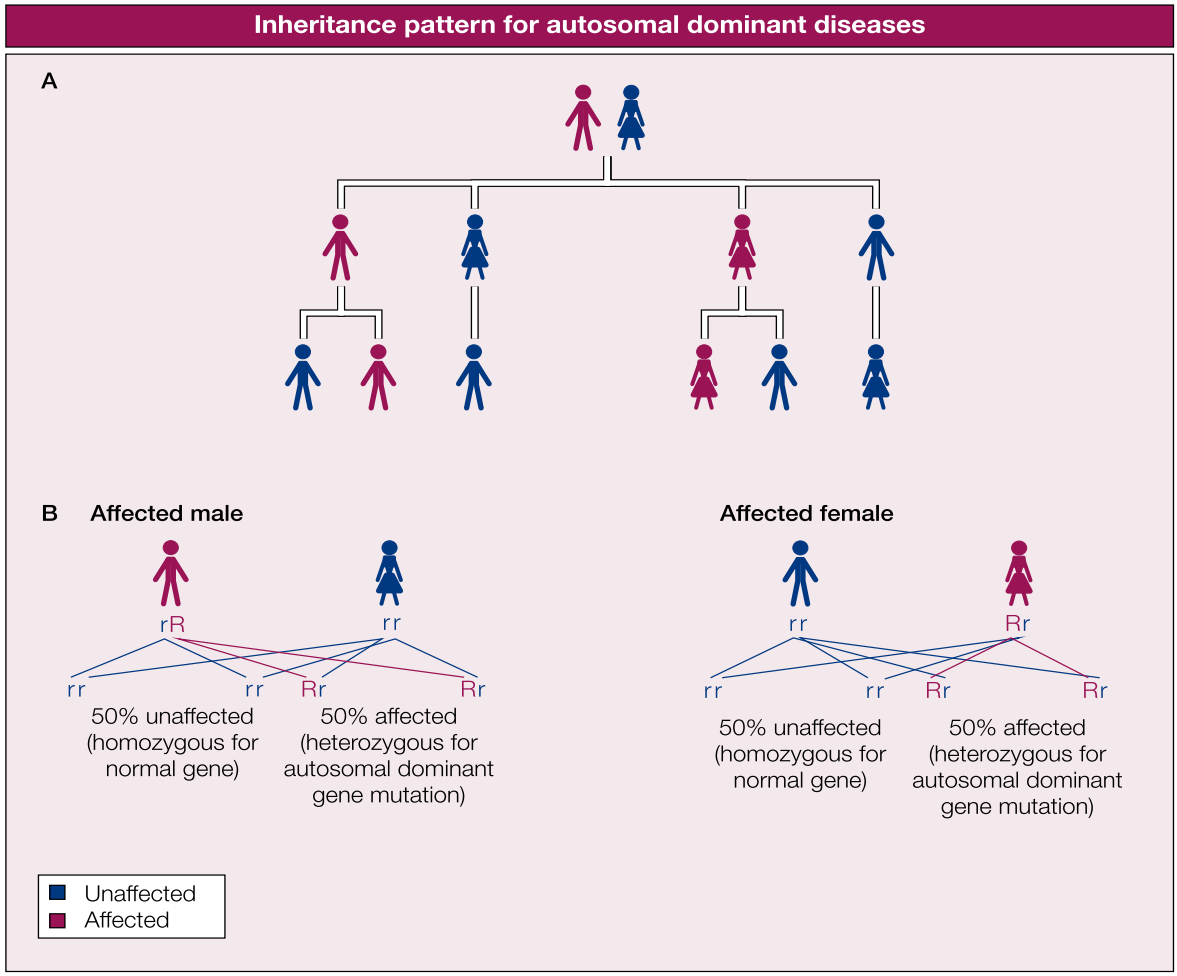

Table 14.1 (**A**) Pedigree illustrating autosomal dominant inheritance pattern: autosomal dominant conditions are often seen in multiple generations; mothers and fathers are equally likely to transmit or inherit the disorder; sons and daughters of an affected parent are equally likely to inherit and transmit the disorder. (**B**) Probability of transmitting an autosomal dominant gene mutation to offspring (R = autosomal dominant mutant gene; r = normal gene).
Adapted with permission from Panayiotopoulos (2007).[9]

in susceptibility genes, some of which have been identified or localised. Most of the genes discovered code for either voltage-gated or ligand-gated ion channel subunits, which indicates that, at least in part, familial (autosomal dominant) focal epilepsies are a family of channelopathies. Familial lateral temporal lobe epilepsy was the first non-ion channel disease in this group to be described. Marked phenotypic variability and genetic heterogeneity underlie all known monogenic epileptic syndromes.

The following syndromes have been recognised (Table 5.2):

- benign familial neonatal seizures (Chapter 8)
- benign familial infantile seizures (Chapter 9)
- autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- familial temporal lobe epilepsy:
  - familial mesial temporal lobe epilepsy
  - familial lateral temporal lobe epilepsy
- familial focal epilepsy with variable foci (syndrome in development).

Useful glossary

Autosomal dominant: a pattern of inheritance in which an affected individual has only one copy of a mutant gene and one normal gene on one of the 22 pairs of autosomal (nonsex) chromosomes (Figure 14.1). One mutated copy of the gene is sufficient for a person to be affected. Each affected person usually has one affected parent. The chance of passing the gene to offspring is 50% for each pregnancy.

Chromosome: The self-replicating genetic structure of cells containing the cellular DNA that bears in its nucleotide sequence the linear array of genes. In prokaryotes, chromosomal DNA is circular, and the entire genome is carried on one chromosome. Eukaryotic genomes consist of a number of chromosomes whose DNA is associated with different kinds of proteins.

Chromosome region p: A designation for the short arm of a chromosome.

Chromosome region q: A designation for the long arm of a chromosome.

Gene: The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product (i.e. a protein or RNA molecule).

Gene mapping: Determination of the relative positions of genes on a DNA molecule (chromosome or plasmid) and of the distance, in linkage units or physical units, between them.

Genetic screening: Testing a group of people to identify individuals at high risk of having or passing on a specific genetic disorder.

Genetic testing: Analysing an individual's genetic material to determine predisposition to a particular health condition or to confirm a diagnosis of genetic disease.

Genome: All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.

Genotype: The genetic constitution of an organism, as distinguished from its physical appearance (its phenotype).

Insertion: A chromosome abnormality in which a piece of DNA is incorporated into a gene and thereby disrupts the gene's normal function.

Linkage: The proximity of two or more markers (e.g., genes, RFLP markers) on a chromosome; the closer the markers, the lower the probability that they will be separated during DNA repair or replication processes (binary fission in prokaryotes, mitosis or meiosis in eukaryotes), and hence the greater the probability that they will be inherited together.

Linkage map: A map of the relative positions of genetic loci on a chromosome, determined on the basis of how often the loci are inherited together. Distance is measured in centimorgans (cM).

Locus (pl. loci): The position on a chromosome of a gene or other chromosome marker; also, the DNA at that position. The use of locus is sometimes restricted to mean expressed DNA regions.

Mendelian inheritance: Inheritance pattern based on a single affected gene. The inheritance pattern of a Mendelian disease depends on whether it is autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, or Y-linked. Also related but not truly Mendelian are some of the rarer inheritance patterns (e.g. mosaicism, anticipation, triplet repeat).

Monogenic disorder: A disorder caused by mutation of a single gene.

Mutation: Any heritable change in DNA sequence.

Penetrance: The probability of a gene or genetic trait being expressed. "Complete" penetrance means the gene or genes for a trait are expressed in all the population who have the genes. "Incomplete" penetrance means the genetic trait is expressed in only part of the population. The percentage penetrance also may change with the age range of the population.

Phenocopy: A trait not caused by inheritance of a gene but appears to be identical to a genetic trait.

Phenotype: The physical characteristics of an organism or the presence of a disease that may or may not be genetic.

Polygenic disorder: Genetic disorder resulting from the combined action of alleles of more than one gene (e.g., heart disease, diabetes, and some cancers). Although such disorders are inherited, they depend on the simultaneous presence of several alleles; thus the hereditary patterns usually are more complex than those of single-gene disorders.

Recessive gene: A gene which will be expressed only if there are 2 identical copies or, for a male, if one copy is present on the X chromosome (Figure 17.1).

Sequencing: Determination of the order of nucleotides (base sequences) in a DNA or RNA molecule or the order of amino acids in a protein.

Single-gene disorder: Hereditary disorder caused by a mutant allele of a single gene (e.g. Duchenne muscular dystrophy, retinoblastoma, sickle cell disease).

Patients and their families should be offered genetic counselling as for autosomal dominant disorders of known aetiology and gene mutations.

The heterogeneity of mutations described to date has precluded the development of simple diagnostic tests for familial autosomal dominant focal epilepsies.[7] However, identification of a *KCNQ2*, *KCNQ3*, or *SCN2A* mutation in neonatal autosomal-dominant epilepsies can prevent unnecessary investigations and diagnostic uncertainties in these patients. Similarly, identification of LGI1 mutations in the familial lateral temporal lobe epilepsy and nicotinic receptor abnormalities in ADNFL is clinically valuable.[2] Currently, testing for these genes is not routinely available in clinical practice and is expensive because of their size and the distributions of mutations.[2]

Autosomal dominant nocturnal frontal lobe epilepsy

ADNFLE[10–17] is the first distinctive syndrome of focal epilepsy to be described with a single gene inheritance pattern.[18]

Demographic data

Onset is mainly in late childhood at 7–12 years of age (mean 11 years), although it ranges from infancy (2 months) to adulthood (56 years). Overall, 90% of patients have their first seizure before the age of 20. Men and women are equally affected. The prevalence is unknown, but the increasing number of publications from 1994 indicates that ADNFLE may not be an uncommon disease.

Clinical manifestations

ADNFLE manifests with frequent (almost every night) clusters of brief (20–50 s) nocturnal motor seizures with hyperkinetic/dystonic features and/or tonic manifestations. These hypermotor seizures of ADNFLE are identical to those of the supplementary sensorimotor area (SMA) as detailed in Chapter 15 (page 459).

Seizures are of sudden onset and their termination is devoid of post-ictal symptoms. Motor symptoms consist of thrashing hyperkinetic movements and dystonic posturing (shoulder or pelvic thrashing movements, bipedal and fencing postures), or tonic stiffening of the limbs and the body, often with superimposed clonic components. Patients may be thrown out of bed or find themselves prone in a crawling position. Injuries may occur. Paroxysmal arousals or awakening during non-rapid eye movement (NREM) sleep may also represent mild seizures that may or may not be associated with transient dystonic posturing. Two-thirds of patients experience a non-specific aura of somatosensory, sensory, psychic and autonomic symptoms. Consciousness is usually preserved. Sleep is abruptly interrupted, but immediately resumes with the end of the seizure. The post-ictal state is entirely normal.

Secondarily generalised tonic–clonic seizures (GTCSs), which occur in two-thirds of patients, are very infrequent, nocturnal and are mainly seen in untreated patients or after withdrawal of medication.

ADNFLE shows marked intra- and interfamily variability in severity. Affected family members usually have clusters of seizures with a weekly or monthly frequency, but some patients have attacks every night; a few individuals have mild and rare attacks that are identified only during systematic study of the family. However, in one study the clinical phenotypes were homogeneous in two families and difficult to separate on clinical grounds, irrespective of chromosomal linkage and mutations.[19]

Circadian distribution

Seizures are most likely to occur in the hypnagogic state of sleep or shortly before awakening. Diurnal attacks are rare.

Precipitating factors

Stress, fatigue and alcohol increase the frequency of fits. Seizures in children provoked by movement and sound stimulation are reported.[11]

Aetiology

ADNFLE is an autosomal dominant disorder. Penetrance is about 70%, although it can be much lower in some families.

Initially, two human ADNFLE gene loci were identified: *CHRNA4*, which encodes the neuronal nicotinic acetylcholine receptor (nAChR) α_4-subunit protein and is located at chromosome region 20q13.2–q13.3; and *CHRNB2*, which encodes the nAChR β_2-subunit protein and is located at chromosome region 1q21.3. The nAChRs are members of a superfamily of ligand-gated ion channels that mediate fast signal transmission at synapses. Later, in other families with ADNFLE, the above genes were excluded and one family was linked to chromosome 15q24.[20]

Recently, a large pedigree segregating sleep-related epilepsy has been reported in which seizures are associated with fear sensation, tongue movements and nocturnal wandering, closely resembling nightmares and sleep walking. The identified gene for this familial sleep-related focal epilepsy is *CHRNA2*, which encodes the neuronal cholinergic receptor α_2-subunit protein and is located on chromosome 8p21.[6,21]

Current evidence indicates that ADNFLE manifests with considerable genetic heterogeneity despite its homogeneous clinical features.[22]

Diagnostic procedures

The diagnosis of ADNFLE is based on clinical history. Video-EEG during sleep shows ictal frontal discharges in 32% of patients and ictal, anterior, rhythmic, slow-wave activity in another 47% of patients.[23] Molecular genetics testing reveals mutations in *CHRNA4* or *CHRNB2* in about 20–30% of individuals with a positive family history and fewer than 5% of individuals with a negative family history.[14] Brain imaging is normal.

Prognosis

Seizures are lifelong, although in mild cases they may appear for only a brief period. Spontaneous remissions and relapses occur. Some patients have frequent attacks that are refractory to medication. Attacks may become milder in the fifth or sixth decade of life and be described as fragments of previous seizures.

Differential diagnosis

Misdiagnosis of seizures as benign nocturnal parasomnias, night terrors, nightmares, or psychiatric and medical disorders is common (around 80% of patients).[23] 'Nocturnal paroxysmal dystonia'[24] and 'hypnic tonic postural seizures of frontal lobe origin'[25] are certainly frontal lobe seizures and most patients probably have ADNFLE.

Symptoms of awakening with the feeling of choking, abnormal motor activity during sleep and excessive daytime sleepiness are relatively common in both obstructive sleep apnoea syndrome and nocturnal frontal lobe epilepsy. All-night video-polysomnographic monitoring is needed to provide a firm diagnosis.[23]

On clinical and EEG grounds, ADNFLE may be identical to non-familial symptomatic or cryptogenic frontal lobe epilepsy from the supplementary SMA (Chapter 15, page 459). Family history in ADNFLE and MRI abnormalities in symptomatic SMA epilepsy are the main distinguishing features.

Management

Management is the same as for the focal epilepsies. Carbamazepine monotherapy is effective. A third of patients are resistant to treatment. Levetiracetam

may be a first option (Table 15.3). Add-on clobazam may be useful, or lamotrigine and topiramate may be effective. Cognitive impairment due to topiramate appears to be easily overlooked and underestimated in patients treated with this drug.[26]

Nicotine patches, together with appropriate anti-epileptic drugs (AEDs), may be of benefit in some individuals with ADNFLE.[16,27] Seizure freedom was significantly associated with tobacco use.[16]

Genetic counselling as per the autosomal disorders should be carried out.

Familial (autosomal dominant) temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is largely acquired and caused by lesions, such as hippocampal sclerosis, tumours, trauma, vascular or malformations of cortical development. The genetic involvement in some forms of TLE has been elucidated only recently. Familial TLE is of autosomal dominant inheritance and has two types:[28]

1. familial mesial temporal lobe epilepsy (FMTLE)
2. familial lateral temporal lobe epilepsy (FLTLE), which is also described as 'partial epilepsy with auditory symptoms'.[29]

Both these forms of familial TLE begin in adolescence or adult life and usually have a benign course.

Familial mesial temporal lobe epilepsy

FMTLE is an autosomal dominant disease characterised by seizure symptomatology of mesial TLE, such as déjà vu, experiential and autonomic manifestations (see Chapter 15).[1,30–36]

Demographic data

Onset is typically in teenage or early adult life with a median in the middle of the third decade of life. No children under the age of 10 years have been identified with this disorder. Women (58%) may be affected more than men. Epidemiology is unknown. Berkovic proposes that this may be a common condition.[30,31,34]

Clinical manifestations

Seizures are generally mild, infrequent and well controlled with AEDs. Simple focal seizures (90%) are far more common than complex focal seizures (66%) and may be the only seizure type (18%). The main ictal manifestations consist of déjà vu, other experiential phenomena and hallucinations (almost all) alone or together with autonomic disturbances. Emotional symptoms of fear and panic, visual and auditory illusions of distortions of light and sound, and somatosensory sensations of diffuse, not localised, numbness and tingling are other common ictal symptoms.

Ascending epigastric sensation does not occur in familial mesial TLE.

Secondarily GTCSs occur in only two-thirds of patients with FMTLE and, in 50% of cases, they occur before initiation of appropriate treatment. GTCSs are infrequent with the worst possible scenario of one GTCS per year.

Patients are neurologically and mentally normal, and the condition does not appear to affect their otherwise normal life, particularly when on medication.

Aetiology

Autosomal dominant inheritance with reduced penetrance (60%) is the most likely mode of inheritance.[31,33,36] A recent study identified a genetic locus for FMTLE on chromosome 4q13.2-q21.3, spanning a 7-cm region.[35]

Diagnostic procedures

MRI is often normal,[30,31,35] but in severe cases hippocampal atrophy can be found, as well as some rare examples of familial hippocampal sclerosis.[30,37] Minor and non-specific abnormalities, which manifest as diffuse, small, high signal areas on T2-weighted images, may be seen. However, in a recent study hippocampal atrophy was present in 90% of cases of FMTLE and in 83% of cases of non-familial MTLE.[38]

Inter-ictal FDG-PET may show ipsilateral temporal hypometabolism in patients with active seizures.

Electroencephalography

The inter-ictal EEG is usually normal (50% of cases), and shows mild, focal, slow waves (28%) or sparse, usually unilateral (22%), sharp–slow-wave complexes localised to the temporal region.[31,39] Sleep may occasionally activate epileptiform abnormalities.

Only three seizures have been recorded.[34] In one seizure, a right temporal ictal discharge appeared during the attack, which began with fear and was followed by loss of awareness, staring, swallowing and left-hand automatisms. The two other seizures occurred in the same patient. No definitive epileptiform changes were recorded in one seizure, which comprised an aura of buzzing in the ears, followed by oral automatisms and impaired awareness. No lateralised EEG changes occurred in the other seizure, which started with an aura and early left-sided dystonia that rapidly progressed to secondarily generalised convulsions.

Differential diagnosis

The main difficulty is probably in differentiating patients with very mild and infrequent seizures of predominantly déjà vu from normal phenomena. This may be impossible in individual cases without other overt seizure symptoms or other family members with TLE.

FMTLE should be mainly differentiated from hippocampal epilepsy. The main differentiating features in favour of FMTLE are:

- onset in the teens or early adult life
- no febrile convulsions or other antecedent factors of epilepsy
- no ictal symptoms of rising epigastric aura
- mild and infrequent seizures that may remit
- usually normal MRI (see however reference 38).

Table 15.1 shows the key differences between mesial and lateral temporal lobe epilepsy.

Prognosis

The prognosis is usually good. A sixth of cases with mild simple focal seizures alone (16%) would never know that they have an epileptic disorder if other family members were not affected. Of the cases with more overt seizure manifestations, only 66% have complex focal seizures and GTCSs that are again rather infrequent and respond well to AEDs. It is rare for seizures to continue after drug treatment (10–20% of cases). The cross-sectional nature of the study of Berkovic, *et al*[30,31,34] precluded accurate determination of remission rates, but the histories of affected individuals suggested that long remissions, with or without therapy, were common. Conversely, in the Montreal series, drawn largely from patients considering surgical treatment for epilepsy, a more severe clinical spectrum was observed.[33,40]

Management

Seizures are usually easily controlled with carbamazepine or phenytoin.[30,31,34] Patients with refractory FMTLE have a good surgical outcome when unilateral or clearly asymmetrical hippocampal atrophy are identified.[40] Pre-operative investigation should be the same as that in patients with sporadic refractory FMTLE.[40]

Familial lateral temporal lobe epilepsy

Synonyms: partial epilepsy with auditory symptoms, autosomal dominant focal epilepsy with auditory features.

'Familial (autosomal dominant) lateral temporal lobe epilepsy (FLTLE)' and 'autosomal dominant focal epilepsy with auditory features' are the same disorders caused by defects in the same gene.[41–48] Their symptomatology is of lateral TLE (see page 454). FLTLE is the first non-ion channel familial epilepsy to have been discovered.

Demographic data

Onset of FLTLE is typically in teenage or early adult life, but may be earlier (5–10 years of age) or later.

Clinical manifestations

FLTLE is characterised by:

- mild seizures with mainly auditory hallucinations
- mainly nocturnal and infrequent GTCSs
- excellent response to treatment.

Seizures are generally mild, infrequent and well controlled with AEDs. Simple focal seizures are the most common of all. They mainly consist of simple auditory hallucinations such as ringing, humming, clicking or unspecified noises. Other sensory symptoms, such as visual (lights, colours and simple figures), olfactory, vertiginous or cephalic features, are frequent. Autonomic, experiential and motor symptoms are less common. Infrequently, simple focal seizures may progress to complex focal seizures. FLTLE with mainly brief aphasic seizures has also been described.[49]

Secondarily GTCSs are rare and predominantly nocturnal.

Aetiology

FLTLE has autosomal dominant inheritance with high penetrance (about 80%). Mutations of the leucine-rich, glioma-inactivated 1 (*LGI1*)/epitempin gene on chromosome 10q are responsible for the syndrome.[45,47,48,50,51] FLTLE is genetically heterogeneous. *LGI1* mutations are specific for FLTLE but do not occur in all families.

Diagnostic procedures

EEG and MRI are often normal or show usually mild and non-specific abnormalities. Inter-ictal EEG epileptiform abnormalities rarely occur.

Prognosis

The prognosis is excellent. Patients are neurologically and mentally normal, and the condition does not appear to affect their otherwise normal life, particularly when on medication. However, a recent report describes a family with documented FLTLE with drug resistant seizures and recurrent episodes of status epilepticus with dysphasic features.[52]

Differential diagnosis

FLTLE should be differentiated from other structural causes of lateral TLE (page 455), which lack a similar family history. FLTLE is markedly different from hippocampal and other types of FMTLE (see Table 15.1). Auditory hallucinations are the main ictal symptom of FLTLE, but may not occur in some patients. Conversely, déjà vu and other experiential phenomena are the predominant seizure manifestations of FMTLE.

Management

Management is the same as for the focal epilepsies (Table 15.3). Most authors found carbamazepine monotherapy very effective. Usually, the response to carbamazepine is excellent. Levetiracetam is the next AED option. Drug-resistant cases have been described.[52]

Familial focal epilepsy with variable foci

Familial focal (partial) epilepsy with variable foci is an autosomal dominant syndrome characterised by focal seizures originating from different brain regions in different family members in the absence of detectable structural abnormalities.[8,53–57]

Demographic data

Age at onset varies markedly (range from months to 43 years), although the mean age at onset of seizures is 13 years. To date, the disorder has been reported in around eight unrelated families.

Clinical manifestations

The defining feature of this syndrome is that different family members have focal seizures emanating from different cortical locations, including temporal, frontal, centroparietal and occipital regions. Each individual patient has the same electroclinical pattern of single location focal epilepsy. Seizures are often nocturnal, and there is great intrafamilial variability. Severity varies among family members: some are asymptomatic manifesting with only an EEG spike-focus; and most are easily controlled with AEDs, but a few may be intractable to medication.

Aetiology

Familial focal epilepsy with variable foci is a rare inherited syndrome with autosomal dominant inheritance and penetrance of about 60%. In two families, the disease has been mapped to a locus in a 3.8-cM interval on chromosome 22q11-q12, between markers *D22S1144* and *D22S685*.[8,55,57] However, in the original Australian family, the disorder was not found to be linked to chromosome 22, indicating genetic heterogeneity. In this family, a genome-wide search failed to demonstrate definitive linkage, but a suggestion of linkage was found on chromosome 2q.[53]

Diagnostic procedures

Neuroimaging is usually normal.

Electroencephalography

Inter-ictal focal epileptiform abnormalities occur in most patients. Their locations vary between family members and may occur in the temporal, frontal, centroparietal or occipital regions, but for each individual a single focus remains constant over time. These abnormalities are facilitated or brought on by sleep. Clinical seizures are concordant with EEG localisation. EEG severity varies significantly in different individuals and does not correlate with seizure frequency. Normal family members may also have an EEG spike focus, which indicates that this is likely to be a marker for the familial partial epilepsy with variable focal trait.

Prognosis

Development is usually normal.

Management

The effects of the AEDs described in Chapter 18 have not been evaluated directly, but carbamazepine and phenytoin appear to be effective (Table 15.3).

Other possible familial (autosomal dominant) focal epilepsies not yet recognised

Of those syndromes not yet recognised by the ILAE Task Force, the most important and well documented are:

- autosomal dominant rolandic epilepsy and speech dyspraxia[58,59]
- focal epilepsy with pericentral spikes and evidence for linkage to chromosome 4p.

Autosomal dominant rolandic epilepsy and speech dyspraxia[58,59]

'Autosomal dominant rolandic epilepsy and speech dyspraxia: a new syndrome with anticipation' appears to be a rare hereditary condition that was described by Berkovic, Scheffer and associates.[58] They extensively studied a family of nine affected individuals in three generations with nocturnal oro-facial focal seizures, secondarily GTCSs and centrotemporal epileptiform discharges, associated with oral and speech dyspraxia and cognitive impairment. The speech disorder was prominent, but differed from that of Landau–Kleffner syndrome and epilepsy with continuous spike-and-wave during sleep. Patients in previous generations were not so severely affected, but they also had neurological deficits, mainly of oral and speech dyspraxia with no evidence of dysarthria.

The authors assessed that:

> The electroclinical features of this new syndrome of autosomal dominant rolandic epilepsy resemble those of benign rolandic epilepsy, a common inherited epilepsy of childhood. This family shows clinical anticipation of the seizure disorder, the oral and speech dyspraxia, and cognitive dysfunction, suggesting that the genetic mechanism could be expansion of an unstable triplet repeat. Molecular studies on this syndrome, where the inheritance pattern is clear, could also be relevant to identifying a gene for benign rolandic epilepsy where anticipation does not occur and the mode of inheritance is uncertain.[58]

However, the clinical presentation of these patients with a permanent neurological deficit, sometimes preceding the seizures, can hardly be considered as 'resembling benign rolandic epilepsy' or 'epitomising the archetypal benign rolandic epileptic attack'. A new family with autosomal dominant rolandic epilepsy and speech disorder has been recently described.[61]

Focal epilepsy with pericentral spikes

Focal epilepsy with pericentral spikes is based on the study of a single family.[60] All affected members manifested a variety of seizure types, including hemiclonic, hemitonic GTCSs, and simple focal (stereotyped episodes of epigastric pain) and complex focal seizures consistent with temporal lobe semiology. The syndrome is benign, either it does not require treatment or it responds to a single AED. Seizure onset is in the first or second decade of life, with seizures persisting up to the age of 71 years and documented EEG changes up to the age of 30 years. A key feature of this syndrome is a characteristic EEG abnormality of spikes or sharp waves in the pericentral region (centroparietal, centrofrontal or centrotemporal). The syndrome may be overlooked, because of the variability in penetrance and seizure types among affected family members. There is evidence for linkage to chromosome 4p15.

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fifteen

Symptomatic and cryptogenic (probably symptomatic) focal epilepsies

Symptomatology and classification

Focal (anatomical, topographical or localisation related) epilepsies manifest with seizures that emanate from an epileptogenic focus anywhere within the brain.[1] Ictal symptoms, particularly at onset, are determined by localisation and not aetiology. However, specific anatomical localisation is sometimes difficult, as, for example, when seizures originate from clinically silent epileptogenic regions.

The ILAE Commission (1989)[1] classifies focal epilepsies, according to their topographical/anatomical origin (Table 5.1), as:

- temporal lobe epilepsies (TLEs)
- frontal lobe epilepsies
- parietal lobe epilepsies
- occipital lobe epilepsies.

These epilepsies may be idiopathic, cryptogenic or symptomatic. The new diagnostic scheme considers symptomatic and probably symptomatic (cryptogenic) focal epilepsies as a separate group from idiopathic focal epilepsies (Table 5.2).[2] This distinction is important in practice because the prognosis and treatment of the idiopathic focal epilepsies differ significantly from those of the symptomatic focal epilepsies. There is now concrete evidence to classify, diagnose and treat certain focal epilepsies on the basis of their aetiology rather than, simply, their localisation. Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), which is one of the more common and most distinct epileptic syndromes, is a striking example of this.

The new ILAE diagnostic scheme further classifies focal epilepsies according to whether they are limbic or neocortical (Tables 2.3 and 5.2).[2,3] Simple and complex focal seizures may account for 60–70% of all epilepsies, and almost half originate from temporal lobe structures.[4–6]

There are numerous causes of symptomatic and cryptogenic focal epilepsies, such as:

- benign or malignant tumours
- viral and other infectious and parasitic diseases
- cerebrovascular disorders
- malformations of cortical development
- genetically determined brain and metabolic disorders
- trauma and other injuries.

The exact prevalence of these aetiological factors in various types of focal epilepsies has not been precisely estimated, and certainly varies significantly between developed and developing countries; for example, cysticercosis and tuberculomas are among the most common causes of epilepsies in resource-poor countries but have a minimal prevalence in developed countries. Malformations of cortical development, which are a significant cause of focal epilepsies, are often revealed only by high-resolution MRI.[7]

Terminology

The terms 'focal' and 'partial' seizures are synonymous and interchangeable. Focal seizures or focal epilepsies are the preferred terms.

The idiopathic and hereditary forms of focal epilepsies have been thoroughly described in Chapters 9, 11, 12 and 14.

Useful recommendation for further reading and video-EEG presentations

All focal epileptic seizures and syndromes[8] and their aetiology, diagnostic procedures, differential diagnosis and management[9] have been recently detailed by expert authorities in two volumes of a multimode publication edited by C.P. Panayiotopoulos, S.R. Benbadis, and S. Sisodiya. These volumes also contain numerous real-life video presentations edited by C. P. Panayiotopoulos, P. Thomas and E. Hirsch.

Temporal lobe epilepsies

TLEs share the same topographical seizure onset (the temporal lobe), but they are often of diverse aetiology, age at onset, prognosis and response to medical or surgical management. They constitute 30–35% of all epilepsies.

Anatomically, TLEs are broadly divided into those originating from the lateral or mesial regions of the temporal lobe (Figures 15.1–15.3).

The ILAE Task Force classifies temporal lobe epilepsies as:[2]

1. Limbic TLE:
   a. MTLE with hippocampal sclerosis
   b. MTLE defined by specific aetiologies
2. Neocortical epilepsy:
   a. lateral TLE (LTLE)

Limbic TLE make up two-thirds of TLE.

Semiology of TLE

TLEs manifest with the following:

- simple focal seizures
- complex focal seizures
- secondarily generalised tonic–clonic seizures (secondarily GTCSs)
- focal non-convulsive status epilepticus (limbic or neocortical)
- secondarily generalised convulsive status epilepticus.

Ictal clinical symptoms of TLE can be subjective (aura), objective or both.

Simple focal seizures manifest with subjective symptoms that last from a few seconds to 1 or 2 min. They commonly progress to complex focal seizures during which objective symptoms appear. Secondarily GTCSs may be frequent or rare and a tenth of patients may never experience a GTCS. Post-ictal fatigue and drowsiness are common.

Subjective ictal clinical manifestations

Subjective ictal clinical manifestations constitute a galaxy of various simple or complex internal sensations of illusions, hallucinations or both. These symptoms are experienced by almost all patients (>90%) with TLE. They can be the only ictal symptom of a focal seizure, but frequently progress to other manifestations of complex focal seizures.

Epigastric aura and fear are the most common and are frequently the initial manifestations of MTLE. Simple or complex auditory hallucinations mainly characterise LTLE. Complex internal sensations are common in both.

Subjective ictal symptoms of temporal lobe seizures, in order of prevalence, include:

- ascending epigastric aura
- complex internal sensations:
  – fear and panic
  – déjà vu or jamais vu and their variations
- auditory hallucinations and illusions
- olfactory and gustatory hallucinations
- other symptoms including autonomic disturbances.

MRI of two patients with lateral (A) and mesial (B) temporal lobe epilepsy due to dysembryoplastic neuroepithelial tumours

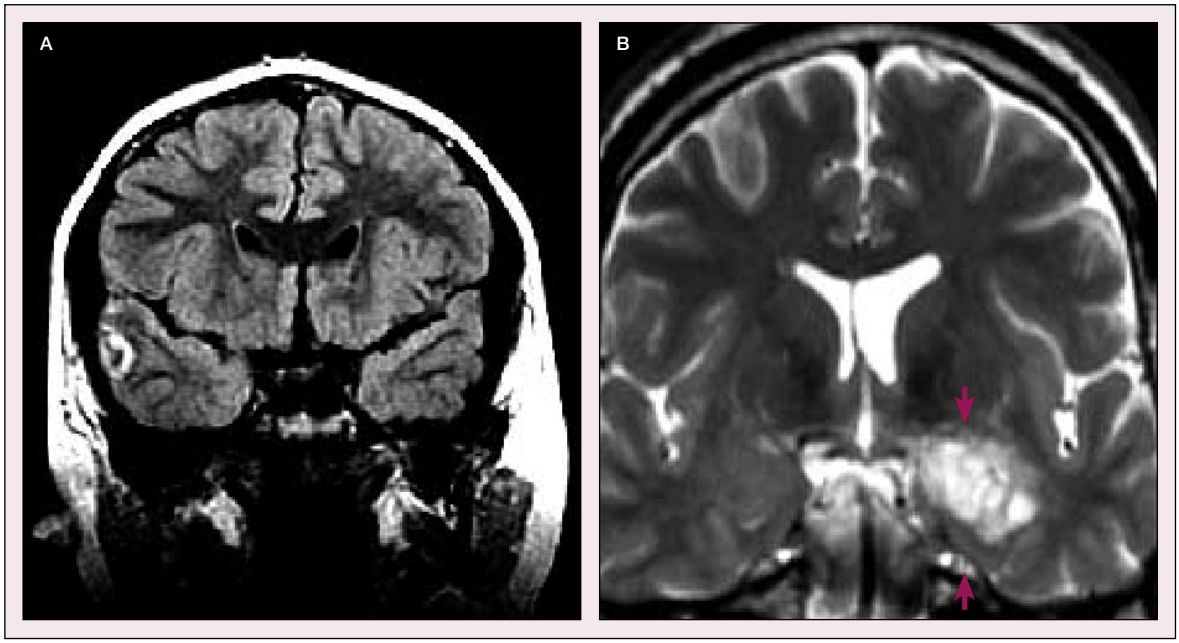

Figure 15.1 (**A**) Coronal FLAIR MRI showing a discrete ring-like lesion in the lateral aspects of the right middle temporal gyrus consistent with a small neoplasm. Pathology revealed a dysembryoplastic neuroepithelial tumour. (**B**) Coronal T2-weighted MRI showing a large dysembryoplastic neuroepithelial tumour occupying most of the left mesial temporal lobe.
Figure A courtesy of Dr Ruben Kuzniecky, NYU Epilepsy Center, New York, USA.
Figure B courtesy of Dr Rod C. Scott, Institute of Child Health, London.

Ascending epigastric aura

Ascending epigastric or visceral aura is by far the most common symptom of MTLE.[10–12] It is usually felt in the upper half of the abdomen. It is a strange 'difficult-to-describe' sensation of emptiness, rolling, whirling, tenderness, fluttering, butterflies, pressure, burning, emptiness and their variations.[10] An epigastric aura is often initially described as pain, but genuine pain, sometimes excruciating, is exceptional and usually lasts for 2–10 s. Irrespective of quality, this sensation often moves upwards (ascending) and when it reaches the level of the throat the patient loses consciousness. A downwards movement towards the feet is exceptional.

Fear

Fear is the most common aura after epigastric sensations in MTLE. The intensity and quality of ictal fear vary considerably from patient to patient, although it is stereotypical in each individual. Most patients use the terms 'fear' and 'panic' synonymously. It is not directed towards any particular circumstance, event or person. It is just fear or panic that may be the first, and sometimes the only, ictal symptom (Figure 15.4).

> I am scared, I have my panic.

More often, fear appears with other symptoms at the beginning or during the course of the seizure.

> It starts with my panic and that stomach feeling, and then I pass out.

Fear is not specific only to MTLE. Although it is mainly associated with amygdaloid, periamygdaloid and hippocampal stimulation, neocortical areas can also be responsible. A typical example is the fear of frontal lobe seizures (see page XXX). However, there is a major difference between the fear of TLE and the fear of frontal lobe epilepsy:

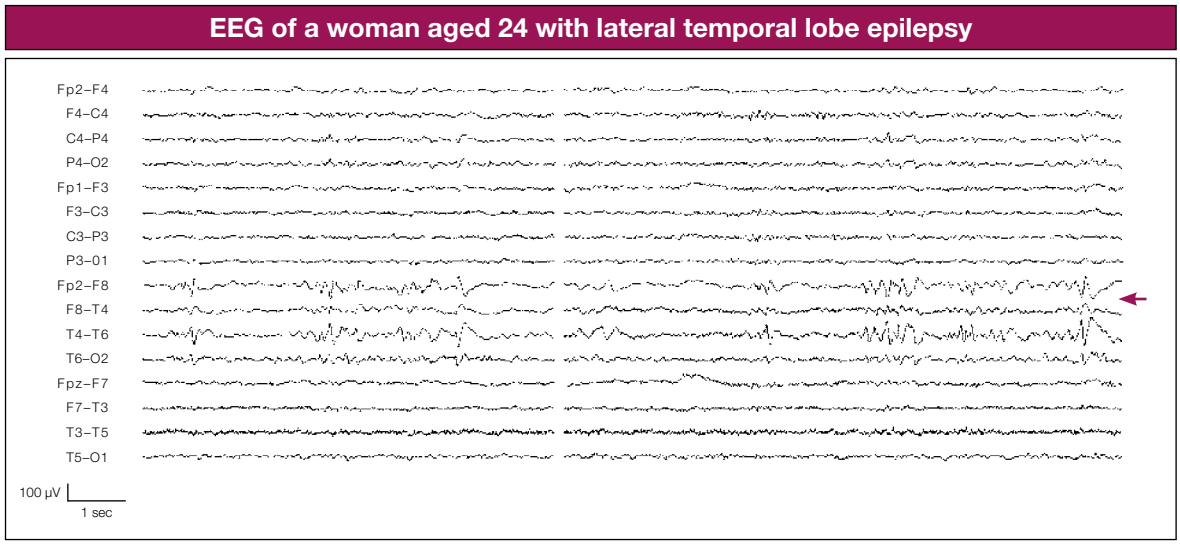

Figure 15.2 Note the marked focal abnormalities of slow waves and sharp–slow-wave complexes around the right anterior-midtemporal regions.

- Fear in MTLE is predominantly subjective 'I am scared, I am in a terrible panic', which is not apparent to the observer.
- Conversely, in frontal seizures, 'fear' is predominantly expressive, such as 'his face is fearful'.

Briefly, 'fear' is mainly felt emotionally in mesial temporal lobe seizures and is mainly expressed facially in frontal lobe seizures.

Complex internal sensations (experiential, mental, intellectual or psychic symptoms, dreamy states)

Complex internal sensations[13] of TLE are complex perceptual distortions of hallucinations, illusions or both. They may involve any faculty of the human mind: thinking, emotion, memory and recollection, chronological assessment and order, speed, sensation, reality and unreality, and their interactions with past, present and imaginary experiences. Events and experiences may be reproduced intact or disturbed: the present may be misplaced to the past, and the past to the present; real may be seen as unreal and *vice versa*; time may be speeded up or slowed down; and shape and other morphology may be natural or unnatural, and deformed or undistorted. They may be very simple and natural, such as the 'déjà vu' phenomenon, a sensation of 'fear and panic' or a mild sense of depersonalisation (e.g. 'who am I?'), which may also be experienced by normal people who do not have seizures. On other occasions, these symptoms may be more complicated with a complete distortion of time, space, morphology, direction, experience and normality.

Nomenclature issues

'Complex internal sensations',[13] 'dreamy states', 'psychic or mental symptoms', 'intellectual aura' and 'experiential phenomena' are the terms most widely used to denote symptoms of temporal lobe seizures that uniquely relate to the patient's personality regarding identity, experience, emotion, thought and memory. These terms are not necessarily synonymous, because they are used in the relevant literature to encompass either limited or much wider ictal manifestations.

The complex internal sensations of temporal lobe seizures typically combine elements of perception, memory and affect, which, as in real life, are often encompassed in a unified subjective symptom.[14] Perceptual, mnemonic or affective aberrations usually cluster in various combinations and various degrees of disturbance. However, one aberration may be

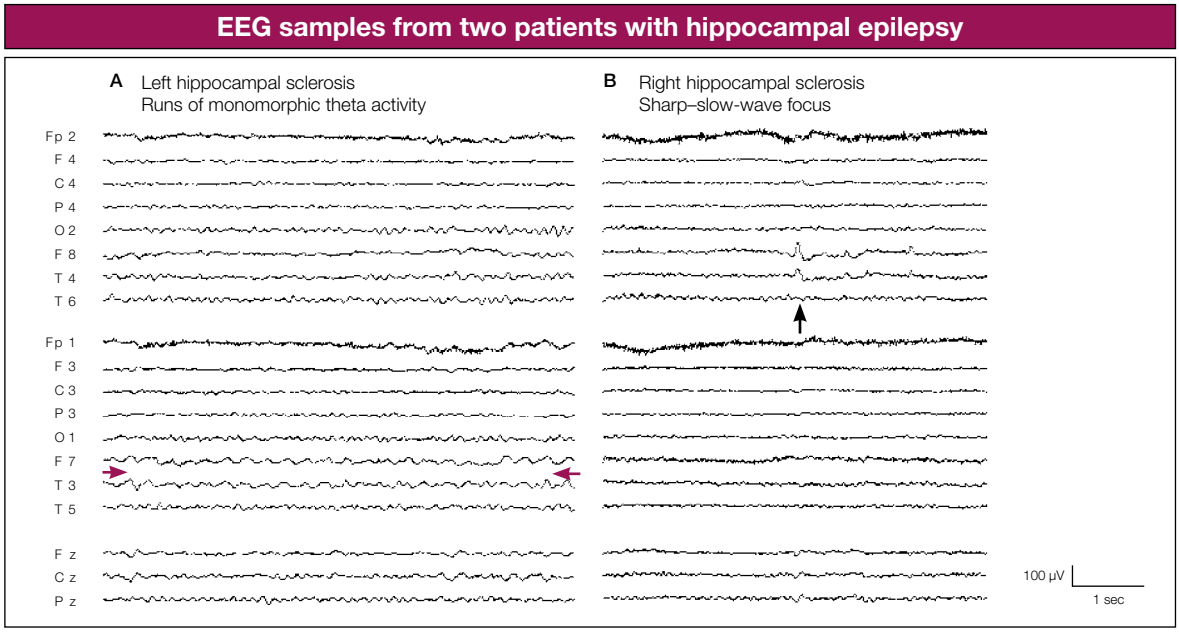

Figure 15.3 (**A**) Discrete runs of monomorphic theta activity are localised in the left anterior temporal regions in this patient with left hippocampal sclerosis. There were no spikes or other 'conventional' epileptogenic abnormalities. (**B**) The conventional epileptogenic focus of sharp–slow-wave complexes is localised in the right anterior temporal electrode. The patient had right hippocampal sclerosis.

more involved than another; sometimes, one may be exclusively affected and may occur in isolation. Depending on the predominant mental aberration, they are subdivided under various names, such as *ideational* (impairment of thoughts), *dysmnesic* (impairment of memory), *affective* (emotional impairment) and *dyscognitive* (impairment of perception, cognition).

Déjà vu

'Déjà vu' is a subjectively inappropriate impression of familiarity of a present experience with an undefined past. 'Déjà vu' (already seen) is commonly used, in a much broader sense, to include 'déjà entendu' (already heard) and 'déjà veçu' (already lived, experienced), as a false feeling of having seen, heard or experienced something before that is actually happening now. In déjà vu, the physical recognition is correct, but it is inappropriately connected with mental, emotional, experiential and timing processes that are associated with other physical presentations. The feeling of familiarity supervenes. It is mainly a feeling of immense and vivid familiarity with the present situation, irrespective of whether the content is visual, auditory or of any other sensorial presentation. The patient may say 'that it is as if I have seen, heard or lived this before', but more often the expression is 'it was so familiar to me'.[15,16]

> Extreme familiarity with people and surroundings, as if I knew them well, as if they were close friends or relatives, intimate relations, as if it was my everyday experience. It is more of a feeling of knowing them well than of visual or auditory recognition and experience.
>
> Seizures start with a strong feeling of extreme familiarity with what I see, hear or what is happening at that moment. The feeling is so intense and vivid that on one occasion when this happened while playing cards with my wife, I thought that I knew exactly the next sequence of cards to be played.

Déjà vu is a natural event that has been experienced by most people and the term is used in everyday life. In TLE, déjà vu is a common ictal symptom that is recognised as abnormal by the presence and the sequence of other epileptic events that may precede, coincide or follow it.

Jamais vu, jamais entendu and jamais veçu

Jamais vu (never seen), jamais entendu (never heard) and jamais veçu (never experienced before) are illusions during which the subject's surroundings, even when familiar, are no longer recognised, although they are clearly perceived by the subject. Jamais vu is commonly used in a much broader sense to include jamais entendu and jamais veçu. It is a false feeling of unfamiliarity (has not been experienced, seen or heard) with something that has been previously encountered.

Jamais vu is much rarer than déjà vu, but it is well described by some patients with TLE. Similar to 'déjà vu/familiarity', in 'jamais vu/unfamiliarity', the feeling of unfamiliarity is stronger than the visual, auditory or other sensorial component. Visual, auditory or any other physical recognition is correct, but the connections to the mental and emotional processes associated with them are missing.

> I know that she is my mother but I do not feel that she is. Her features do not change. She is still my mother but I do not have the same human attachment to her. She is a stranger with the looks, the voice and the manners of my mother. She is a stranger.

Auditory hallucinations and illusions

Elementary or complex auditory hallucinations are attributed to LTLE.

Elementary auditory hallucinations are crude and described as buzzing, ringing, hissing, fizzing, whistling, humming, shrilling, sizzling or clicking auditory sensations. High pitch noises are more frequently reported. They mainly originate from the activation of Heschl's auditory cortex in the superior temporal gyrus.

For many patients, this 'buzz' is the aura and the start of the seizure itself.

> Here it is again. That buzzing in both ears. It is just buzz. I cannot describe it. A buzz. There is nothing else. No voice, no identifiable noise that simulates anything else, just a buzz.

Complex auditory hallucinations consist of voices, music or other sounds that may be familiar or unfamiliar, friendly or aggressive and offensive, clear or indefinable, meaningful or incomprehensible. Complex auditory hallucinations are rarely the first ictal symptom and they usually combine with other visual or mental ictal symptoms of the 'dreamy state'. These are mainly elicited by activation of the associated auditory cortex. Auditory hallucinations of hearing a voice are almost always without semantic content, even though the voice may sound familiar and may be identifiable.[17] The affective tone of the voice is, however, often recognised.

> 'It is a clear voice of a woman, she says something that I do not remember', 'conversations of people talking next door', 'a hoarse voice of a man saying that I have to go', 'sounds of human voices and animals', 'I hear the same voice saying the same thing. I know it at the time but I cannot recall it afterwards', 'a voice filtered as if spoken through a handkerchief', 'it is my own voice talking to myself', 'voices through an amplifier or a loud speaker'.

Hearing music, often the same piece for every seizure, is uncommon, although it is frequently cited in the literature and can be reproduced during electrical stimulation studies.[18–21] A song, usually a nursery rhyme, may be more common than music.

Auditory illusions are altered perceptions and interpretations of sounds, voices and conversations in the actual environment during the seizure. This may refer to simple changes of intensity, resonance, spatial orientation, tone, echo and clarity, or be more complicated. Sounds and voices may appear louder/deafening/ear-splitting or dim/faded, nearer or further away, clearer or disturbed, higher or lower pitched, echoed and variations of all of these.

> 'The voices fade away', 'my hearing is heightened so I can hear everything loud and high pitched', 'as if talking from a distance', 'the voices become hoarse', 'a woman's voice sounds like a man's voice or like that of an animal', 'the sounds become so intense as if somebody has put the radio at maximum volume next to your ears', 'I hear the echo of the voices', 'as if you are in an empty church, you hear the sounds and their echoes'.

Olfactory and gustatory hallucinations

Olfactory epileptic auras are rare, constituting approximately 0.9% of all auras, and are typically, but not necessarily, unpleasant.[22–24] The amygdala is the most likely symptomatogenic zone of olfactory

auras. Tumours[22] and hippocampal sclerosis[24] are common causes.

'A strong smell of gas or something like this', 'a smell of rotten leaves', 'a smell of perfume', 'a peculiar odour that I cannot describe'.

Gustatory epileptic auras are hallucinations of taste that are usually unpleasant (rotten food) or strange. They are usually generated in the insula or superior bank of the sylvian fissure.[23,25,26]

'A strange taste of food in my mouth', 'a taste of burnt food', 'a taste of rotten food', 'taste of funny food in my mouth'.

Visual hallucinations and illusions

Visual hallucinations and visual illusions are detailed in the discussion of occipital lobe epilepsies (see page XXX).

Elementary visual hallucinations originate in the visual cortex (see page XXX). They do not feature in temporal lobe seizures except after secondary spread to the occipital lobes.

Complex visual hallucinations originate from the occipito–parietal–temporal junction and therefore may be part of any seizure that starts from or spreads to this area.

Complex visual hallucinations may take the form of people, animals, objects, figures or scenes. They may be static or moving, real or unreal, normal or distorted in size, shape and dimension. They often progress to more complex visual hallucinatory experiences. They may be familiar or unfamiliar, friendly, frightening or grotesque. They may be related to a past visual experience or connected with past events.

Usually, auditory and visual hallucinations occur together. These are complex hallucinations of a scene, people, animals, objects, voices, music or the noise of a train. The content of these hallucinations usually appears familiar, but it may be entirely strange or unidentifiable.

> More complicated subjective visual phenomena associated with local lesions in the neighbourhood of the uncus of the temporal lobe are different in origin and nature to those of occipital epilepsy. These uncinate epileptic seizures frequently begin with subjective smells and tastes, which are almost invariably of an unpleasant, usually of an extremely disagreeable, character; often there is, too, an epigastric sensation which may account to actual nausea. Then comes that peculiar mental state which Jackson called the 'dreamy state' or 'intellectual aura' characterised by a feeling of unreality of the present or familiarity with the events of the moment as though they had been experienced before. Often visions, which the patient associates with the past come up. A patient whom I had under observation always saw, in this stage a woman with a red cloak approaching nearer and nearer until, as the spectre reached her, she lost consciousness. In other cases, the vision may be of a scene tinted with a tone of familiarity, a building or a similar object. In such cases the visual hallucinations, for to these the term hallucination can be applied, is only part of the intellectual aura of Jackson and is obviously the result of more complicated cerebral and psychological processes than the perception and projection of lights and colour.
>
> Gordon Holmes (1927)[27]

Other subjective ictal manifestations

Other subjective ictal manifestations include autonomic disturbances such as nausea and urinary urge.

Objective ictal symptoms

Objective ictal symptoms of TLE usually occur when consciousness is impaired. The patient is seldom aware of them. They are described by witnesses or captured on video recordings.

Objective ictal symptoms in order of prevalence include:

- automatisms
- autonomic disturbances, including ictal vomiting
- speech disturbances
- head and eye deviation as well as dystonic postures
- motor arrest with staring
- unilateral ictal paresis
- unilateral eyelid blinking.

In general, almost all of these ictal symptoms are not specific to temporal lobe seizures. Recent reviews and reports of TLE have emphasised objective symptoms only because of their lateralising value.

Automatisms

Oro-alimentary automatisms, which are often followed by gestural automatisms, are characteristic of MTLE *only if* preceded by epigastric aura, fear and complex

internal sensations, alone or in combination.[28–34] They are more likely to begin in the first part of a complex focal seizure after the aura, and are attributed to seizures originating in the amygdala and periamygdaloid region, and not in the hippocampus. However, hippocampal after-discharges invariably spread to the amygdala, which explains the high prevalence of these automatisms in MTLE.

Simple automatisms, devoid of behavioural changes, are of no diagnostic significance in TLE. They are among the most common symptoms in childhood and juvenile absence epilepsy (see Chapter 13). They are differentiated by clustering of other symptoms, duration and EEG manifestations.

Definitions of automatisms

Automatisms are coordinated, involuntary, simple movements or more complex acts performed by a patient who is unaware of them, because consciousness is sufficiently impaired. The patient is completely amnesic of this behaviour.

Automatisms are defined by the ILAE as:

> A more or less coordinated, repetitive, motor activity usually occurring when cognition is impaired and for which the subject is usually amnesic afterwards. This often resembles a voluntary movement, and may consist of inappropriate continuation of ongoing preictal motor activity.[35]

According to Jackson:

> They have one common character – they are automatic; they are done unconsciously, and the agent is irresponsible. Hence... the term mental automatism.[36,37]

In the *Dictionary of Epilepsy*[38] automatisms are:

> More or less coordinated adapted (eupractic or dyspractic) involuntary motor activity occurring during the state of clouding of consciousness either in the course of, or after an epileptic seizure, and usually followed by amnesia for the event. The automatism may be simply a continuation of an activity that was going on when the seizure occurred, or, conversely, a new activity developed in association with the ictal impairment of consciousness. Usually, the activity is commonplace in nature, often provoked by the subject's environment, or by his sensations during the seizure: exceptionally, fragmentary, primitive, infantile, or antisocial behaviour may occur.[38]

Simple automatisms, devoid of behavioural changes, manifest with simple involuntary movements and include the following types:

- *Oro-alimentary:* lip smacking, lip pursing, chewing, licking, tooth grinding or swallowing.
- *Vocal:* single or repetitive utterances consisting of sounds such as grunts or shrieks.
- *Verbal:* single or repetitive utterances consisting of words, phrases or brief sentences, such as uttering, shouting, talking or singing words, sentences or phrases.
- *Gestural:* often unilateral: (1) fumbling or exploratory movements with the hand directed towards self or environment; fiddling, fumbling, picking, tapping, patting or plucking, rubbing or scratching the face, and other gestural movements; and (2) movements resembling those intended to lend further emotional tone to speech.
- *Ambulatory:* well-coordinated acts, such as walking straight or in circles, continuing cycling or even driving.
- *Manual or pedal:* bilateral or unilateral fumbling, tapping or manipulating movements. Bicycling movements are also common in extratemporal seizures.
- *Mimetic:* facial expression suggesting an emotional state, often fear.[35]

Complex (behavioural) automatisms: Rich in behavioural changes with complex acts performed without apparent awareness. Semi-purposeful or well-organised exploratory or inappropriate behavioural manifestations, such as embarrassing actions, undressing in public, chewing objects that are not edible, wandering or running inappropriately, or aggressive behavioural acts.

Spontaneous and interactive automatisms: (1) *spontaneous* are stereotyped, involve only self and are virtually independent of environmental influences; and (2) *interactive* are not stereotyped, involve more than self and are environmentally influenced.

Verbal automatisms of coherent speech are associated with seizure onset in the non-dominant hemisphere.[39,40] Ictal vocalisation probably has no lateralising value.[40] Both ictal vocalisation and verbal

automatisms can occur in extratemporal epilepsies, such as frontal lobe seizures; they often occur in childhood and juvenile absence epilepsy.[41]

Complex automatisms rich in behavioural aberrations are common in TLE, but they also occur in extratemporal seizures; they are exceptional in typical absence seizures.

Spitting, as either an ictal or post-ictal event,[42] and bicycling movements[43] are also common in extratemporal seizures.

Automatisms involving masturbation or other sexually related behaviour are uncommon, although they are often mentioned, even in brief textbook reviews; I have never encountered them. Ictal penile erection and ejaculation are autonomic disturbances.[44,45]

It is generally considered that unilateral automatisms are ipsilateral to the seizure onset.[39] However, this has been debated by Elger[46] and does not apply in patients with bilateral independent temporal spikes.[47]

Autonomic disturbances[45,48–51] and ictus emeticus[47,52–55]

Autonomic disturbances of any type are among the most frequent ictal symptoms of TLE.[49,56–59]

Cardiovascular symptoms, mainly tachycardia and arrhythmias, and less often bradycardia, asystole (Figure 1.2) or hypertension, are very common and may be a common cause of sudden death in TLE.[45,48,49,59–63]

A brief respiratory arrest, sigh or gasp is common in the initial part of complex focal seizures. Hyperpnoea, hypopnoea or even apnoea may occur in the late seizure phase.[45]

Mydriasis, sometimes asymmetrical, is a frequent symptom associated with the arrest reaction.[39,45] Miosis and hippus pupillae are also common.[45]

A feeling of 'shivering cold' is sometimes associated with piloerection.[45,50] Salivation is common, but lacrimation and nasal secretion are rare.[45]

There are occasional reports of penile erection, and even ejaculation or other sexual ictal manifestations.[44]

Flushing or, more often, pallor is commonly encountered.[45]

Ictus emeticus (nausea, retching and vomiting), and particularly ictal vomiting, are exceptional in adult patients with temporal lobe seizures, but very common in children with Panayiotopoulos syndrome (see page XXX).

In adults, there have been no more than 30 reported cases of ictal vomiting, which chiefly emanates from the non-dominant temporal lobe and usually occurs after seizure onset, together with other symptoms; the patient is amnesic of the events.[47,52–55] Conversely, ictus emeticus in children is very common, usually occurs at the onset of the seizures and the patient has a good recollection of the event.[64–66]

Language and speech ictal disturbances

In addition to vocal and verbal automatisms, speech arrest and language disturbances are frequent manifestations of temporal lobe seizures. The most common is the inability to speak.

'I know what is going on and I understand what they are saying, but I cannot speak' is much more common than 'I know what it is but I cannot find the word'.

Ictal aphasia and ictal speech arrest have been attributed to seizure onset in the language-dominant temporal lobe.[67] Clear ictal speech and quick recovery mainly characterise seizures of the non-dominant temporal lobe,[29,39] while post-ictal aphasia and prolonged recovery are mainly features of seizures of the dominant temporal lobe.[39]

Motor arrest, staring and temporal lobe absence

Motor and speech arrest, together with staring and loss of consciousness, may be the first objective symptom of a temporal lobe seizure. As a rule, they follow other subjective symptoms, but, in about 10% of patients, they may occur alone from the beginning of the seizure. These symptoms are clinically similar to those of generalised absence seizures when examined in isolation. For this reason, this type of focal seizure is also called 'temporal lobe absence', a term that should be discouraged to avoid confusion with 'generalised absence seizures', which are completely different if other symptoms and duration are considered in their entirety (Table 2.7).

The duration of motor arrest, staring and loss of consciousness varies, but usually lasts for 1 min. Occasionally, this may be the only manifestation of

the seizure. The patient usually recovers without other concurrent symptoms, such as automatisms.

Motor manifestations

Motor manifestations include eye and head deviation, as well as dystonic postures that occur in about a fifth of patients. These symptoms, which are also detailed in other chapters, are not specific to temporal lobe seizures. Thus, eye and head deviation is a common symptom in frontal and occipital lobe seizures. Dystonic postures are more often related to the frontal than the temporal lobe.

Motor manifestations, despite their insignificance for pure anatomical localisation, are of value with respect to possible lateralisation.

Early and casual deviation of the eyes and head, in the setting of other more typical mesial temporal lobe ictal symptoms, may be ipsilateral to the epileptogenic focus.[39,68–70] Conversely, it is almost always contralateral if it occurs during the progression of the seizure, when it is also more violent and often followed by secondarily GTCSs.[32]

Unilateral tonic or dystonic posturing of arm, leg and face was described by Ajmone-Marsan and Ralston[71] who called it 'larval M2e' to differentiate it from that of frontal lobe seizures. It is often associated with ipsilateral automatisms. It is reliably contralateral to the epileptogenic focus.[39]

Unilateral eyelid blinking is ipsilateral to the epileptogenic focus.[72]

Unilateral ictal paresis is contralateral to the origin of the seizure.[73]

Gelastic seizures of TLE

Ictal laughter is rare in TLE.[74] The clinical descriptions are variable; the laughter being natural or forced, unmotivated, associated or even reactional to a pleasant event or feeling. In 50% of cases, other types of seizures occur concomitantly or precede the gelastic seizures.[74]

See also hypothalamic (gelastic) epilepsy on page XXX (Chapter 10).

Amnesic seizures

In pure amnesic seizures, the *only* clinical manifestation is the patient's inability to retain in their memory what occurs during the seizure. Other cognitive functions are preserved and patients interact normally with their physical and social environment.[75]

Pure amnesic seizures of TLE never represent the only type of seizure in a patient. This may suggest that they result from selective ictal inactivation of mesial temporal structures without neocortical involvement.

Amnesic seizures occur most often in patients with neuropsychological and EEG evidence of bilateral dysfunction of mesial temporal lobe structures. More rarely, in unilateral dysfunction, amnesic seizures may result from seizure discharge limited to the mesial temporal structures on both sides, probably as a result of contralateral spread from one to the other through the dorsal hippocampal commissure (see the brief reminder below).[75]

Catamenial temporal lobe seizures

Some women have exclusively catamenial seizures, which may demand different management.[76–78]

A brief reminder

'Catamenial epilepsy is often vaguely defined as the occurrence of seizures around the time of menses or an increase in seizures in relation to the menstrual cycle.'[76] Catamenial seizures increase in approximately a third of women with focal or generalised epilepsies, but only a small proportion of these patients suffer from pure catamenial epilepsy (i.e. seizures occurring only in relation to their menses). Catamenial epilepsy may be perimenstrual, periovulatory or luteal.[78] The diagnosis is based on careful assessment of menstrual and seizure diaries, and characterisation of cycle type and duration.

Of a variety of mechanisms proposed, hormonal influences are the best established and exert significant effects on seizure threshold. Oestrogens have a proconvulsant effect, whereas progesterone has mainly anticonvulsant properties.[76] However, in contrast to focal and secondarily GTCSs, progesterone may exacerbate absence seizures and generalised spike–wave discharges (GSWD).[78,79]

The most common therapies proposed in small, uncontrolled or anecdotal reports include acetazolamide, the cyclical use of benzodiazepines (mainly clobazam) or anti-epileptic drugs (AEDs), and hormonal therapy.[76]

Post-ictal symptoms

Post-ictal symptoms are common, often characteristic and some may be of lateralising value. Such symptoms include mental and physical fatigue, drowsiness, headache, language aberrations, an inability to concentrate and confusion to varying degrees, which is often severe and associated with automatic behaviour of which the patient may be amnesic. Some patients may wander about in the streets, behaving normally or in a socially unacceptable manner, and have no recollection of the events when they recover.

In an attempt to reorient to the current situation, an embarrassing smile, coughing, spitting and sighing are early post-ictal symptoms (Figure 15.4).[46,80]

Post-ictal symptoms may be disproportionately more severe than the ictal manifestations and may last for hours.

Marked post-ictal manifestations may follow seemingly mild attacks and *vice versa*.

> I am so drained and exhausted with irresistible drowsiness. I write the rest of my day off.

Differentiating temporal lobe seizures from other extratemporal seizures on the basis of post-ictal symptoms

Post-ictal symptoms are far more common after temporal lobe than extratemporal seizure onsets. Post-ictal confusional states and automatisms are exceptional in extratemporal seizures. In frontal lobe seizures, the patient immediately recovers after the fit with no post-ictal manifestations (see page XXX). In visual occipital seizures, the only post-ictal abnormality is the severe migraine-like headache that often follows (see page XXX).[41]

Mesial TLE with hippocampal sclerosis

Synonym: MTLE-HS, hippocampal epilepsy.

MTLE with hippocampal sclerosis is the most common and distinct epileptic disease. It has defined underlying hippocampal pathology shown on MRI, rather characteristic clinical seizure features and frequent neurosurgical cure or post-resection seizure improvement.

The clinical features and prognosis of MTLE-HS derive almost exclusively from neurosurgical series of medically intractable cases. Therefore, they may not accurately represent the clinical spectrum of MTLE-HS, particularly with respect to severity and prognosis. The neurosurgical cases may represent the tip of the iceberg and the worst cases (about 20%). The vast majority of cases (80%) are not seen in these specialised neurosurgical centres, and some cases may be very mild and easily controlled with appropriate AEDs. I have seen an impressive number of professionals (physicians, nurses, solicitors, successful businessmen, teachers) and ordinary working class people who live a normal life, some with minor focal seizures, but others with an occasional secondarily GTCS often controlled with AED monotherapy. A more complete clinical picture is expected to emerge now that MRI enables an *in vivo* diagnosis of hippocampal sclerosis/atrophy (Figures 6.4 and 15.5).[81,82]

A recent expert ILAE report[83] discusses the definition, natural history, pathological features, pathogenesis and electroclinical, neurophysiological, neuropsychological, and structural and functional imaging findings of MTLE-HS.

Clarifications on classification

The ILAE Commission (1989)[1] classifies MTLE-HS among other temporal lobe epilepsies under the name 'amygdalo-hippocampal (mesiobasal limbic or rhinencephalic) seizures'.

Ictal EEG of two patients with hippocampal epilepsy

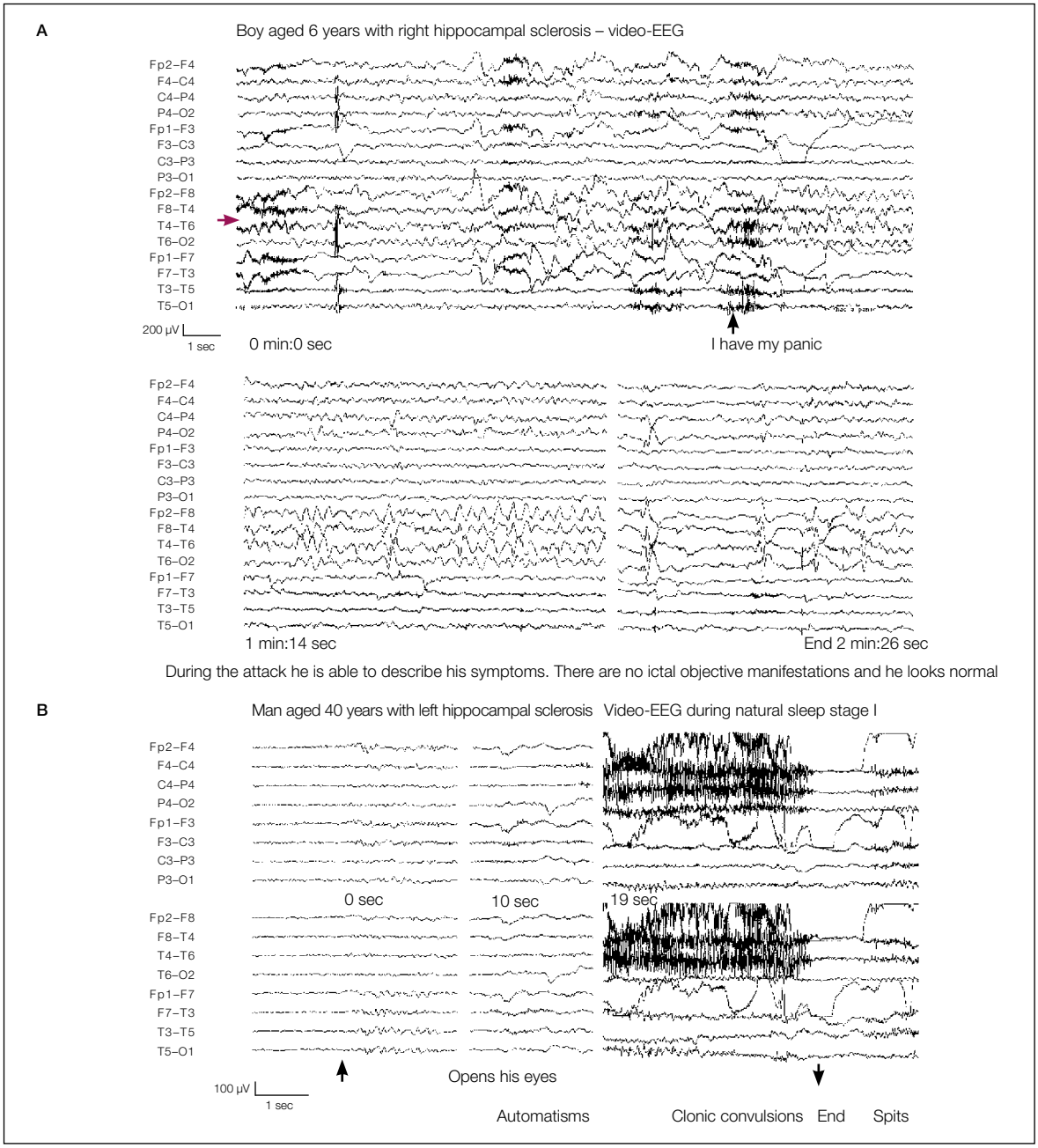

Figure 15.4 (**A**) This was the second EEG of a boy aged 6 years, referred for episodes of panic attacks and a recent GTCS. The resting EEG was entirely normal but one of his seizures was recorded from onset (0 min:0 s; red arrow) and lasted for 2 min and 26 s. The child looked disturbed, complaining, 'I have my panic' (black arrow). He was able to communicate well during the whole seizure. Speech and cognition were normal. Brain MRI documented right hippocampal sclerosis. (**B**) Sample of video-EEG during a brief seizure of a man aged 40 years with increasing numbers of complex focal seizures typical of hippocampal epilepsy. The MRI documented left hippocampal sclerosis. Note that towards the end of the attack the patient had mild right-sided clonic convulsions (see muscle artefacts), although he never had a GTCS. Also note that he immediately spits after the cessation of the seizure.

MRI findings in hippocampal sclerosis

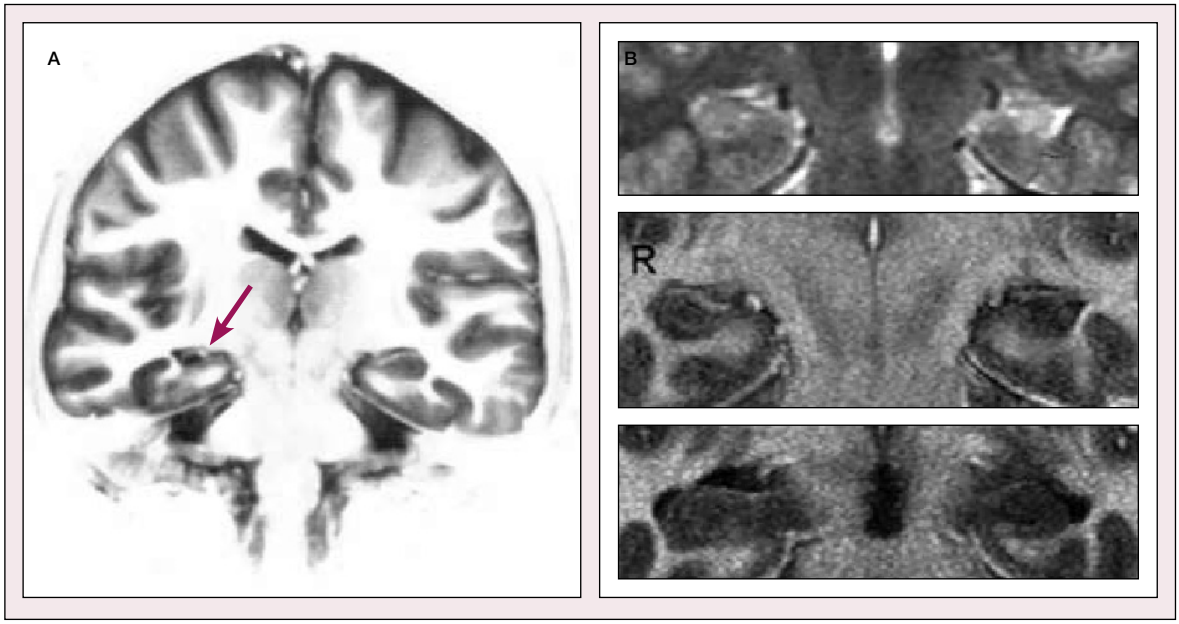

Figure 15.5 (A) Coronal T1-weighted MRI scan showing right hippocampal sclerosis (arrow). (B) Coronal T2-weighted and magnified T1-weighted MRI scan showing left hippocampal sclerosis.
Courtesy of Professor John S. Duncan and the National Society for Epilepsy MRI Unit, London, UK.

The new ILAE reports consider MTLE-HS to be an epileptic syndrome among the limbic epilepsies, but not a disease.[2,3,83] I would support that this is a disease because of its common pathology.[83]

MTLE-HS is usually described under the heading 'mesial temporal lobe epilepsy', although only 65% of patients have mesial temporal lobe seizures due to hippocampal atrophy. The remainder are the result of mesial temporal lobe pathology other than hippocampal sclerosis.

The term 'complex focal (partial) seizures' has been erroneously used as a synonym of 'temporal lobe epilepsy'.[2] Ictal impairment of consciousness in focal epilepsies is a symptom of either neocortical or limbic seizures.

Demographic data

Onset usually occurs between 4 and 16 years of age. Both sexes are equally affected. MTLE-HS is the most common epileptic syndrome, probably accounting for around 20% of patients with epilepsy and for 65% of patients with TLE.[84] Of children with TLE, 30–60% appear to have MTLE-HS.[85,86]

Clinical manifestations

Many patients with MTLE-HS usually have a previous history of febrile seizures, trauma, hypoxia and intracranial infections before the age of 5 years.[83] Complex focal seizures or generalised convulsions are the initial non-febrile seizure types that attract medical attention. As a rule, they are preceded by simple focal seizures that may have been considered, sometimes for years, as normal phenomena.

Epigastric aura, fear and oro-alimentary automatisms are the most common ictal symptoms.

It starts with that strange stomach feeling and my panic, and then I pass out.

Simple focal seizures

Simple focal seizures are the most frequent seizure type in MTLE-HS, and occur in more than 90% of patients. They mainly start with an ascending epigastric aura and less often with fear. The complex internal sensation of déjà vu and its variations occur, but not as commonly as in other extrahippocampal epilepsies. Olfactory and gustatory hallucinations occur less often.

Ascending epigastric or visceral aura is by far the more common aura (around 80% of cases), and the most characteristic of all other ictal symptoms of simple hippocampal seizures.

Ictal fear is the second most frequent aura after epigastric aura, but only accounts for about 20–30% of cases. It is not specific to hippocampal seizures alone.

Complex internal sensations occur less often than epigastric aura and fear.

Unspecified somatic sensations or olfactory and gustatory hallucinations may occur. Elementary or complex visual and auditory hallucinations do not occur.[32]

Urgency to urinate is exceptional and associated with right-sided foci.[87]

Language impairment during simple focal seizures has not been examined thoroughly. Most patients are able to understand conversations fully, but they are unable to speak or carry on conversations; they answer monosyllabically or with movements of the head or hands.

> I know well what they say, but I cannot speak or I reply in the simplest possible way with 'yes' or 'no' until I am back to normal again in a minute or so.

Simple focal seizures may be the only seizure type, sometimes for years, and can vary in duration from a few seconds to, although rarely, 1 or 2 min. They may be entirely inconspicuous to the observer, although close relatives or friends are able to recognise them when they occur.

> 'He has it now', the relative points out. The patient and the EEG confirm it, but nothing significant can be detected on the video record of events.

Simple focal seizures may be the only seizure type, although they often progress to *complex focal seizures*.

Complex focal seizures

Complex focal seizures usually emerge as a progression of simple focal seizures with gradual or abrupt impairment of consciousness that is typically associated with oro-alimentary automatisms in about 70% of cases.

The initial objective symptoms in this stage of impairment of consciousness are staring, motor restlessness or motor arrest, oro-alimentary automatisms and unforced head deviation. The patient has no recollection of this phase, but may still be responsive (70% of cases in one study).[46] Gestural automatisms, other forms of automatisms, vocalisations and dystonic posturing may occur soon after. Hypersalivation (dominant hemisphere) is exceptional.

Complex focal seizures last for 2 or 3 min, occur on average once or twice a week and usually appear in clusters of two or three. They may also occur during sleep and, in some women, they are exclusively or predominantly catamenial.

Oro-alimentary automatisms are characteristic of MTLE only if they are preceded by epigastric aura.

Autonomic manifestations of any type (see page XXX) are among the most frequent ictal symptoms of MTLE-HS.[45,49,56–59,83]

Lateralising signs of ictal and post-ictal symptoms

Dystonic posturing occurs in 20–30% of patients and is contralateral to the side of seizure onset.[39,88,89]

Head deviation early in the seizure is usually ipsilateral to the seizure focus, but head deviation late in the seizure is contralateral and often a prelude to generalisation.[39]

Ictal or post-ictal aphasia and prolonged recovery are mainly seen after seizures in the dominant temporal lobe,[39] whereas clear ictal speech and quick recovery mainly characterise seizures of the non-dominant temporal lobe.[29,39]

It is generally considered that unilateral automatisms are ipsilateral to the seizure onset.[39]

Although non-specific for right or left disease, impaired consciousness,[46] motion arrest,[46] escape automatisms[46] and fear[58,90] occur more often in patients with left rather than right MTLE-HS.

Hyperventilation during the seizure is rare and occurs in left mesial onset.[46] Vocalisations,[46] motor restlessness,[46] staring,[46] oral automatisms,[39] pupillary dilatation,[39] impaired consciousness[39] or generalised rigidity[39] do not predict the side of origin.

GTCSs

Secondarily GTCSs are usually infrequent in patients receiving appropriate AEDs.[83] They are not uniform in their clinical presentation, but are more stereotyped in their final phases than the initial clinical signs of generalisation.[91] Some patients (probably around 10%) may never have GTCSs.

Post-ictal symptoms

Post-ictal symptoms of complex focal seizures in MTLE-HS are very frequent and often severe.

Complex focal status epilepticus of temporal lobe origin

Complex focal status epilepticus (also called dyscognitive or psychomotor status epilepticus)[3] is characterised by continuous or rapidly recurring complex focal seizures that may involve temporal or extratemporal regions (see Chapter 3). Cyclic disturbance of consciousness is considered characteristic of complex focal status epilepticus of temporal lobe origin. However, its differential diagnosis from that of frontal lobe origin is often a challenge.[92] In a third of cases, a frontal lesion is revealed.[93]

Complex focal status epilepticus features, particularly in untreated patients with TLE. It is less common than the absence status epilepticus of idiopathic generalised epilepsy (IGE), but its prevalence may be underestimated.[94–96] It may also be confused with transient global amnesia.[97]

Neurological, mental state and behaviour

Neurological examination is usually normal; facial asymmetry contralateral to the epileptogenic zone may be apparent in some patients. Specific baseline and follow-up memory testing are necessary. The only clearly defined behavioural disturbance in MTLE-HS is a material-specific memory deficit, but this may also be seen in MTLE due to other mesial temporal lesions.[83] Many other psychiatric and psychological problems, especially depression, have been reported to be more prevalent in MTLE-HS, but there is inadequate information to determine the extent to which these disturbances are a direct biological result of either the hippocampal sclerosis or the mesial temporal lobe seizures, or of a non-specific biological result of brain injury or a consequence of external psychological and social factors.[83] More recent studies on MTLE-HS have shown that for depression:

- the extent of hippocampal dysfunction is a more important factor than seizure frequency or the degree of disability[98]
- relative preservation of the contralateral amygdala is more significant than hippocampal abnormalities[99]
- it has significant positive relationships with both the right and left amygdala.[100]

Febrile convulsions and other initial precipitating events

Of patients with MTLE-HS, 90% have a previous history of prolonged febrile convulsions (a third) or other cerebral insults in early life (see page XXX).[83,101] Patients with a prolonged febrile seizure before 5 years of age are likely to have unilateral hippocampal atrophy and a good neurosurgical response.[102]

Aetiology

By definition, all patients with MTLE-HS have hippocampal sclerosis. Conversely, hippocampal sclerosis is found in only two-thirds (65%) of patients with MTLE.[84,103] Hippocampal sclerosis is predominantly unilateral in about 80% of neurosurgical series. A third of patients have functional and structural extrahippocampal abnormalities.[104] Other mesial temporal lobe structures may also be affected.[45,104]

'Dual pathology' is common[105] and includes microdysgenesis, temporal lobe malformations of cortical development and indolent tumours, such as dys-

embryoplastic neuroepithelial tumours. Patients with 'dual pathology' are more likely to have bilateral hippocampal atrophy.[105]

A genetic predisposition may be found in MTLE-HS, but this is not a uniform process.[83] Usually, there is no increased family history of similar hippocampal seizures and hippocampal sclerosis does not occur in clinically unaffected twins.[106]

Hippocampal sclerosis

A hypocellular and gliotic (hence the word 'sclerotic') hippocampus is the pathological substrate of MTLE-HS. Hippocampal sclerosis presents with a unique pattern of cellular loss that is not found in other brain diseases:[84]

- Selective regional hippocampal, mainly CA1, pyramidal cell loss occurs (about 30–50% of cases), predominantly involving the hilar region and dentate granule cells. Somatostatin and hilar neuropeptide-Y-containing neurones are particularly susceptible. Preservation of the subiculum is pathognomonic.
- GABA neurones and terminals are relatively well preserved. CA2 are relatively spared.
- Dispersion of dentate gyrus granule cells and sprouting of their axons (mossy fibres), which form aberrant monosynaptic excitatory feedback synapses on to the dendrites of granule cells.
- Changes in neuropeptide Y and somatostatin expression and reorganisation that occur.

Hippocampal sclerosis and temporal lobe epilepsy: cause or consequence?[107]

The cause of hippocampal sclerosis is unknown. There are two opposing views:

- The traditional concept is that prolonged febrile convulsions and other cerebral insults in early life cause hippocampal sclerosis and hippocampal epilepsy.
- A current trend is that pre-existing hippocampal abnormalities predispose to febrile convulsions. If these are prolonged, they may cause further hippocampal damage evolving to mesial temporal sclerosis, which may manifest with MTLE-HS.[108–110]

Pathophysiology

How does this 'atrophic' and 'sclerotic' hippocampus become one of the most powerful and common epileptogenic agents in human epilepsy?

The role of the hippocampus in epilepsy is due to synaptic remodelling and reorganisation of the hippocampal region. An enhanced sensitivity to glutamate may be important.[111] These changes predispose surviving hippocampal neurones to abnormal hypersynchronous discharges that then propagate to other limbic and non-limbic structures, producing the manifestations of complex focal seizures.

Engel, *et al*[112] summarised the current state of our knowledge as follows:

> Most current parallel human/animal invasive research indicates that epileptogenesis in MTLE-HS is initiated by specific types of cell loss and neuronal reorganisation, which results not only in enhanced excitation, but also in enhanced inhibition, predisposing to hypersynchronisation. Also, evidence is found for more than one type of ictal onset, and individual seizures can demonstrate a transition from one ictal mechanism to another. *In vivo* and *in vitro* parallel, reiterative investigations in patients with MTLE-HS, and in rats with intrahippocampal kainate-induced hippocampal seizures, have revealed the presence of interictal epileptiform events, termed '*fast ripples*', which appear to be unique in tissue capable of generating spontaneous seizures.

Diagnostic procedures

A clinical diagnosis of MTLE-HS demands confirmation with high-resolution MRI and EEG. CT brain scanning is unrewarding.

The serum prolactin concentration may rise markedly 10 min after seizure onset in three-quarters of patients.[113]

MRI is the most important investigational tool (Figures 6.4 and 15.5).[83,114]

With improvements in MRI techniques, modern MRI scanners are of sufficiently high resolution to allow *in vivo* visualisation of hippocampal sclerosis

and other structural 'dual pathologies' in all patients.[82,115]

In straightforward cases of incontrovertible unilateral MTLE-HS confirmed by MRI, other tests may be unnecessary. However, the following should be remembered:

MRI evidence of hippocampal sclerosis is not necessarily related to seizure severity and may occur in individuals who have never had seizures.[116]

Functional brain imaging and magnetoencephalography (MEG) provide insights in neurosurgical cases for which further information about lateralisation is required (Figures 6.11–6.13). Invasive intracranial recordings are necessary in exceptional cases.

Important points

Diagnostic procedures

High-resolution MRI provides *in vivo* visualisation of hippocampal sclerosis in almost all patients.

A single routine inter-ictal EEG is more likely to be normal (two-thirds of patients) than show the classic spike–wave focus in the anterior temporal lobe electrode (a third of patients).

Inter-ictal EEG

Routine inter-ictal EEG shows the classic sharp– or spike–slow-wave focus in nearly a third of patients (Figure 15.3). Thus, in two-thirds of patients with MTLE-HS, a single, routine, 30-min EEG recording may be normal or show mild and non-specific abnormalities. The yield is doubled in repeat EEG, particularly when a longer sleep recording is made. Epileptiform abnormalities nearly always occur during prolonged monitoring.[117]

The traditional 'epileptogenic complexes', when present, are unilateral in two-thirds of patients and occur independently, on the right or left, in the other third.[45,117] Regional temporal lobe inter-ictal runs of slow waves, which are of lateralising value, are recorded in about 50% of patients (Figure 15.3).[118–120]

Bilateral GSWD do not occur, although occasionally bilateral fronto-polar spikes may be seen.

Ictal EEG

The ictal scalp EEG may be 'normal' or inconclusive in around 60% of cases at seizure onset in MTLE-HS.

A typical ictal EEG pattern consists of rhythmic, crescendo-like theta activity with decreasing frequency and increasing amplitude (Figures 6.1 and 15.4). It first appears over the affected temporal lobe; it usually starts around 30 s before subjective or objective clinical seizure manifestations and commonly spreads to neighbouring and other regions.[45] Simultaneous EEG and clinical onsets are uncommon.[121]

Onset with regional attenuation of background rhythms and disappearance of the inter-ictal spikes is less common.[45] There are no fast spikes or fast rhythmic discharges in the ictal EEG of hippocampal seizures, and spikes are relatively absent (Figures 6.1 and 15.4).

Concordant outpatient EEG and unilateral MRI hippocampal atrophy would obviate the need for inpatient EEG monitoring.[115]

Differential diagnosis

MTLE-HS needs to be differentiated from non-epileptic conditions (see Chapter 4) and from seizures arising from other brain locations.

Non-epileptic conditions: The diagnosis of hippocampal seizures should be suspected from their very brief duration, the ascending character of the epigastric sensations, the occasional nocturnal appearance and often an associated feeling of depersonalisation. However, simple focal seizures of epigastric aura and 'panic attacks' are unlikely to raise suspicion of epilepsy (Figure 15.4). These patients are often investigated for gastroenterological and psychological disorders[122] or hypoglycaemia until more salient seizure features appear with the development of complex focal seizures and secondarily GTCSs. Patients are often reassured by normal relevant tests or told that their symptoms are the result of anxiety. It is rare, at this stage, for a general physician to request an EEG, but again, if this is normal (as is the case in two-thirds of patients), a diagnosis of stress-related events would be reinforced.

Non-epileptic paroxysmal events (NEPEs) may be difficult to differentiate. An increase in serum prolactin level post-ictally may be helpful in differentiating between epileptic seizures and 'pseudo-seizures'.[123]

'Please exclude temporal lobe epilepsy' is the most frequent reason for requesting an EEG for any kind of transient behavioural aberration; it is often an impossible task. About two-thirds of patients have a normal routine inter-ictal EEG or show non-specific abnormalities with an excess of slow waves in one temporal lobe.

Mesial temporal epilepsy with aetiologies other than hippocampal sclerosis: The differential diagnosis of hippocampal from other MTLE aetiologies is practically impossible without MRI (Figure 15.5).

Hippocampal versus other temporal lobe seizures: The rising epigastric aura and early oro-alimentary automatisms predominate in MTLE-HS compared with other neocortical temporal lesions (Table 15.1). Conversely, MTLE-HS is unlikely when seizures manifest with early focal motor, somatosensory, visual or auditory ictal symptoms or frequent secondarily GTCSs, or if they occur in patients with neurological or cognitive deficits other than memory impairment.

Hippocampal versus familial MTLE: The main differentiating features in favour of familial MTLE (see page XXX) are:

- onset in teenage or early adult life and familial occurrence
- no febrile convulsions or other initial precipitating events
- no ictal symptoms of rising epigastric aura
- mild and infrequent seizures that may remit
- usually normal MRI.

Hippocampal versus extratemporal epilepsies: A single ictal symptom makes no significant contribution to topographical diagnosis; for example, head deviation can occur in seizures from many brain locations, which are identified by other concurrent symptoms, such as elementary visual hallucinations in occipital seizures, epigastric and other auras in MTLE, and stereotypical and rather violent jerks of the head in frontal lobe seizures.

Dystonic motor manifestations are common in both TLE and frontal lobe epilepsy. However, in frontal lobe seizures, these manifestations are usually the very first symptom; they are brief and often occur without severe impairment of consciousness, mainly during sleep and with no post-ictal symptoms. There are no preceding symptoms of rising epigastric sensations, oro-alimentary automatisms, olfactory and gustatory hallucinations, or mental illusions and hallucinations.

Typical absence seizures are more likely to be misdiagnosed as complex focal seizures than *vice versa* (Table 2.7).[124]

Prognosis

Despite the high prevalence and known pathology, the prognosis and many other important aspects of MTLE-HS are largely unknown.

Neurosurgical series

The neurosurgical cases show a specific clinical pattern.[32,83] Seizures are initially relatively well controlled with AEDs for several years. Seizures relapse in adolescence or early adulthood, occurring several times per week or usually several times per month, and become refractory to medication. Memory and behavioural disturbances may occur. Neurosurgery is probably mandatory at this stage, because spontaneous remission is unlikely, drugs do not work and polypharmacy makes it worse.

Community studies

Community-based studies have shown that 10–40% of patients with TLE may go into remission.[125]

Overall, it is probable that:

- About 50% are intractable and require neurosurgical evaluation and management.
- Around 30% are relatively well controlled with appropriate AEDs. These patients may have simple or complex focal seizures and occasional GTCSs that interfere with their daily life, but without significantly disturbing their function within their families and their jobs. How many

Mesial versus lateral temporal lobe epilepsy

	Mesial temporal lobe epilepsy	Lateral temporal lobe epilepsy
Epigastric aura, fear and early oro-alimentary automatisms	Predominate	Rare
Non-specific auras, early focal motor, somatosensory, visual or auditory symptoms	Rare	Predominate
Contralateral hand dystonia	Common	Less common
Whole body rotation	Rare	Common
Early clonic activity after automatisms	Rare	Common
GTCSs	Infrequent	Frequent
History of febrile seizures	Predominates	Rare
Inter-ictal EEG	Ipsilateral anterior temporal spikes	Ipsilateral middle and posterior temporal spikes
MRI	Hippocampal sclerosis	Neocortical lesions, such as malformations of cortical development

Table 15.1

of these patients need or would accept neurosurgical intervention is uncertain.

- The other 20% of patients are otherwise normal, with occasional simple or complex focal seizures for which they may be treated or untreated. These patients may come to our attention because of an occasional GTCS, a lengthy or severe complex focal seizure or an EEG performed for reasons other than epilepsy.

Management

Medical treatment of MTLE-HS with AEDs may be relatively effective in half of patients; for the other half (or possibly more) with intractable seizures, neurosurgical resection of the offending epileptogenic region is usually successful.

AED treatment

Drug treatment is similar to that for any other type of focal seizure (see page XXX). Carbamazepine and levetiracetam are the first choice (Table 15.3).

If treatment with one or two of the main AEDs fails, the chances of achieving pharmaceutical control in MTLE-HS are negligible. Polypharmacy with more than two or three AEDs, even when rational, will add more misery, memory problems and drowsiness rather than any benefit. These patients, even in childhood, need urgent evaluation for neurosurgical treatment, for which they are the best candidates of all the symptomatic focal epilepsies and the most likely to have excellent and sustained benefit.

Neurosurgical treatment

With early surgical intervention, patients have an excellent chance of cure and, subsequently, leading a normal life.[83,126–129] After anterior temporal lobe resection with hippocampectomy, around 60% of patients become seizure free even after all AEDs have been withdrawn, 20% will need to continue with AEDs and may have reduced numbers of seizures, 10% will have no benefit, and 10% may have neurosurgical complications and get worse.

A class 1 RCT of surgery for MTLE-HS found that 64% of those who received surgery were free of disabling seizures compared with 8% free in the group randomised to continued medical therapy. Quality of life and social function significantly improved in

the patients who underwent surgery; morbidity was infrequent and there was no mortality.[126] In general, 'the benefits of anteromesial temporal lobe resection for disabling complex partial seizures of temporal lobe epilepsy is greater than continued treatment with AEDs, and the risks are at least comparable'.[126]

The quality of life after surgical treatment depends on psychosocial factors, as well as pre-existing vocational and interpersonal skills.[130] Attention to psychosocial and possible memory deficits is of paramount importance. Appropriate rehabilitation after successful surgery is needed.

MTLE defined by specific aetiologies other than hippocampal sclerosis

In MTLE with aetiologies other than hippocampal sclerosis,[32,45,46,88] seizure symptomatology is the same irrespective of cause and location within the mesial temporal lobe structures. Thus, seizures of hippocampal sclerosis are indistinguishable from those caused by other lesions in the mesial temporal lobe. Their differentiation is also practically impossible using surface EEG. High-resolution MRI provides anatomical evidence of localisation in almost all symptomatic cases. The sensitivity of MRI in the diagnosis of tumours and other lesions of the temporal lobe is estimated to be around 90%,[81] but this will soon be exceeded.

Structural causes include malignant and benign tumours (i.e. astrocytomas, gangliogliomas, dysembryoplastic neuroepithelial tumours), vascular abnormalities (i.e. cavernous and venous angiomas, arteriovenous malformations), malformations of cortical development, trauma and other injuries, viral and other infective agents, and cerebrovascular disease.

Drug treatment is similar to that for any other type of focal seizure (see page XXX).

Neurosurgical intervention often provides an excellent chance of cure and a subsequent normal life in certain pathological conditions of MTLE.

Lateral temporal lobe epilepsy

LTLE[1,46,80,88] is neocortical, as opposed to MTLE, which is a limbic epilepsy.

Clinical manifestations

Simple seizures of LTLE are characterised by auditory hallucinations (ringing, humming, clicking, unspecified noises) or illusions, vestibular phenomena, mental illusions, hallucinations and visual misperceptions of complex internal sensations. Language disturbances occur in dominant hemisphere focus.

Motor ictal symptoms include clonic movements of facial muscles, grimacing, finger and hand automatisms, dystonic posturing of an upper extremity, leg automatisms, restlessness and unformed vocalisations. Rotation of the whole body is common and of value in differentiating lateral from mesial TLE.

Symptoms may progress to complex focal seizures by spreading to mesial temporal or extratemporal

structures. Impairment of consciousness is not as pronounced as in MTLE.[46]

See also familial (autosomal dominant) lateral TLE (page XXX).

Aetiology

The structural causes of LTLE are similar to those of MTLE apart from hippocampal sclerosis.

Diagnostic procedures

MRI often determines structural causes of LTLE (Figures 15.1 and 15.6).

Axial proton density-weighted MRI showing left temporal lobe cavernoma in a patient with LTLE

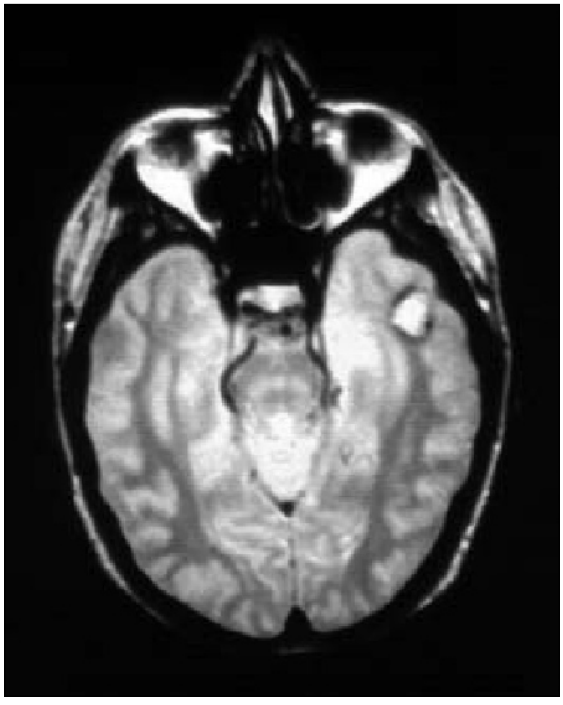

Figure 15.6 *Courtesy of Professor John S. Duncan and the National Society for Epilepsy MRI Unit, London, UK.*

Scalp inter-ictal EEG shows unilateral or bilateral mid-temporal or posterior temporal spikes (Figure 15.2).[1,46] However, this is often indistinguishable from MTLE.

Ictal EEG is not significantly different from that of MTLE.[131–133] It mainly consists of regional ipsilateral rhythmic 4–7 Hz activity (Figure 15.4). Attenuation of the background rhythms and remission of the inter-ictal spikes is common in MTLE and uncommon in LTLE.[131] In one study, the ictal EEG in LTLE revealed a lower mean frequency of lateralised rhythmic activity, which frequently had a hemispherical distribution, whereas in MTLE seizures this was maximal over the ipsilateral temporal region.[80]

Differential diagnosis

Lateral temporal lobe seizures usually lack the features commonly exhibited in MTLE (Table 15.1).

Patients with MTLE have an earlier onset of habitual seizures and are more likely to have a prior history of febrile seizures and other initial precipitating incidents.[80]

Eye blinking, aggressive behaviour, dystonic posturing, early or late oro-alimentary automatisms and hypersalivation, which are common in MTLE, do not occur or are rare in epilepsy of non-mesial onset.[44] Furthermore, impairment of consciousness is not as pronounced as in MTLE.

Arrest reaction, vocalisation, speech, facial grimace, post-ictal cough, late oral automatisms and late motor involvement of the contralateral arm and hand occur with similar frequency in mesial and lateral TLE.[88]

Management

Drug treatment is similar to that for any other type of focal seizure (see page XXX).

Neurosurgical treatment provides an excellent chance of cure and a subsequent normal life in certain pathological conditions of LTLE.

Frontal lobe epilepsies

Frontal lobe epilepsies manifest with seizures originating from a primary epileptic focus anywhere within the frontal lobe. The clinical and EEG manifestations vary greatly and depend on the origin and spread of the epileptogenic focus.[134–144]

The frontal lobe occupies 40% of the cerebral cortex and is the largest of the brain lobes. On the basis of cyto-architectural and functional studies, the frontal lobe can be subdivided into the primary motor cortex, premotor cortex, prefrontal cortex, and limbic and paralimbic cortices,[140] with distinct cortico-subcortical organisations and immense connections with the temporal and parietal cortices.[137,145] Complex and varied patterns in the spread of seizure discharges explain the variability in the clinical and EEG manifestations of frontal lobe seizures.[136,146] Also, exact localisation is often hindered because of the rapid propagation of seizures within the frontal lobe from and to extrafrontal areas. It is difficult to assign the origin of seizures with pre- and post-central symptomatology to the frontal or parietal lobe. Such overlap to adjacent anatomical regions also occurs in opercular epilepsy.[1]

Seizures arising from the primary motor cortex and the supplementary motor area (Figures 15.7 and 15.8) have been relatively well defined, but seizures generated in other regions of the frontal lobe are less well specified.

Considerations on classification

The seizures of frontal lobe epilepsy were included in the 1989 ILAE classification[1] among the 'localisation-related (focal, local, partial) epilepsies and epileptic syndromes' (see Chapter 12). Frontal lobe epilepsies other than epilepsia partialis continua (EPC) of Kozhevnikov and Kozhevnikov–Rasmussen syndrome have not been detailed in the new ILAE diagnostic scheme.[2,3] The 1989 classification defines the frontal lobe epilepsies as follows.

'Frontal lobe epilepsies are characterised by simple partial, complex partial, secondarily generalised seizures or combinations of these. Seizures often occur several times a day and frequently occur during sleep. Frontal lobe partial seizures are sometimes mistaken for psychogenic seizures. Status epilepticus is a frequent complication.

A number of seizure types are described below; however, multiple frontal areas may be involved rapidly and specific seizure types may not be discernible.

Supplementary motor seizures: In supplementary motor seizures, the seizure patterns are postural, focal tonic, with vocalisation, speech arrest and fencing postures. See details on page XXX.

Cingulate: Cingulate seizure patterns are complex partial with complex motor gestural automatisms at onset. Autonomic signs are common, as are changes in mood and affect.

Anterior frontopolar region: Anterior frontopolar seizure patterns include forced thinking or initial loss of contact and adversive movements of head and eyes, with possible evolution including contraversive movements and axial clonic jerks and falls and autonomic signs.

Orbitofrontal: The orbitofrontal seizure pattern is one of complex partial seizures with initial motor and gestural automatisms, olfactory hallucinations and illusions, and autonomic signs.

Dorsolateral: Dorsolateral seizure patterns may be tonic or, less commonly, clonic with versive eye and head movements and speech arrest. See page XXX for further details.

Opercular: Opercular seizure characteristics include mastication, salivation, swallowing, laryngeal symptoms, speech arrest, epigastric aura, fear and autonomic phenomena. Simple partial seizures, in particular partial clonic facial seizures, are common and may be ipsilateral. If secondary sensory changes occur, numbness may be a symptom, particularly in the hands. Gustatory hallucinations are particularly common in this area.

MRI of two patients with symptomatic frontal lobe epilepsy

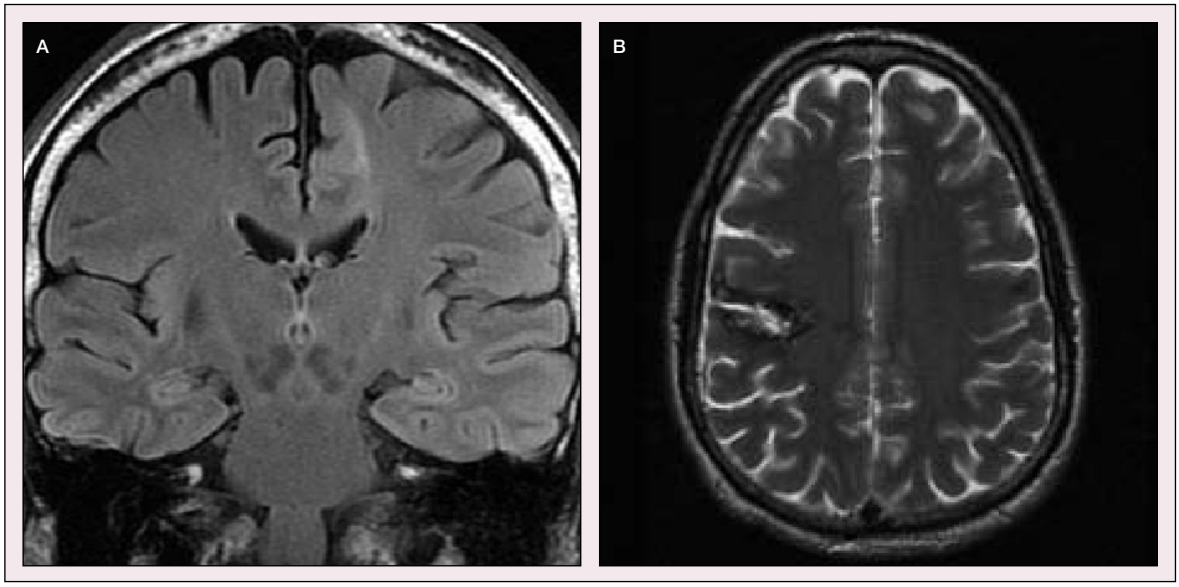

Figure 15.7 (**A**) Coronal FLAIR MRI showing focal cortical dysplasia in the supplementary motor area of the left frontal lobe. Note the tail extending down towards the frontal horn of the lateral vehicle. This patient was 60 years old and had experienced left SMA seizures for 7 years. All previous MRI studies were negative. (**B**) Axial T2-weighted MRI showing a heterogeneous lesion in the left precentral area. The signal changes are consistent with haemosiderosis suggestive of a cavernous angioma. *Figure A courtesy of Professor John S Duncan and the National Society for Epilepsy MRI Unit, London, UK. Figure B courtesy of Dr Ruben Kuzniecky, NYU Epilepsy Center, New York, USA.*

Motor cortex: Motor cortex epilepsies are mainly characterised by simple partial seizures, and their localisation depends on the side and topography of the area involved. In cases of the lower prerolandic area there may be speech arrest, vocalisation or dysphasia, tonic–clonic movements of the face on the contralateral side, or swallowing. Generalisation of the seizure frequently occurs. In the rolandic area, partial motor seizures without march or jacksonian seizures occur, particularly beginning in the contralateral upper extremities. In the case of seizures involving the paracentral lobule, tonic movements of the ipsilateral foot may occur as well as the expected contralateral leg movements. Postictal or Todd's paralysis is frequent.'[1]

'In frontal lobe epilepsies, the inter-ictal scalp recordings may show (a) no abnormality; (b) sometimes background asymmetry, frontal spikes or sharp waves; or (c) sharp waves or slow waves (either unilateral or frequently bilateral or unilateral multilobar). Intracranial recordings can sometimes distinguish unilateral from bilateral involvement.

In frontal lobe seizures, various EEG patterns can accompany the initial clinical symptomatology. Uncommonly, the EEG abnormality precedes the seizure onset and then provides important localising information, such as: (a) frontal or multilobar, often bilateral, low-amplitude fast activity, mixed spikes, rhythmic spikes, rhythmic spike waves, or rhythmic slow waves; or (b) bilateral high amplitude single sharp waves followed by diffuse flattening. Depending on the methodology, intracranial recordings may provide additional information regarding the chronologic and spatial evolution of the discharges; localisation may be difficult.'[1]

Demographic data

Frontal lobe epilepsies may start at any age and both sexes are equally affected. They are probably rare,

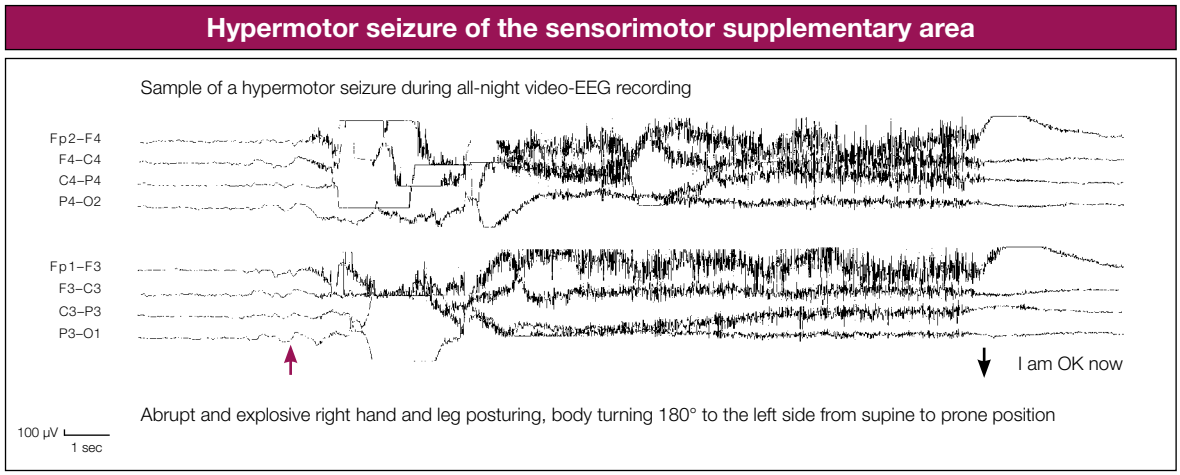

Figure 15.8 Sample from one of ten stereotypical hypermotor seizures recorded during an all-night video-EEG. Note the abrupt and explosive character of the seizure, which lasted for only 14 s. There are no discernible ictal EEG abnormalities, although occasionally some bilateral slow waves precede the onset of the seizures. Frequent EEGs, ictal and inter-ictal, over a 20-year period, failed to reveal any conventional epileptogenic abnormalities. The patient is an intelligent man who has experienced numerous nocturnal hypermotor seizures from the age of 4 years. He is fully aware of the attacks, but he cannot speak during them, although he hears and understands. He has a somatosensory aura of 'a tight sensation in my chest and a feeling that I cannot breathe as all the holes of my body are closed'. All possible drug treatments had failed. High-resolution brain MRI and PET scans were normal.

accounting for about 1% or 2% of all epilepsies, although they are second in prevalence after TLE in neurosurgical series. In a prospective community-based study,[147] the prevalence of frontal seizures (22.5%) among focal epilepsies was comparable to that of temporal lobe (27%) and central sensori-motor (32.5%) localisation. Seizure onset from the frontotemporal (5.6%), parietal (6.3%) or posterior cortex (6.3%) was less common.[147]

Clinical manifestations

According to their origin within the frontal lobe, various seizure patterns have been recognised, although multiple frontal areas may be involved. Rapid and specific seizure types may not be discernible.[1]

In general, frontal lobe seizures are short with prominent tonic or postural motor manifestations (90% of frontal lobe seizures) and often with minimal or no post-ictal confusion. Rapid secondarily generalisation occurs more commonly than in TLE. Frequent falling occurs when the ictal discharge is bilateral.[1] Certain clinical features of frontal lobe seizures have lateralising value.[148]

The following are the most common frontal lobe seizures.

Seizures from the motor cortex

Seizures from the motor cortex are mainly simple focal motor seizures.

Simple focal motor clonic or tonic–clonic seizures with or without jacksonian march: These seizures manifest with localised, rhythmic or arrhythmic, clonic movements that may affect the thumb only, the thumb and ipsilateral side of the lips, the hand, the whole arm or any other body part contralateral to the focus. Distal segments are more frequently affected than proximal segments. The hand (mainly the thumb) and face (mainly the lips) are preferentially affected because of their larger cortical representation (homunculus of Penfield). These ictal motor manifestations may remain highly localised for the whole of the seizure or march in an ordinary anatomical fashion to neighbouring motor regions, which constitute the classic jacksonian (or Bravais–Jackson) seizure.

> Usually there are a few jerks of the right corner of my mouth and the right thumb. That is all. However, the jerks may become more intense and spread gradually to my eye and my fingers on the same side. Then my elbow and shoulder also start jerking violently and this may also go to my leg. The whole right side of my body is jerking and jerking, and there is nothing I can do before this stops suddenly or I lose consciousness and I have whole body convulsions.

Myoclonic seizures that may be unilateral or bilateral are predominantly facial or distal in the limbs. EPC of Kozhevnikov is one type of myoclonic seizure (see page XXX).

Tonic postural motor seizures associated with clonic movements are asymmetrical, unilateral or bilateral.

Seizures from the supplementary sensorimotor area

Seizures from the supplementary sensorimotor area (SMA) have distinct and characteristic clustering of symptoms, and are usually stereotyped (Figure 15.7).[149–154] These are hypermotor seizures with bizarre movements and vocalisations. They are characterised by:

- abrupt onset and abrupt termination
- nocturnal circadian distribution; they rarely occur in awake states
- high frequency, sometimes many per night
- lack of post-ictal confusion.

Hypermotor seizures[155] of bizarre bilateral, asymmetrical tonic posturing and movements

Hypermotor seizures consist of 'complex, organised movements which affect mainly the proximal portions of the limbs and lead to a marked increase in motor activity. Consciousness may be preserved. They are most frequently associated with frontal lobe epilepsy'.[155,156]

The characteristic hypermotor seizure of the SMA consists of sudden and explosive, bilateral and asymmetrical tonic posturing of limb girdles at shoulder and pelvis, often with contraversion of the eyes and head, vocalisation or speech arrest.

Fencing posturing[157] is the best known descriptive term for these SMA seizures, although it may not be common.[154] In fencing posturing, one arm is raised and semi-extended above the head, whereas the other remains by the body semi-flexed at the elbow. Bilateral asymmetrical posturing is the most common.

M2e posture is another term used to describe flexion of the elbow of one arm, abduction of the shoulder to 90°, with associated external rotation.[71] The head looks at the postured hand, and the opposite arm shows slight flexion. The leg ipsilateral to the involved arm extends, whereas the opposite leg flexes at the hip and knee. M2e of SMA seizures is different from 'larval M2e' of MTLE (see page XXX).

Posturing is extremely variable among patients with SMA seizures, but it is stereotypical for each individual patient.

This variability of hypermotor seizures is reflected well by other descriptive terms of SMA seizures, such as complex gestural automatisms, extreme motor restlessness, complex motor automatisms and agitation, frenetic complex motor automatisms of both arms and legs, intensely affective vocal and facial expression associated with powerful bimanual–bipedal and axial activity, repetitive rhythmical and postural movements accompanied by bizarre vocalisation, complex motor automatisms with kicking and thrashing, and complex and global gesticulations.

Somatosensory or other ill-defined auras (not epigastric), vocalisations and speech arrest that are common ictal manifestations

Somatosensory auras are described by more than half and probably about 80%[156] of patients, mainly at onset. Unilateral somatosensory sensations usually accurately predict contralateral lateralisation.[159] Cephalic sensations are probably more common.[158] Auras are described as: pressure on the chest, difficulty breathing, floating away, paraesthesia of a hand, dizziness and light-headedness, cephalalgia or electrical sensation in the head, discharge in the whole body, sensation of body heat, feeling of coldness or heat in the back and the head, vertebral column shivering, moving outside oneself, or crawling sensation in both legs, one leg or somewhere in the body.[155,157,160,161]

Epigastric auras do not occur.

Vocalisations

In a third of patients, seizures manifest with vocalisations that may vary from a brief deep breath or air expiration and palilalic vocalisations to the most bizarre, loud and scaring noises.

Speech arrest is a well-documented and frequent ictal manifestation. Pure paroxysmal speech arrest without other motor activity is exceptional.

Consciousness is usually well preserved; as a rule, these are simple focal seizures.

Other frontal lobe seizures of particular clinical interest

Dorsolateral seizure patterns may be tonic or, less commonly, clonic with versive eye and head movements and speech arrest. Seizures are often characterised by unusual symptoms of 'forced thinking' and 'forced acts'. The patient is forced into an obsessive thought (*forced thinking*) associated with a fairly well-adapted attempt to act on this thought (*forced acts*), with 'eye-directed automatisms' and 'pseudo-compulsive behaviour'.[136,142]

> The patient is compulsively 'forced to fix on something with the eyes', 'the brain commands him to do something that he should not do', 'a sensation of being forced to open the eyes'. This is often associated with forced bizarre actions of hypermotor seizures.[136,142]

> A 30-year-old man, holder of a karate black belt, had a cluster of 30–50 such seizures while dozing in the waiting room of my clinic. Each seizure, which lasted for 10–15 s, was of sudden onset and termination. His facial expression was very aggressive and he would perform various karate acts, often kicking or punching objects in the office (without damaging them), with simultaneous and irregular roaring and other vocalisations. Immediately, after each attack, he would go back and sit in his chair, and fully aware of what was happening he would then apologise, 'I cannot resist doing this. It will be OK after a while', before jumping off again to perform a similar enforced act. The staff and the other patients were terrified and maintained a safe distance from him, while I had to put on a brave face to approach him until he recovered.

Frontal absences are similar and often indistinguishable from generalised absence seizures in their clinical and EEG manifestations (Figure 15.9).[162,163]

Negative motor seizures manifest with ictal loss of localised muscle power or inability to produce a voluntary movement.

Focal status epilepticus of frontal lobe origin

Focal (non-convulsive) status epilepticus of frontal lobe origin is of undetermined prevalence.[92,93] It manifests with prolonged impairment of consciousness and inappropriate behaviours (Figure 3.2).[92,93,164] Symptoms fluctuate in intensity and severity over time. Concurrent turning of the head and focal jerking may occur. It commonly ends with GTCSs. Ictal EEG shows repetitive frontopolar, frontocentral and frontotemporal epileptiform discharges with unilateral emphasis. It is difficult to differentiate from frontal or idiopathic absence status epilepticus without an EEG (Figures 3.1 and 3.2).

See also Chapter 3 on status epilepticus.

Aetiology

Frontal lobe epilepsies may be symptomatic, probably symptomatic or idiopathic. Two-thirds of patients in neurosurgical series are symptomatic[165] as a result of malformation of cortical development (57.4%), tumours (16.4%), or trauma and other lesions (26.2%).[166]

Of the idiopathic forms, autosomal dominant nocturnal frontal lobe epilepsy is detailed in Chapter 14.

Diagnostic procedures

High-resolution brain MRI is mandatory. This reveals abnormalities in around two-thirds of patients (Figure 15.7).

Functional neuroimaging and MEG are important for localisation in the presurgical evaluation.[167,168]

Serum prolactin concentration (>700 μU/ml) may be raised after frontal lobe seizures, with or without secondarily GTCSs. However, failure of prolactin levels to rise does not help in the clinical differenti-

ation of frontal lobe complex focal seizures from psychogenic NEPEs (see Chapter 4).

Ictal and inter-ictal surface EEG has a notoriously low yield. They are often normal (50–60% of cases), particularly when seizures originate from the mesial frontal regions.[1,143,166,169] The EEG of patients with lateral seizures is far more revealing than that of mesial frontal seizures (Figure 15.10). Prolonged video-EEG recording increases the EEG yield.[170] Normal EEG is often misinterpreted as evidence of non-epileptic attacks.

> A video-EEG carried out over two nights of one of my patients showed ten violent clinical SMA seizures but was entirely normal, except for a single, left frontal, giant sharp and slow wave that occurred only once.

If abnormal, inter-ictal EEGs may show background asymmetry, frontal spikes or sharp waves (either unilateral or frequently bilateral or unilateral multilobar).[1] Generalised discharges of 3 Hz spike–waves may occur with or without evidence of secondary bilateral synchrony (Figure 15.9).

Abnormal ictal EEG patterns consist of the following:

- Frontal or multilobar, often bilateral, of low amplitude, fast activity, mixed spikes, rhythmic spikes, rhythmic spike–waves or rhythmic slow waves (Figure 15.10). Ictal, fast, rhythmic paroxysms may be of very high frequency (>50 Hz) and low amplitude, requiring specialised recording systems with fast sampling rates and high sensitivity.[171]
- Bilateral, high-amplitude, single sharp waves followed by diffuse flattening. Uncommonly, this EEG abnormality precedes the seizure onset, providing important localising information.[1,172]

Even when the EEG is abnormal, its localisation value is often unreliable without focal ictal paroxysmal patterns at seizure onset. This is probably because of:

- early seizure spread within and outside of the frontal lobe
- widespread distribution of the epileptogenic brain tissue
- secondary bilateral synchrony and secondary epileptogenesis.

Although seizures predominately occur in sleep, sleep organisation is normal.

Differential diagnosis

The typical motor seizure with or without jacksonian march is unlikely to impose any diagnostic difficulties. However, hypermotor seizures with the bizarre movements, posturing and vocalisations aetiology are frequently misdiagnosed as psychogenic[173] or other movement non-epileptic paroxysmal event disorders.[144,154] Usually, normal inter-ictal and often ictal EEGs reinforce this error. Nowadays, this should be an unlikely misdiagnosis, because the constellation of hypermotor seizures is probably unique with their sudden onset and termination, stereotypical appearance in each patient and nocturnal occurrence in clusters.

Chapter 4 details the differentiation of frontal lobe seizures, particularly of the SMA, from non-epileptic paroxysmal movement disorders (psychogenic movement disorders, familial paroxysmal dystonic choreoathetosis, paroxysmal kinesiogenic choreoathetosis and episodic ataxia type 1) and from sleep-related movement disorders (pavor nocturnus in children or rapid eye movement [REM] behaviour disorder, and other parasomnias detailed in Chapter 4).

Misconceptions

So-called 'paroxysmal nocturnal dystonia' or 'hypnogenic paroxysmal dystonia' is frontal lobe epilepsy and not a movement disorder.

Symptomatic frontal lobe absences may have similar clinical and EEG features to typical absence seizures (Figure 15.9).[174–176]

Prognosis

Seizures of frontal lobe epilepsies are frequent and do not usually remit. In addition, poor seizure outcome is often associated with poor behavioural outcomes and learning disabilities.[177] Compared with patients with TLE, these patients have less pronounced memory and language but more pronounced atten-

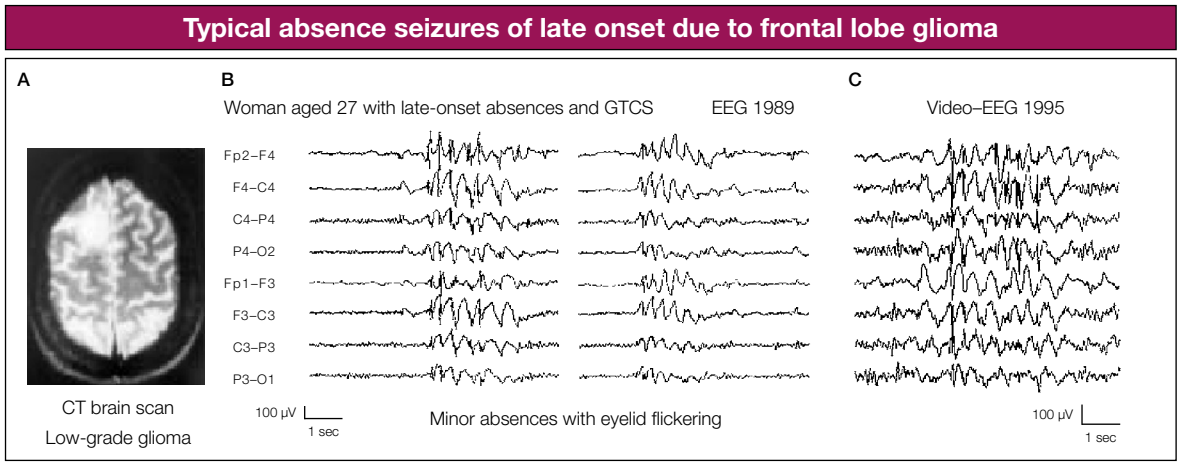

Figure 15.9 (**A**) Brain imaging showing a right-sided frontal glioma in a woman who started having absences at 28 years of age (1989). (**B**) Initially, the EEG GSWD were entirely symmetrical; there was nothing to suggest that these were symptomatic absences. Clinically, during the GSWD, the woman made minor and occasional errors on breath counting, with consistent eyelid flickering. In her daily life, these were manifested as 'losing control of thoughts, repeating simple phrases and occasional mild jerking of the head to the right'. This could last from a few seconds to 1 min and once she had non-convulsive status epilepticus with mild confusion and expressive dysphasia. (**C**) A video-EEG 6 years later showed that she continued to have similar GSWD with right-sided asymmetry.

tion and behaviour problems associated with learning disabilities.[177]

Management

The focal seizures of frontal lobe epilepsies are commonly resistant to AEDs, but AEDs usually protect patients against secondarily GTCSs. Drug treatment is similar to that for any other type of focal seizure (see page XXX). Topiramate may be a first option.[178]

Neurosurgery has limited success,[152,179] which may be improved by proper selection criteria.[180] Focal frontal lobe MRI lesions and pathological abnormalities correlate strongly with good outcome. In contrast, less favourable results are reported in patients with normal MRI and gliosis or normal pathology. Multilobar MRI abnormalities have the poorest outcome.

Surface EEGs and location of abnormality have no predictive value in neurosurgical cases. However, generalised epileptiform discharges and generalised inter-ictal slow activity indicates a poor neurosurgical outcome.[166] The absence of generalised EEG abnormality is the most predictive variable for a seizure-free outcome.[166]

Epilepsia partialis continua of Kozhevnikov

Synonyms: Kozhevnikov syndrome type 1, EPC of Kozhevnikov.

EPC of Kozhevnikov is a rare type of epileptic seizure/status epilepticus of heterogeneous causes in children and adults.[181–185]

Clarifications on classification

The 1989 ILAE classification considers EPC as 'Kozhevnikov syndrome type 1'.[1] Rightly, the new

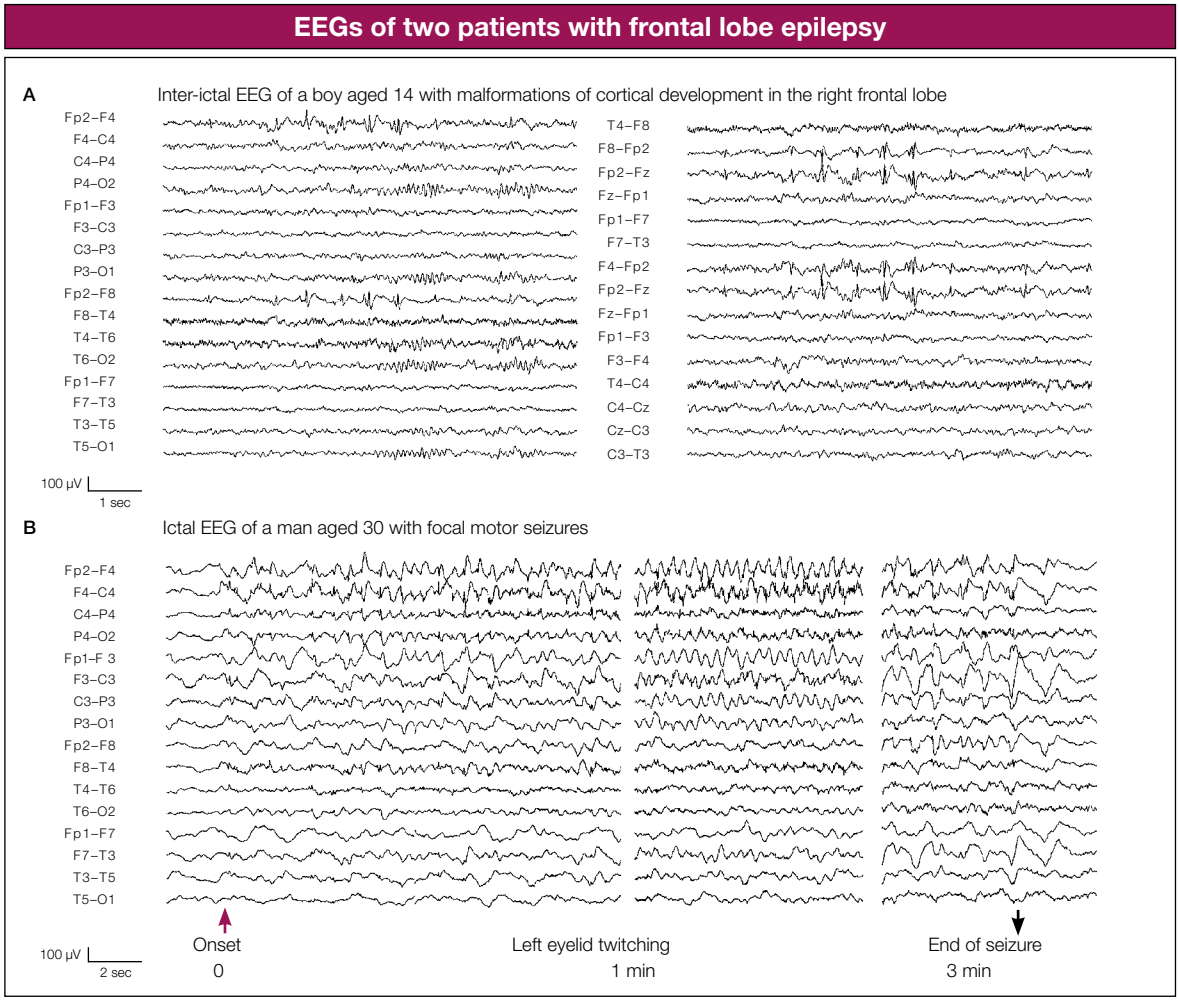

Figure 15.10 (**A**) Inter-ictal EEG of a 14-year-old child with malformations of cortical development in the dorsolateral aspect of the right frontal lobe. The same EEG sample is presented in different montages. Note frequent clusters of high-amplitude spikes intermixed with slow waves in the right frontopolar electrode (Fp2). (**B**) Ictal EEG of a 30-year-old patient with left-sided focal motor seizures.

diagnostic scheme recognised 'epilepsia partialis continua of Kozhevnikov' as a seizure type/status epilepticus and not as a syndrome (Table 3.1).[2,3] See Chapter 11.

Demographic data

Onset occurs at any age. A third of cases start before 16 years of age. Both sexes are equally affected. Prevalence is extremely small, probably less than one per million population.[181]

Clinical manifestations

The defining symptom of EPC is 'spontaneous regular or irregular clonic muscle twitching of cerebral cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body, and continuing for a period of hours, days or weeks'.[186] In other words, EPC is a lengthy segmental myoclonic seizure lasting a few milliseconds repeated almost every second for hours, days or months. The twitching is limited to a muscle or a small group

of contiguous or unrelated muscles on one side of the body. Agonist and antagonist muscles are simultaneously contracted. Facial and hand muscles are preferentially affected.

The muscle twitching of EPC is characterised by location, frequency, intensity, duration and coexistence with other types of more conventional s eizures.[160,181,182,185,187,188] Activation, reflex, by movement or other means, is characteristic in some patients.[181,186,189]

Location: EPC may involve one muscle or a small muscle group of agonists and antagonists. These may be in the same region (corner of the mouth, thumb and other fingers) or occur simultaneously in other locations on the same side without direct anatomical continuity. Thus, a patient may stereotypically experience twitching of the eyelid and the shoulder or abdominal muscles simultaneously, leaving other facial or limb muscles unaffected (Figure 15.11). Facial and distal muscles of the upper limbs are more commonly affected than proximal or leg musculature. Single truncal muscles on one side may be involved.

EPC that involves both sides of the body alternately is exceptional.[190]

Frequency: Typically, every jerk occurs about once every 1–5 s.[181] EPC usually persists during slow-wave sleep, although it is often of diminished frequency and intensity. It may be reduced or exaggerated during REM.[191]

Intensity: Commonly, the jerks in EPC are not violent. Intensity varies from almost inconspicuous to clearly visible repetitive rapid movements.

Duration is lengthy, ranging from hours to months, although each jerk lasts for only a few milliseconds.[186]

Activation: EPC is sometimes 'aggravated by action or sensory stimuli'.[186] Movement or other means of activation of the affected muscles may be a characteristic feature in some patients.[189]

Other types of seizures

About 60% of patients exhibit, in addition to EPC, other types of seizures, such as motor focal seizures or secondarily GTCSs and, more rarely, complex focal seizures.[160,181,182,185,187] These may occur independently, or precede or follow the appearance of EPC. More often, motor focal seizures are interspersed with EPC (Figure 15.11).

Neurological signs and symptoms

Varying degrees of muscle weakness and neurological signs occur during EPC.[160,182,185] Permanent neurological and mental deficits may be static or progressive, and precede or follow the appearance of EPC.

Patients with localised neoplastic, vascular or infectious brain lesions may have neurological deficits and isolated seizures before the onset of EPC.[160] In non-ketotic hyperglycaemia or drug-induced EPC, the onset is sudden.[189]

Aetiology

There are multiple and diverse causes of EPC (Table 15.2). Kozhevnikov–Rasmussen syndrome and malformations of cortical development are the main causes in children (see Chapter 11); cerebrovascular disease and brain space-occupying lesions are the main causes in adults. Non-ketotic hyperglycaemia is the most common reversible cause. Other metabolic, mitochondrial or hereditary disorders are well described.

Dereux (1955),[192] in a thesis comprising 102 cases, found that more than 50% were caused by an 'encephalitic process'.

Russian spring–summer tick-borne encephalitis is a rare cause that occurs in endemic areas. This condition is overemphasised based on the erroneous assumption that it caused the cases of EPC described by Kozhevnikov (see page XXX).[193,194]

Pathophysiology

The current consensus is that EPC is primarily of cortical origin and emanates mainly in the primary motor cortex.[181]

Diagnostic procedures

The yield of investigative procedures is cause dependent (Table 15.2). Around two-thirds of

Aetiology of epilepsia partialis continua	
Chronic or acute encephalitis	Kozhevnikov–Rasmussen syndrome Acute encephalitis including tick-borne encephalitis Human immunodeficiency virus infection Renal and hepatic encephalopathy Anti-Hu-associated paraneoplastic encephalomyelitis
Metabolic disturbances	Non-ketotic hyperglycaemic diabetes mellitus, particularly when associated with hyponatraemia Alpers syndrome Kufs' disease NADH–coenzyme Q reductase deficiency
Lesional diseases of the brain	Cerebrovascular disease, brain tumour, abscess, trauma, metastasis, granuloma, cysticercosis, haemorrhage, infarct, arteriovenous malformation and cortical vein thrombosis Malformations of cortical development Multiple sclerosis
Drugs	Penicillin and azlocillin–cefotaxime (and the old contrast media metrizamide) may induce EPC
Others	Mitochondrial disorders, Creutzfeldt–Jakob disease
Unknown (20%)	–

Table 15.2

patients have abnormal brain MRI scans and EEGs, which get worse in progressive disorders such as Kozhevnikov–Rasmussen syndrome. Ictal EEG may or may not show epileptiform abnormalities concomitant with the jerks (Figure 15.11). Typically, jerk-locked back-averaged cortical potentials appear in the contralateral primary motor area preceding the jerks by a few milliseconds; sensory evoked potentials are of high amplitude (Figure 15.12) and there is a rostro-caudal pattern of muscle recruitment with co-contraction of agonist and antagonist muscles. Positron emission tomography (PET) and single photon emission CT (SPECT) scans often localise the abnormal region, but they are not specific. Screening for metabolic and mitochondrial disorders may be necessary and a few cases are of unknown origin.

Differential diagnosis

There are not many other conditions that exhibit the characteristic segmental, continuous muscle twitching of EPC. EEG may or may not be useful. A normal ictal EEG does not exclude this diagnosis. Brain imaging may or may not be abnormal. The main difficulty is in differentiating between the genuine cortical and non-cortical cases, and this is often a formidable task without appropriate neurophysiological examinations illustrated in Figure 15.12 (jerk-locked back averaging, somatosensory evoked responses and sequential electromyography). In clinical terms, the coexistence of other types of focal epileptic seizures practically identifies cortical EPC.

Tremors, ticks and extrapyramidal disorders rarely, if ever, have this constant, unilateral and highly localised appearance of EPC (see Chapter 4). However, difficulties may be imposed by 'hemifacial spasm', which is probably due to ipsilateral facial nerve root compression and segmental demyelination. *Hemifacial spasm*, similar to EPC, manifests with unilateral painless, irregular and continuous clonic twitching of the facial muscles. It affects mainly women, aged 50–60 years, without known

Ictal EEG of epilepsia partialis continua progressing to hemiconvulsions

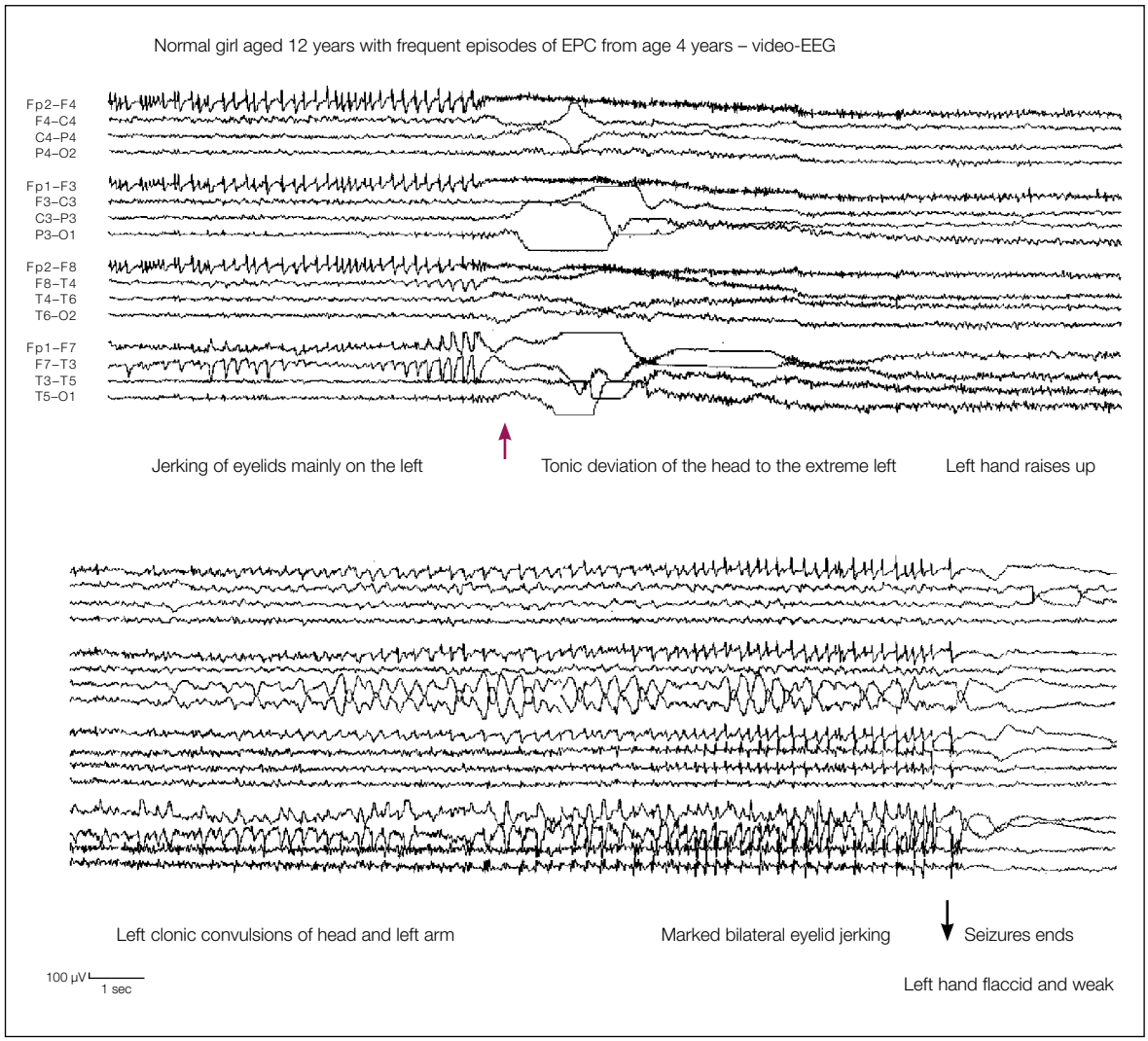

Figure 15.11 Sample from a video-EEG of a girl aged 12 years. She has EPC, which started at the age of 4 years and continues to date with increasing frequency and duration. Fast (3–10 Hz) twitching of the left eyelids occurs simultaneously with the left rectus abdominis (she points close to the midline by the umbilicus) and a muscle in the armpit (probably the latissimus dorsi). This lasts from hours to 2 or 3 days and is continuous day and night. This is interspersed with left-sided, focal tonic–clonic motor seizures mainly affecting the face and upper limb. Additionally, there is post-ictal, and probably ictal, left hemiparesis mainly of the upper limb. She does not lose consciousness during these attacks and communicates well. She is also able to understand, but cannot speak during the focal motor seizures. She has never had a full-blown GTCS. Initially the seizures occurred once or twice per year, but now occur every 2 weeks. Neurological and mental status is normal. High-resolution brain MRI was normal. All appropriate tests for metabolic or other diseases associated with EPC were normal. Drug treatments have failed; only rectal diazepam provides temporary relief during the attacks. *Differential diagnosis:* EPC is a non-specific seizure type that may occur in a number of diverse conditions and have a number of different causes. In a child, the first syndrome that comes to mind is Kozhevnikov–Rasmussen chronic encephalitis. However, her good clinical status over the years, as well as the normal MRI and the lack of background EEG abnormalities, is rather against this diagnosis, although some unusual cases in which deterioration occurs 10 years after onset of EPC have been recorded.

Neurophysiological abnormalities in a patient with epilepsia partialis continua

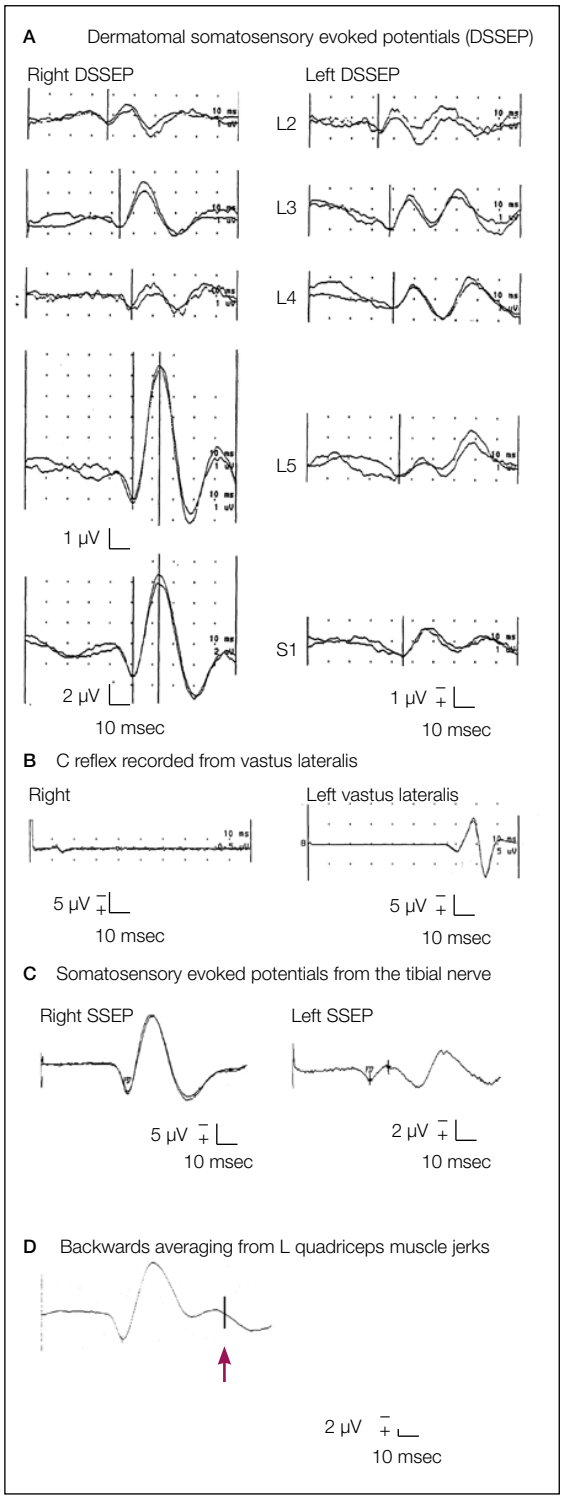

Figure 15.12 Neurophysiological investigations in a man aged 26 years with onset of EPC at the age of 25. This consisted of continuous and arrhythmic twitching of various muscles of the left leg and particularly the toes. There was great variation in intensity, spread and severity. It was exaggerated on dorsiflexion of the foot and improved when resting. On five occasions, this progressed in a jacksonian manner to GTCS. The clonic movements of the toes spread to the foot and then to the knee for 5 min prior to GTCS. On neurological examination, there were mild pyramidal signs of the left leg. All possible tests to discover the cause of this were negative, including high-resolution MRI and PET scanning, and cerebrospinal fluid with appropriate metabolic screening. Mitochondrial disease was also excluded. After a short course of steroids and drug treatment with mainly clonazepam, the situation improved dramatically. Ten years later, he is well, although he has some infrequent clusters of irregular twitching of the toes of the left leg and is still on clonazepam. (**A**,**C**) Dermatomal and somatosensory potentials are gigantic on the right side (from stimulation of the left). Note that the maximum amplitude of the dermatomal potentials is obtained when the S1 dermatome is stimulated. (**B**) C reflex of around 65 ms latency is obtained only from muscles of the left leg stimulating the peroneal nerve (similar responses were also obtained from other left-sided leg muscles by stimulating other left leg nerves or by tapping for the knee jerk). (**D**) Jerk-locked back-averaged cortical potentials appear in the contralateral primary motor area preceding the jerks by 25 ms (positive peak).

antecedent causes other than Bell's palsy in a few cases. The spasms usually begin in the orbicularis oculi and gradually spread to other facial muscles and the platysma of the face. They may be induced or aggravated by voluntary and reflex movements of the face.[195]

A 50-year-old woman had almost continuous twitching in the left side of the face for 2 months. The diagnosis of hemifacial spasms was made by eminent neurologists. However, MRI and subsequent surgery revealed a large glioblastoma in the right side of the brain.

Once the diagnosis of EPC is made, the underlying cause should be thoroughly sought (Table 15.2).

Prognosis

The long-term prognosis of EPC is cause dependent and usually poor (Table 15.2). Most patients will continue with intractable EPC and also develop neurological and mental defects. Only a few patients may have a remission. Drug-induced EPC or EPC occurring in the setting of non-ketotic hyperglycaemia is reversible once the offending agent has been removed or the metabolic defect corrected.

Management

EPC is resistant to treatment with AEDs. Clonazepam, valproate, carbamazepine and new broad-spectrum AEDs, such as levetiracetam and topiramate, are probably the most effective. Successful treatment with multiple subpial transections has been reported in only a minority of operated patients.[181,184]

Parietal lobe epilepsies

Parietal lobe epilepsies manifest with seizures originating from a primary epileptic focus anywhere within the parietal lobes.[1,196–202]

The clinical seizure characteristics, EEG findings and results of neuroimaging studies have been established mainly in neurosurgical series of patients with a carefully documented seizure of parietal lobe origin.

The report by Kim, *et al*[201] is an excellent description of the modern approach to parietal lobe epilepsies.

Clarifications on classification

Parietal lobe epilepsies have not yet been detailed in the new ILAE diagnostic scheme.[2,3] The 1989 ILAE Commission classifies parietal lobe epilepsies among the 'localisation-related (focal, local, partial) epilepsies and epileptic syndromes', but describes parietal seizures rather than parietal lobe syndromes.[1]

Demographic data

Parietal lobe epilepsies may start at any age. Both sexes are equally affected. Age at onset is much later in patients with tumours[199] than in those without tumours.[198] Parietal lobe epilepsies are relatively rare and probably account for 6% of all focal epilepsies in neurosurgical series.[203]

Clinical manifestations

Seizures emanating from the parietal lobes are mainly *simple focal* without impairment of consciousness. They manifest with subjective symptoms (auras), which are, in order of prevalence:

- somatosensory
- somatic illusions (subjective disturbances of body image)
- vertiginous
- visual illusions or complex formed visual hallucinations
- receptive or conductive linguistic disturbances.

Clinical seizure manifestations are usually related to the epileptogenic location, anterior or posterior, of the dominant or non-dominant parietal lobe. Onset with sensorimotor symptoms is usually associated with anterior parietal lobe foci, whereas more complex symptomatology emanates from posterior parietal lobe regions. Approximately 50% of patients experience more than one type of seizure.[201]

Somatosensory seizures

Somatosensory seizures are by far the most common type (around two-thirds of cases).[199]

Quality: Various types of paraesthetic, dysaesthetic and painful sensations are described, such as tingling, numbness, thermal, burning, tickling, pricking, creeping, tight, crawling, electric and their

variations. Tingling may be the most characteristic symptom (76% in one study).[204] There may be tongue sensations of crawling, stiffness or coldness.

> They all start with a tingling sensation around the left side of my lip. This lasts for 10–20 seconds before spreading to my left arm. Then I lose coordination and power in my left arm, which may start convulsing with little if any manifestations from my leg. The whole seizure lasts for approximately one and a half minutes. During this time, I am able to talk and understand.

Pain, sometimes excruciating, is experienced by 25% of patients with somatosensory seizures.[198,199,205–208] Pain is usually unilateral, but may be cephalic or abdominal.[205] When lateralised, the painful symptoms are contralateral to the side of seizure origin.[205]

Symptom location: The face (mainly the lips and tongue) and hand (mainly the thumb) and arm that have the largest cortical representation (homunculus of Penfield) are more likely to be involved. Facial sensory phenomena may occur bilaterally.[209] Symptoms may be static and remain confined to their region of origin during the whole seizure (40% of cases). Somatosensory symptoms often march in a manner similar to the jacksonian motor seizure. A bilateral or discontiguous manner of spread is rarer. Unilateral somatosensory seizures are usually contralateral to the epileptogenic zone. Seizures ipsilateral to the side of seizure origin are exceptional.[210]

> It is numbness or a hot feeling restricted to the corner of my left lip of the size of no more than a 2-pence piece. This lasts for 1–3 seconds and comes approximately once every week. On rare occasions, this numbness spreads to my left hand for a second and at the same time I am unable to articulate words. This also may be followed by 'shaking of the lips'. On eight occasions in 14 years, this was followed by convulsions.

Ictal sensations in the genital areas and the rectum, and orgasmic seizures are infrequent, but patients may be embarrassed to report them. Peri-ictal or post-ictal true masturbation may happen.[211] Sexual dyspraxic automatisms (i.e. fondling the genitals) occur only in the post-ictal phase of seizures.

Objective ictal somatosensory deficits: Objectively demonstrable transient somatosensory deficits may be common if tested during the seizure; for example, a patient of Penfield's, while undergoing electrocorticography under local anaesthesia, had an electrically induced seizure restricted to the parietal lobe.[18] The patient was unaware of any specific symptoms, but two-point discrimination was impaired in the contralateral hand and returned to normal at seizure termination.

Disturbances of body image and somatic illusions

Disturbances of body image and somatic illusions are the second most common ictal symptoms of parietal lobe seizures. They include illusions of distorted posture, limb position or movement, a feeling that an extremity or a body part is alien or absent, dissociations and misperceptions of location and body part identity. Patients describe sensations of twisting, swelling, shrinking, turning or movement in one extremity or in the body, a feeling that one leg is absent and displacement of a limb or the body:

> Having my body bend toward the left, I just sort of swayed.[198]

Most patients have paraesthesia associated with these illusions. Ictal somatosensory hallucinations are rare.[18,212]

Ictal somatic illusions probably reflect seizure discharges in the inferior parietal lobule and superior part of the postcentral gyrus of the non-dominant hemisphere.[208]

Somatoagnosia (*soma* = body; *agnosia* = ignorance, inability to recognise) is the inability to recognise the affected body part as one's own. Somatoagnosia and most of the somatic sensations occur more frequently with dysfunction of the non-dominant cerebral hemisphere.[213–215] Ictal *limb agnosia* and *phantom limb sensations* (the sense that the limb is in a position that is not the true position) probably originate in the posterior parietal region.[216,217] *Neglect* is more commonly associated with the right rather than the left inferior parietal lobe. These auras may reflect ictal impairment '*in the body image mechanism of the posterior parietal lobe*'.[216]

Illusions of movement are often typical of parietal lobe seizures,[218,219] whereas the sensation of

a desire to move emanates from the precentral gyrus.[220]

Other ictal subjective symptoms

Vertigo and other vertiginous sensations of an illusion of rotatory motions of the body are well reported and probably about 10% are ictal manifestations of parietal lobe seizures.[198,199,208,221] They are elicited predominantly from the temporoparietal border.[222,223]

Visual illusions and complex formed visual hallucinations occur in about 12% of patients with parietal lobe epilepsy. Images may appear larger or smaller, closer or further away, or moving though static. Ictal visual illusions, such as *micropsia*, *metamorphopsia*, *autoscopia* and *palinopsia*, most probably emanate from the non-dominant parietal regions.

Linguistic disturbances: Dominant temporoparietal lobe seizures are associated with a variety of linguistic disturbances, alexia with agraphia and significant calculation defects. Non-dominant parietal-occipital-temporal seizure activity usually results in significant spatial disturbances.

Inhibitory motor seizures, ictal hemiplegia[207] or negative motor manifestations, including drop attacks,[198] are exceptional. An inability to move one extremity or a feeling of weakness in the hand contralateral to the epileptogenic zone may be more common than reported.[199]

> On most occasions my left hand becomes numb, but in a few other instances, it becomes heavy and I am unable to move it for a minute or so.

Seizure spreading to extraparietal regions

Simple focal seizures often spread to extraparietal regions, producing unilateral focal clonic convulsions (57% of patients), head and eye deviation (41%), tonic posturing of usually one extremity (28%) and automatisms (21%).

Most patients also suffer from secondarily GTCSs, but these are usually infrequent.[201]

Duration of seizures

The duration of seizures varies from a few seconds to 1 or 2 min.[224] Prolonged isolated sensory auras comparable to EPC, but without any motor manifestations, have been reported[18,198,199] and this condition may be misdiagnosed as psychogenic NEPEs.[225]

Post-ictal manifestations

Post-ictal manifestations are usually short,[224] although Todd's paralysis (22%) and dysphasia (7%) may be common.[198]

Epileptogenic localisation

Seizures of the primary sensory cortex typically produce contralateral positive or negative symptoms. However, focal sensorimotor phenomena at the onset also occur with seizures emanating from posterior parietal regions.[203] This means that the primary epileptogenic focus is clinically silent and that symptoms are produced by spreading of the ictal discharge to the eloquent ictal symptomatogenic zone of the postcentral gyrus.[18,201] Bilateral sensory symptoms usually derive from the secondary sensory area.[18,225]

Ictal sensations in the genital areas usually emanate from the parietal paracentral lobule.[1,198,208] Ictal pain is usually reproduced by stimulating area 5a, behind the postcentral gyrus.[198,199,226,227]

Precipitating factors

Seizures may be provoked by movements of the affected part of the body, tapping or other somatosensory stimuli.[228,229] These are exceptional in neurosurgical series.[198]

> In one patient, seizures frequently occurred when she was trying to open a container or package.[205,207,208]

> Accidental finger amputation resulted in seizure control in a boy whose seizures included ictal sensory loss in one arm provoked by using cutlery while eating.[230]

Sensorimotor seizures may also be triggered by music[231] or toothbrushing.[232]

Giant EEG spikes evoked by somatosensory stimuli in benign childhood seizure susceptibility syndrome are detailed in Chapter 12.

Aetiology

The aetiology is diverse and includes symptomatic (Figure 15.13), cryptogenic and idiopathic

causes.[198,199] Malformations of cortical development, mild or severe, are probably the most common cause.[201,204]

Diagnostic procedures

Neurological examination is usually normal in patients with non-tumoral parietal lobe epilepsy or the abnormalities are mild. Sensory deficits, such as impaired two-point discrimination or stereoagnosia (of which patients may be unaware), mild limb atrophy and inferior quadrantic visual field defects, should be sought. Patients should also be examined for disturbances of written language, aphasia, spatial orientation and right–left disorientation.[203,204] Patients with tumoral parietal lobe epilepsy have similar neurological deficits, but mild contralateral weakness is common (38%), whereas unilateral limb atrophy is exceptional.[199]

Brain imaging, preferably with high-resolution MRI, is mandatory for any patient with parietal lobe epilepsy and may be abnormal in around 60% of patients (Figure 15.13).[199] Other brain imaging modalities, such as FDG-PET and ictal SPECT, are useful in neurosurgical evaluations.[201]

Electroencephalography

Surface inter-ictal EEG may be normal, non-specific or misleading.[201,210] Inter-ictal spikes (Figure 15.14) should be interpreted cautiously with regard to localisation because they may appear in areas other than the parietal regions, involving frontal, temporal or occipital electrodes. Of patients with intractable parietal lobe epilepsy, 16% do not have epileptiform discharges.[198] In these patients, secondary bilateral synchrony may be common (32%).[198] In symptomatic patients, localised slow waves may be the only inter-ictal abnormality.[198,199,210]

The ictal EEG may be normal in 85% of simple focal sensory seizures.[204] The prevalence of scalp EEG changes in simple focal seizures with predominant sensory symptoms is only 15%, as opposed to 33% when motor symptoms are present.[233]

Localised parietal seizure onset is rare (11%).[198,210] Ictal onset may be distant from the area of the predominant inter-ictal spiking,[209] and ictal EEG patterns are occasionally difficult to interpret,[229] particularly when seizures rapidly become generalised.

Post-ictal EEG may have some localising value when attenuation of background activity or spike activation occurs.[234]

MRIs of symptomatic causes of parietal lobe epilepsies

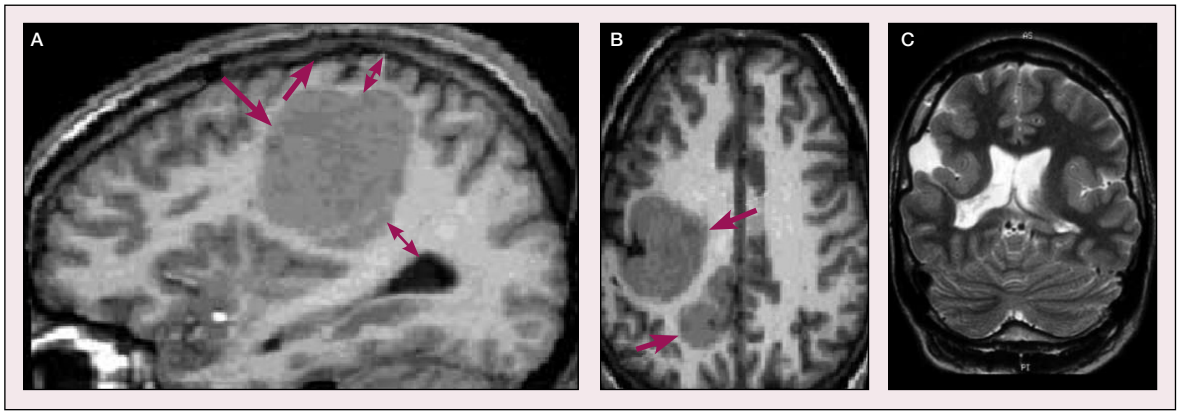

Figure 15.13 (**A**) Coronal and axial T1-weighted MRI demonstrating parietal subcortical heterotopia (arrows). (**B**) Coronal T2-weighted MRI demonstrating bilateral perisylvian polymicrogyria. (**C**) Coronal inverted T2-weighted MRI demonstrating abnormal signal changes (post-traumatic in nature) in the left parietal lobe involving the white matter.
Figures A and B courtesy of Professor John S. Duncan and the National Society for Epilepsy MRI Unit, London, UK. Figure C courtesy of Dr Ruben Kuzniecky, NYU Epilepsy Center, New York, USA.

Inter-ictal EEG of a 5-year-old girl with extensive right-sided porencephaly due to brain anoxia at birth

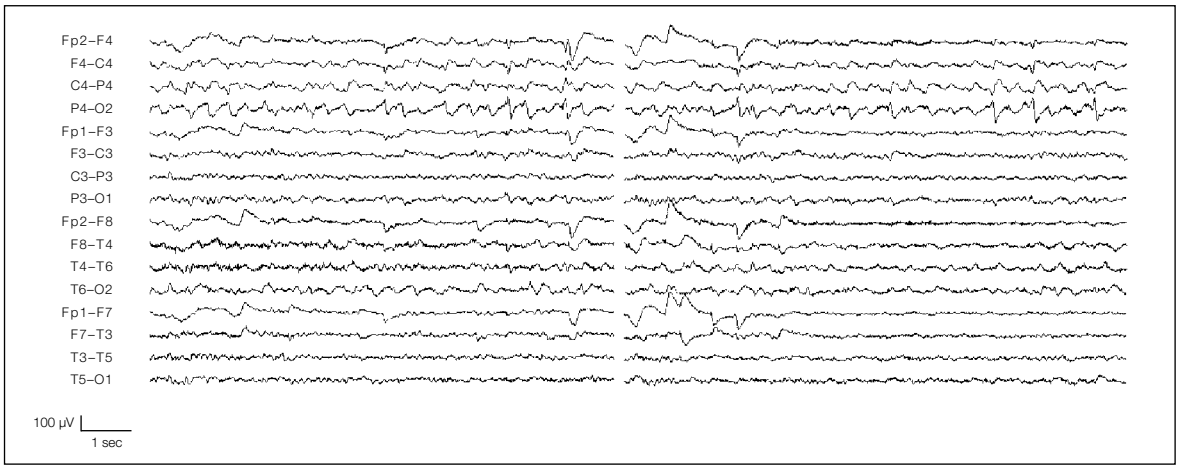

Figure 15.14 Severe right-sided abnormalities of spikes, sharp and slow waves are mainly focused around the parietal regions. Clinically she had frequent and intractable focal sensory-motor seizures.

Differential diagnosis

Simple somatosensory seizures alone, whether brief or prolonged, are a challenging proposition. Even if reported, they are likely to be misdiagnosed as psychogenic NEPEs, transient ischaemic attacks or migraine with aura, in that order (see Chapter 4). Commonly, it is only when they progress to motor symptoms or impairment of consciousness that genuine seizures are suspected and appropriate investigations are initiated.

Differentiating pure somatosensory seizures from psychogenic NEPEs or psychiatric disturbances may be extremely difficult;[225] even ictal EEG changes are not seen in 85% of patients.[204] Ictal pain, sensory EPC, and genital and orgasmic manifestations are unlikely to be diagnosed as epileptic seizures. Sensory jacksonian seizures may imitate migraine with sensory aura.[235] In older patients, transient ischaemic attacks are the most likely diagnostic error.

Management

Drug treatment is similar to that for any other type for focal seizures and is usually effective (see page XXX).

In intractable cases, neurosurgery is associated with a high proportion of patients achieving a seizure-free state or remarkable improvement (>65%).[198,201] MRI abnormality, concordance of different diagnostic modalities and completeness of resection of the epileptogenic zone correlate with better outcome.[197,200,201,210] However, because the parietal lobe contains highly eloquent areas, resection may lead to deficits in vision, language, praxis, attention and higher cortical function, which make surgical resection problematic.[201]

Occipital lobe epilepsies

Occipital seizures originate from an epileptic occipital focus that is triggered spontaneously or by external visual stimuli.[206,208,236–242] These epilepsies may be idiopathic, symptomatic or cryptogenic (probably symptomatic).

This chapter is primarily based on an extensive review of the available literature to date, as well as studies and numerous illustrative cases that have been included in a previous monograph,[206] which has been updated appropriately.[243–245]

Clarifications on classification

The 1989 ILAE Commission classifies occipital lobe epilepsies among the 'localisation-related (focal, local, partial) epilepsies and epileptic syndromes', but describes occipital seizures rather than occipital lobe syndromes.[1] Occipital lobe epilepsies have not yet been detailed in the new ILAE diagnostic scheme.[2,3]

Terminology

Autoscopia (or heautoscopy) means viewing one's own image, viewing oneself.[246,247]

Fortification spectra in migraine are visual hallucinations with similarities to the bastioned, star-patterned, pentagonal fortifications and not the castellated appearances of battlements.[248,249] A bastion is a projecting part of a fortification, consisting of an earthwork in the form of an irregular pentagon, having its base in the main line or at an angle of the fortification. Spectrum is used by Gowers[250] to mean an 'apparition and not a coloured band of light'.

Pallinopsia (visual persevereness) is the persistence or recurrence of visual images after the exciting stimulus has been removed.

Percept is the mental image or product of perception of any object in space.

Phosphenes are subjective sensations of light due to non-luminous stimulation of the retina. Phosphenes are also used to denote visual percepts from stimulation of the visual cortex with an electrical stimulus, in which case they are usually coloured spots or circles.[251]

Photopsias (*phos* = light, *opsis* = appearance) are unformed flashes of light and sparks.

Scintillating scotoma (*scintilla* = spark, *skotos* = darkness) is used because of the sparking appearance of the visual hallucinations of migraine (brilliant flashes of light in the periphery of dark areas in the visual fields).

Teichopsia (*teichos* = town wall, *opsis* = appearance) was coined by Airy[252] 'to represent the bastioned form of transient hemiopsia which I have been describing, not without a reminiscence of some words of Tennyson's:

> as yonder walls
> rose slowly to a music slowly breathed,
> a cloud that gather'd shape.'

Visual hallucinations are subjectively experienced images in the absence of an actual external stimulus:

- *elementary visual hallucinations* consist of simple, usually geometric forms, spots or lines
- *complex visual hallucinations* consist of objects, faces or scenes

Visual illusions are misinterpreted false percepts of real images.

Demographic data

Symptomatic occipital seizures may start at any age and at any stage after or during the course of the underlying causative disorder. Idiopathic occipital epilepsy usually starts in late childhood. Occipital epilepsies account for about 5–10% of all epilepsies.[206] In neurosurgical series, the prevalence is about 5%,[239] which is comparable to the 6% seen in demographic studies.[253]

Clinical manifestations

Ictal clinical symptoms of occipital lobe epilepsies are subjective, objective or both. The cardinal symptoms are mainly visual and oculomotor.

Visual subjective symptoms include:
- elementary and less often complex visual hallucinations
- blindness
- visual illusions
- pallinopsia
- sensory hallucinations of ocular movements.

Ocular subjective symptoms comprise of:
- ocular pain.

Objective oculomotor symptoms are:
- tonic deviation of the eyes (pursuit-like rather than oculotonic)
- oculoclonic movements or nystagmus
- repetitive eyelid closures or eyelid fluttering.

Some of these ictal manifestations, such as elementary visual hallucinations, are generated in the primary visual cortex; others, such as visual illusions, emanate from the neighbourhood of the occipitoparietal and occipitotemporal regions. Seizures may spread from the occipital to other more anterior regions of the brain, generating symptoms from the temporal, parietal and frontal lobes and secondarily hemi or generalised convulsions. Ictal or post-ictal headache is frequently associated with occipital seizures.

Elementary visual hallucinations

Elementary visual hallucinations are the most common, characteristic and well-defined ictal symptoms of occipital lobe seizures (Figures 4.1, 12.8 and 15.15). They are usually the first, and often the only, ictal symptom during a seizure and may progress to other occipital and extra-occipital manifestations and convulsions.

Elementary visual hallucinations of visual seizures are mainly coloured and circular, develop rapidly within seconds, and are brief in duration. They often appear in the periphery of a temporal visual hemifield, becoming larger and multiplying in the course of the seizure, and frequently moving horizontally towards the other side. They are fundamentally different from the visual aura of migraine for which they are often mistaken.[241,254,255]

I have studied the elementary visual hallucinations of idiopathic and symptomatic occipital seizures in a qualitative and quantitative chronological manner,[241,255] differentiated them from the visual aura of migraine[256,257] and reviewed them exhaustively.[243] The main conclusions of these studies are briefly described here.

Ictal elementary visual hallucinations are defined by colour, shape, size, location, movement, speed of appearance and duration, frequency and associated symptoms of progression.

Colour, shape and size: The predominant patterns are coloured, usually multicoloured, and circular. Bright red, yellow, blue and green prevail. Shapes are mainly circular; i.e. spots, circles and balls. Individual elements are multiple and rarely single. Their size varies from 'spots' to rarely the size of a 'small ball'. Square, triangular and rectangular or star-like shapes, alone or in combination with circular patterns, are less frequent; they are usually coloured. Flashing or flickering achromatic lights, shades or non-circular patterns are rare. The components of visual hallucinations increase in number, size or both with progression of the seizure, particularly before other non-visual symptoms.

Multi-coloured blue, yellow and red, circular flickering patterns closely packed together and multiplying in the left lateral hemifield. Then it seems that the environment moves slowly and stepwise from left to right.

A 'rainbow' of all colours with dust blocks of shadow-like bricks in the periphery of the right eye.

Location: Their location at onset is usually unilateral, mainly in the temporal visual hemifield (Figure 15.15). They may appear in a normal, blind or damaged hemifield.[258] Central or undefined localisation occurs in 10–30% of patients.

Movement: The components of elementary visual hallucinations usually multiply and become larger without any particular movement other than changing positions and luminance within their visual territory (Figures 12.8 and 15.15). Flickering or flashing is common. Movement towards the centre of vision or the other side is less common. Rarely, the movement is spinning, circling, rotatory, random, approaching or moving away from the patient.[18,258,259]

Visual movement was more frequently present than absent. The image might remain still, but more often

Visual seizures as perceived and drawn by a patient with an interesting form of symptomatic occipital epilepsy

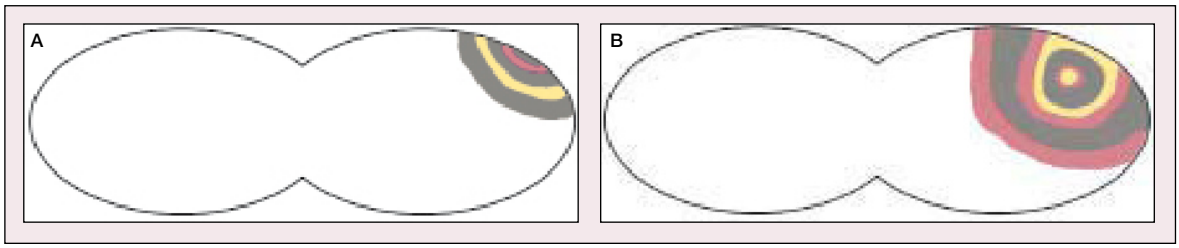

Figure 15.15 Visual seizures as perceived and drawn by a patient with symptomatic occipital epilepsy of cortical dysplasia and angiodysplasia with foci of acquired ischaemic necrosis and chronic inflammation (case detailed in Thom, *et al*[264]). *Reproduced from Panayiotopoulos (1999)*[241] *with the permission of the Editor of* Epileptic Disorders.

> it moved slowly in a certain direction or it danced, flickered or whirled.[260]
>
> There are three or four concentric spherical rings of red and yellow moving from the left to the right of my vision, and repeating the same course again and again after their disappearance on the right.[206]

Lateralisation: The side of unilateral elementary visual hallucinations is contralateral to the epileptogenic focus. Conversely, this is ipsilateral to the epileptogenic focus for unilateral visual hallucinations, moving horizontally towards the other side.[259,261]

Vision: Ictally, vision may be obscured only in the area occupied by the visual hallucinations. However, some patients may even be able to read through them. Blurring of vision at onset, with or without visual hallucinations, may be a common mild form of visual seizure (see page XXX).

Duration: Visual seizures develop rapidly within seconds and they are usually brief, lasting from a few seconds to 1–3 min, rarely longer.[241,255,256] Exceptionally, they last for 20–150 min, sometimes constituting focal visual status epilepticus without other ictal symptoms.[27,243,262,263]

As a rule, elementary visual hallucinations are longer before secondarily generalisation.

Frequency and circadian distribution: Visual seizures occur, often in multiple clusters, daily or weekly. Commonly, several may occur a day. They are usually diurnal, but some patients often wake up with elementary visual hallucinations.

> I would wake up from sleep either with elementary visual hallucinations or with white blindness (all white), before a generalised convulsion.

Stereotypical appearance: Ictal symptoms of elementary visual hallucinations are stereotyped, particularly at onset, in all aspects other than duration. Exceptionally, the same patient may experience different types of seizures.

Progression to other occipital or non-occipital seizure manifestations: Elementary visual hallucinations may be the only seizure manifestation, but they often progress to other ictal symptoms, such as complex visual hallucinations, oculoclonic seizures, tonic deviation of the eyes, eyelid fluttering or repetitive eye closures, impairment of consciousness, experiential phenomena, hemi-anaesthesia, and unilateral or generalised convulsions. On other occasions, they progress to extra-occipital seizure manifestations by spread to the temporal, frontal or parietal regions.

> Bright, multicoloured, blue, red, yellow and green spots of light in the periphery of the right eye multiply rapidly and occupy the whole right visual field, though I can see through them. They cause me a pleasant feeling 'because of the colours'. These are sometimes followed by distortion of the surrounding objects and persons as if 'through the mirrors of a theme park'.
>
> A spinning ball filled with mainly red and yellow colours on the right. This could be followed by visions of distorted bodies.

Complex visual hallucinations, visual illusions and other symptoms from more anterior ictal spreading

These mainly occur in progression of the seizure, which may terminate with hemiconvulsions or generalised convulsions. They may be the first ictal symptom, but more often follow elementary visual hallucinations.

Complex visual hallucinations may take the form of people, animals, objects, figures or scenes. They may be familiar or unfamiliar, friendly or frightening, and simple or grotesque. They may appear in a small or large area of a hemifield, or in the centre and the whole of the visual field. They may be static, move horizontally, expand or shrink, approach or move away. In patients with visual field defects due to structural brain lesions, complex visual hallucinations appear in the defective visual field. Complex visual hallucinations of occipital seizures do not have the emotional and complicated character of temporal lobe seizures.[241,255,265]

> Sudden awareness of rapidly oscillating, vague, dark, disproportionate, face-like, frightening figures moving forwards and backwards in the temporal field of my left eye.

An interesting, but extremely rare, ictal complex visual hallucination is *autoscopia* (*or heautoscopy*), which means viewing one's own image/viewing oneself.[246,247] This mirror self image looks 'real' and is usually undistorted, silent, brief or recurrent, from the present time or from the past, framed or performing complex tasks.

Complex visual hallucinations including ictal autoscopia probably originate from occipitoparietal and occipitotemporal junction areas.

Visual illusions are misinterpretations, false percepts, of real external images. These distorted images (*metamorphopsia*) involve changes in size, dimension, shape, proportions, position, colour, illumination and movement, alone or in combination. Changes in perception of object size are common, the percepts being smaller (*micropsia*) or larger (*macropsia*) than the real image. Objects may be distorted in shape, pulled, compressed or rotated in lateral or vertical directions. They may appear in black and white (*achromatopsia*), in one colour (*monochromopsia*), hazy and dark or highly illuminated and bright. Motion and speed may be affected with or without distortion of direction (horizontal, vertical or rotated, approaching or moving away). Movement is faster or slower. Moving objects may appear stationary and *vice versa*.

Visual illusions also entail changes in spatial interpretation affecting stereoscopic vision:

> Far objects appear near, near ones far, and convex ones concave, or *vice versa*.[266]

Ictal visual illusions may occupy part or the whole visual field, and are probably more likely to be associated with symptomatic than with idiopathic occipital seizures.

Palinopsia

Palinopsia, which is the persistence or recurrence of visual images after the exciting stimulus has been removed, is an interesting form of visual illusion associated with right posterior parietotemporal lesions.

> I looked at a small video display unit and, after I looked away, the image of the screen persisted in the right upper corner of my vision and nearly simultaneously started flashing at a rate of 3–5 Hz for 2 seconds. This was followed by visual illusions of the walls and the passengers closing in on him, ending within 5 seconds with GTCSs.

Sensory hallucinations of ocular movements

Sensory hallucinations of ocular movements, which is a sensation of ocular movement in the absence of detectable motion, is rare.

> 'This involuntary movement of the eyes to the left and at a slight tilt upwards causes the pain. The motion to the left seems out of your control. It can be resisted but this adds to nausea and general pain.' Neither he nor the witnesses could confirm any such movement of the eyes.

Ictal blindness

Ictal blindness (ictal amaurosis) may follow the visual hallucinations and progress to other epi-

leptic symptoms, but often occurs as a starting or only ictal seizure manifestation with abrupt onset.[241,243,255,257,267]

> I usually have millions of small, very bright, mainly blue and green coloured, circular spots of light, which appear on the left side and sometimes move to the right, but on one occasion suddenly everything went black, I could not see and I had to ask other swimmers to show me the direction to the beach.[206,268]

The duration of ictal blindness is usually longer (3–5 min) than ictal visual hallucinations; occasionally, blindness may last for hours or days (status epilepticus amauroticus).[269–271] Ictal blindness and, less frequently, ictal hemianopia occur in a third of patients with symptomatic and two-thirds of patients with idiopathic occipital epilepsy.

An interesting rare variation of ictal blindness is 'white ictal blindness'.[241,243] The patient cannot see because everything is white.

> I cannot see, like a white sheet in front of my eyes.
>
> It is all white.

Blurring of vision as an initial seizure manifestation before visual hallucinations may be common if investigated.[241,255,265]

> It starts with a momentary flickering or blurring of vision (always in the left temporal field only) (case 7.2 in Panayiotopoulos[206]).
>
> My sight deteriorates very slightly as it does before the aura, but flashing does not start. It is a reduction of visual awareness of around 10% (case 30 in Panayiotopoulos[206]).

Tonic deviation of the eyes, oculoclonic seizures and epileptic nystagmus

Tonic deviation of the eyes often, but not necessarily, followed by ipsilateral turning of the head is the most common (40–50% of cases) non-visual symptom of occipital seizures. This is similar to a voluntary, pursuit-like turning of the eyes to one side. This usually follows visual symptoms and mainly elementary visual hallucinations, but it may also occur from seizure onset. Consciousness is often, but not invariably, impaired when eye deviation occurs.

The epileptogenic focus is more likely to be contralateral to the movement of the head and the eyes if consciousness is not impaired.

Ictal nystagmus (epileptic nystagmus) is mainly horizontal and rarely vertical. The quick phase of the nystagmus is opposite to the epileptic focus, in the same direction of eye and head deviation, which may coexist, precede or follow.

Repetitive eyelid closures, eyelid fluttering and eyelid blinking

Repetitive eyelid closures, eyelid fluttering and eyelid blinking are an interesting ictal clinical symptom of symptomatic and idiopathic occipital epilepsy. They usually occur after the visual hallucinations phase, at a stage when consciousness is impaired and herald the impending secondarily generalised convulsions. However, they may also occur alone, be inconspicuous in appearance and not be suspected as seizure events, documented only by video-EEG recordings in occipital photosensitive patients. See also eyelid myoclonia with absences (Chapter 16).

Eyelid opening, or 'eyes widely opened', is another well-described symptom in occipital epilepsy, but it may also be a symptom associated with other cerebral locations. Widened palpebral fissures with fixed staring and dilated pupils are among the typical symptoms of mesial temporal lobe seizures.[272]

Consciousness

Consciousness is not impaired during the elementary and complex visual hallucinations, blindness and other subjective occipital seizure symptoms, but may be disturbed or lost in the course of the seizure, usually at the time of eye deviation or eyelid closures, and generally before convulsions.

Ictal or post-ictal headache

Ictal or post-ictal headache is frequently associated with occipital seizures.[241,243,255,257] Ictal pain is mainly orbital. It is described as a sharp, stabbing, retro-orbital pain, a sensation of bifrontal pressure, a vague ache in the head or a sensation of electricity.

> The visual hallucinations consist of vivid, flashing multicoloured lights and circular patterns that occupy

and obscure my vision. Severe unilateral throbbing headache follows 1 or 2 minutes later, lasts for hours and is often associated with vomiting (case 7.1 in Panayiotopoulos[206]).

Post-ictal headache, often indistinguishable from migraine, is far more common in occipital (occurring in more than 50% of cases) than in any other focal epilepsy,[273,274] and may occur even after brief visual seizures.[241,255] Also, post-ictal headache often occurs 3–15 min from the end of the visual seizure, a situation known in migraine as the 'asymptomatic interval' between the end of migraine aura and the onset of headache.[275]

Post-ictal hemianopia may occur.

When the visual hallucinations ceased completely, I had almost no vision in the left eye, only blackness (case 7.2 in Panayiotopoulos[206]).

Seizure spreading

Seizures may spread from the occipital to other more anterior regions of the brain, generating symptoms from the temporal, parietal and frontal lobes and secondarily hemi or generalised convulsions. Infra-calcarine occipital foci will propagate to the temporal lobe, causing complex focal seizures, whereas supra-calcarine foci tend to propagate to the parietal and frontal areas, giving rise to predominantly motor seizures.

Progression to temporal lobe seizure symptomatology is rather exceptional in idiopathic cases.

Aetiology

Aetiology may be idiopathic, symptomatic (structural or metabolic) or cryptogenic.[241,243,255,257]

In symptomatic occipital epilepsy, lesions may be congenital, residual or progressive, resulting from vascular, neoplastic, metabolic, hereditary, congenital, inflammatory, parasitic or systemic diseases and infections. Malformations of cortical development are a common cause, which is being increasingly recognised with MRI, as is the case today in all focal symptomatic or probably symptomatic epilepsies (Figure 15.7).[239]

Metabolic or other derangements, such as eclampsia, may have a particular predilection for the occipital lobes and cause either occipital '*seizures that do not require a diagnosis of epilepsy*' or permanent occipital lesions leading to symptomatic occipital epilepsy.[276] There is an interesting association between coeliac disease and occipital lobe epilepsy.[277] Occipital seizures may be the first manifestation of a devastating course, as for example, in Lafora disease[278–280] or mitochondrial disorders.[281]

Coeliac disease and occipital epilepsy

The association between occipital seizures and coeliac disease, with or without bilateral occipital calcifications, has been well documented.[282] Diverse epileptic conditions with onset in childhood and early adolescence have been reported in patients with symptomatic or asymptomatic coeliac disease. These conditions include severe epilepsies, such as Lennox–Gastaut syndrome, and myoclonic epilepsies with ataxia, but more commonly symptomatic occipital epilepsy.

Age at onset of epilepsy is 1–28 years, but most commonly occurs between 4 and 13 years. Occipital seizures are by far the most common, although other focal fits, GTCSs and absences may occur from the onset of epilepsy. In most patients, seizures start before the detection of coeliac disease and the institution of a gluten-free diet (GFD), which seems to control the seizures if started soon after the onset of epilepsy and early in childhood. However, seizures may also start after a GFD, in which case they are more likely to be symptomatic, drug-resistant occipital epilepsy manifesting mainly with elementary visual hallucinations. A few cases may have a benign course, but most progress to other seizure types and an epileptic encephalopathy with delayed mental development, despite an initial relatively good response to treatment. The severity of the epileptic seizures is not proportional to the severity of the cerebral calcifications.

EEG abnormalities initially consist mainly of occipital paroxysms, occipital spikes or generalised discharges. Activation of occipital spikes by intermittent photic stimulation (IPS) is not uncommon.

Multispike discharges in the sleep EEG often betray their symptomatic character.

A history of gastrointestinal symptoms, nutritional problems, a positive family history of coeliac disease and an atypical Sturge–Weber syndrome without a cutaneous nevus should raise the possibility of this syndrome. Occipital seizures in Sturge–Weber syndrome are rare.

Eclampsia and occipital seizures

There is a selective vulnerability of the occipital lobes to eclamptic hypertensive encephalopathy. Neurological symptoms of eclampsia include seizures, headache, blindness and impairment of consciousness. Seizures may be GTCSs or focal visual seizures with secondarily GTCSs. Seizures persisting after recovery from eclampsia are rare.[276] Recent reports indicate that eclampsia may also be a risk factor for MTLE-HS.[283]

Lafora disease and occipital seizures

In Lafora disease (see Chapter 17), occipital seizures occur in 30–50% of patients, may be spontaneous or photically induced, and consist of complex and elementary visual hallucinations. Occipital involvement is indicated by occipital polyspikes and visual seizures, but these rarely occur without coexisting myoclonic seizures, GTCSs and EEG-generalised discharges that are also often induced by IPS. Background EEGs may be abnormal before onset of seizures, but may also be normal in the initial stages of the disease. Cognitive decline is relentless either before or soon after (i.e. within months of) the onset of seizures, and death is unavoidable within 1–10 years.

Lafora disease should be suspected when the onset of occipital seizures is combined or followed by myoclonus and progressive mental decline.

Pathophysiology

Elementary visual hallucinations are generated from the primary visual cortex, complex visual hallucinations from the occipitoparietotemporal junction areas, and visual illusions from the non-dominant parietal regions.[206]

Ictal blindness probably results from contralateral seizure spread to involve both occipital lobes or inhibition of the visual cortex by the seizure discharge.[284]

Because of the frequent occurrence of post-ictal headache in occipital epilepsy, it is reasonable to suggest that occipital seizures often generate migraine-like attacks and that the occipital lobes are preferentially associated with the trigeminovascular or brain-stem mechanisms responsible for migraine headache.[285] Post-ictal headache of occipital seizures may be related to serotoninergic mechanisms and respond to oral sumatriptan.[286]

I have emphasised on many occassions that an 'occipital seizure–migraine' sequence[241,255,257,287] appears to be much more evidence-based and more common than the previously prevailing view of 'migraine visual aura triggering epileptic seizures' or 'migraine–epilepsy syndromes' or 'migralepsy' (see Chapter 4).[288–290]

Diagnostic procedures

The discovery of the underlying cause in symptomatic occipital epilepsies may require haematological and biochemical screening for metabolic disorders, molecular DNA analysis, or even skin or other tissue biopsy.[206] High-resolution MRI is necessary in all patients with occipital lobe epilepsy.[206] Unsuspected residual or progressive lesions, tumours, vascular malformations and malformations of cortical development can all be detected by MRI. CT scanning is still a useful form of brain imaging (Figure 15.16), although it is far inferior to MRI and insensitive to focal cortical dysplasia. Calcifications of coeliac disease or of other causes may be missed with MRI. Functional brain imaging for localisation is of practical value in neurosurgical cases.[291]

Electroencephalography

EEG is essential, but certain limitations should be recognised.

CT brain scans documenting discrete occipital lesions of cysticercosis in two patients with typical occipital visual seizures misdiagnosed as migraine with aura

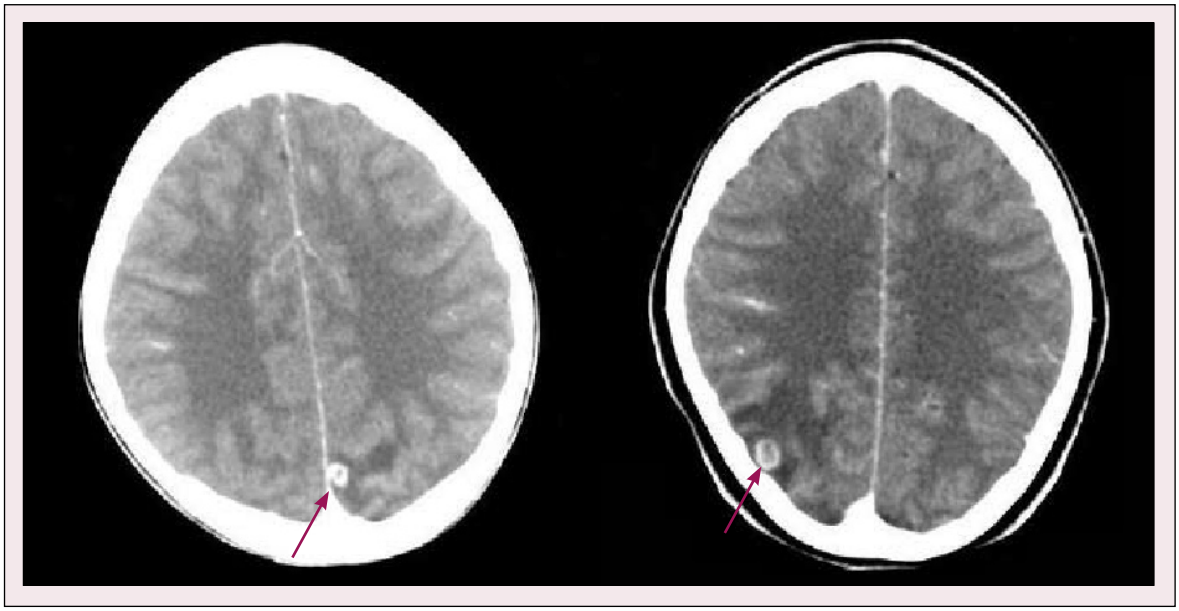

Figure 15.16 This figure serves as a reminder that cysticercosis is still a main cause of focal epilepsies in resource-poor countries and that visual seizures are often misdiagnosed as migraine.
Reproduced with permission from Menon (2007).[292]

Inter-ictal EEG

In symptomatic cases, the background EEG is usually abnormal with posterior lateralised slow waves. Unilateral occipital spikes or fast multispikes and, occasionally, occipital paroxysms occur. There may be occipital photosensitivity.[206] Worsening of the background EEG is significant in the diagnosis of progressive causes.

In idiopathic cases, such as idiopathic childhood occipital epilepsy of Gastaut and photosensitive occipital epilepsy, the background inter-ictal EEG is normal (see Chapter 12).[206] Occipital spikes and occipital paroxysms, spontaneous, evoked or both, are often abundant. They disappear with age frequently long after cessation of the occipital seizures.

Ictal EEG

Surface ictal EEG in occipital seizures, irrespective of cause, usually manifests with paroxysmal fast activity, fast spiking or both, localised in the occipital regions with occasional gradual anterior spreading and generalisation with irregular spike–wave discharges or monomorphic spike–wave activity (Figures 12.4 and 15.17). Brief occipital flattening may be seen before the fast rhythmic pattern. Often, in patients with symptomatic occipital lobe epilepsy, the ictal discharge is more widespread than of a precise occipital localisation. Usually, there is no post-ictal localised slow activity unless the seizure is prolonged or progresses to secondarily GTCS.

In a third of patients (30%), the ictal surface EEG does not show any appreciable changes in occipital seizures.[206]

Differential diagnosis

Occipital seizures should not be difficult to diagnose, but should first be differentiated from migraine,

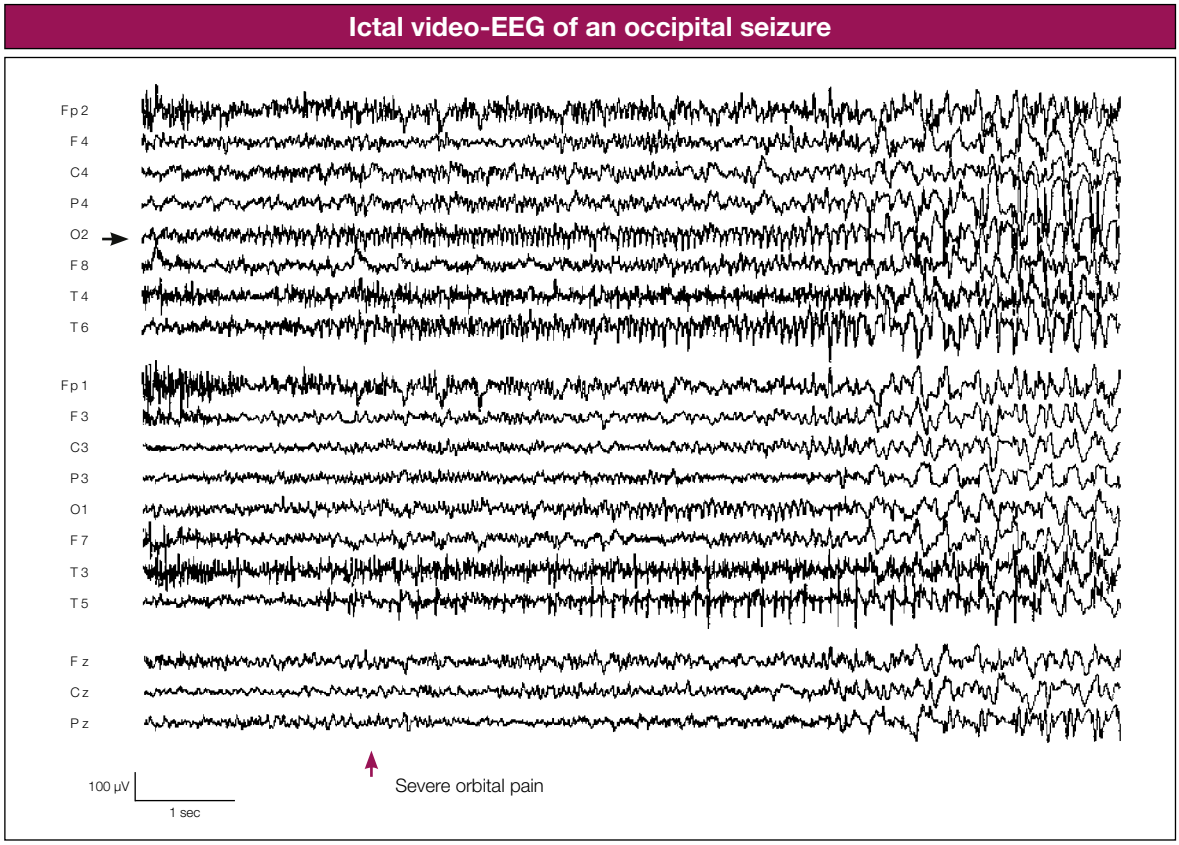

Figure 15.17 The electrical discharge of this seizure started with fast spikes in the right occipital electrode (black arrow) with rapid spread anteriorly and contralaterally. The patient complained of severe pain behind both eyes (red arrow) 2 s after the onset of the ictal discharge.

normal phenomena and psychogenic NEPEs or other causes unrelated to seizures.[206]

The differentiation of visual seizures from migraine, which is the main cause of diagnostic error, is detailed in Chapter 4; see also Figures 4.1, 12.8 and 15.15.

Differentiating ictal deviation of eyes of occipital versus extra-occipital origin

I am not aware of any study that has compared ictal deviation of the eyes, head or both of occipital origin with that of extra-occipital origin. The following conclusions are derived from my personal experience, supplemented by relevant reports in the literature.

In occipital epilepsy, the deviation of the eyes is usually pursuit-like or tonic, and rarely clonic and different to the oculoclonic ictal symptoms that are often seen in focal motor seizures of extra-occipital, mainly frontal origin. Occipital oculotonic seizures are similar to a voluntary, pursuit-like turning of the eyes to one side, which, by itself, could not be considered as an abnormal movement by witnesses. Such seizures usually follow visual symptoms and mainly elementary visual hallucinations, but may also occur from the start. At this stage, consciousness is often, but not invariably, impaired. This phase may progress to unilateral clonic seizures of the face

and the extremities, with or without progressing to GTCSs.

Conversely, ictal eye movements of extra-occipital origin are more violent and look unnatural. Ipsilateral eyelid tonic or clonic convulsions are commonly associated with upward deviation of the eyeballs. It is simultaneous, and precedes or follows tonic or clonic convulsions of other facial, neck and shoulder muscles of the same side (e.g. as in hemifacial rolandic seizures).

Differentiating idiopathic from symptomatic occipital epilepsy

The visual seizures of symptomatic and idiopathic occipital epilepsy are indistinguishable.[241] However, symptomatic visual seizures more frequently progress to other extra-occipital seizure manifestations such as temporal lobe symptoms, which are almost exclusively seen in symptomatic occipital epilepsy. A normal neurological state (including visual fields) and brain imaging may be misleading and suggest an idiopathic cause, unless high-resolution MRI with the new generation scanners are used.[206,239]

Prognosis

Frequency, severity and response to treatment vary considerably from good to intractable or progressive, depending mainly on the underlying cause and extent of the lesions.[206]

Management

AED treatment is similar to that for any other type of focal seizures (see page XXX), is usually effective and should be initiated as soon as possible.[206] Carbamazepine is the drug of choice.

The post-ictal headache of occipital seizures may respond to oral sumatriptan.[286]

Neurosurgery is performed for selective symptomatic cases and may be effective in around 70% of patients, with 30% becoming seizure free.[196,284,293–295]

AED therapy of focal epilepsies

The mainstream treatment of focal epilepsies is with AEDs, with which almost 80% of patients achieve reasonable sustained remission. Only 15–30%[296,297] of those with newly diagnosed focal epilepsy (of any cause) fail to achieve reasonable sustained remission with optimal AED medication. However, the figure is significantly higher (35%) for those with symptomatic focal epilepsy.[296] Of those failing to respond, 25–50% develop intractable disease; i.e. continuation of seizures beyond 2 or 3 years, despite optimal AED treatment. Secondarily GTCSs are more easily controlled than complex focal seizures.[298] For 25–50% with a symptomatic focal epilepsy in which AEDs have failed, neurosurgical options are often life saving.

Physicians now have to choose amongst 9 AEDs licensed for monotherapy (discussed below) and an additional 11 AEDs licensed for adjunctive treatment of focal epilepsies. The optional choice depends on a number of factors intrinsic to the specific AED and to the individual patient. This requires the prescribing physician to be extremely familiar with the pros and cons of each AED as well as the requirements of the particular treated patient with regard to epileptic seizures, syndrome, sex, age, possible comorbidities and genetic predispositions. Best treatment is achieved via a thorough knowledge of AED properties combined with expert assessment of the patient's health – a very difficult task for a physician.

As emphasised in Chapter 7, all efforts have been made in this book to provide the best existing evidence for AED treatment in clinical practice.

RCTs and evidence-based recommendations in focal epilepsies

"Unfortunately, a fully evidence-based approach to the treatment of epilepsy is hampered by the fact that the vast majority of randomised active-control trials in this area have significant methodological shortcomings... Therapeutic outcome in many epilepsy syndromes has never been evaluated in controlled trials.... Because of this, drug choice cannot be based solely on results of therapeutic trials, and a broader range of information must be taken into account."[299]

The problems with RCTs in epilepsies are detailed on pages 17–20 and reviewed in a recent editorial.[300] These are also well illustrated in the RCTs and meta-analyses comparing carbamezapine with the newer AEDs.

Carbamazepine is the superior older AED for focal epilepsies, and is used as the comparator drug in RCTs evaluating newer AEDs. However, carbamazepine has been handicapped in many (if not all) RCTs (and consequently, their resultant meta-analyses) by poor study designs and execution, including broad intention-to-treat populations or interpretations that give a maximal advantage to its competitors.[300–302]

Carbamazepine's best efficacy is for focal epileptic seizures and its best tolerability is with 'start low and go slow' titration schemes. Consequently, carbamazepine is undermined when its efficacy is compared with a broad-spectrum AED in mixed populations of patients with focal and generalised epileptic seizures. Likewise, it is at a disadvantage in studies using a rapid titration scheme (which results in high drop-outs with carbamazepine).[302]

These points are well exemplified by a recent meta-analysis of RCTs comparing patient responses to lamotrigine and carbamazepine monotherapy.[303] The primary outcome of the analysis was that 'lamotrigine is better tolerated than carbamazepine, but carbamazepine has a clinically important advantage in time to remission and time to first seizure.'[303] These results are questionable as masterly highlighted in the accompanying editorial by French:[302]

> To show convincingly that one drug is preferable to the other, one would have to be certain that each drug is being used to its maximum advantage. For example, if lamotrigine had been titrated too rapidly, an increase in the incidence of rash would be expected. In an early study of lamotrigine therapy for migraine, the drug was started at 200 mg per day with a 39% incidence of rash. Similarly, if carbamazepine was started at full dose, rather than titrated, the dropout rate due to adverse events would be extremely high.
>
> Second, all of the studies enrolled patients with generalized onset seizures, one as much as 50%. Carbamazepine can exacerbate some types of generalized onset epilepsy. In contrast, lamotrigine is broad-spectrum, and a more appropriate choice. Clearly, inclusion of generalized onset seizure patients limits the external validity of the trial results.
>
> All five trials included in the meta-analysis[303] were sponsored by the manufacturers of lamotrigine.[302]

The results of a contentious RCT comparing standard (carbamazepine) with newer (gabapentin, lamotrigine, oxcarbazepine and topiramate) AEDs (SANAD)[304] were similar to that of the meta-analysis.[303] This should be of little surprise because in SANAD, like in the RCTs of the meta-analysis, carbamazepine was at a disadvantage in comparison with lamotrigine with regard to efficacy (as mixed populations with focal and generalised seizures were included), tolerability (due to the mode of use) and interpretation of the results (which contained certain presumptions unsubstantiated by the data, subsequently invalidating evidence-based medicine reports), as detailed in three recent editorials.[300,301,305]

The SANAD results only reflect clinical practice in the UK and they should only be used to encourage a lower titration of carbamazepine and discourage its use in generalised epilepsies. Other conclusions and generalisations are inappropriate.

Furthermore, SANAD was already partly outdated by the time of its publication. Levetiracetam, now

licensed as monotherapy for focal seizures in patients aged 16 years or older, was not evaluated in either SANAD or the meta-analysis. A recent RCT compared levetiracetam with controlled-release carbamazepine in patients with newly diagnosed partial or primarily GTCS.[306] At per-protocol analysis, 73% (56.6%) of patients randomised to levetiracetam and 72.8% (58.5%) receiving controlled-release carbamazepine were seizure free at the last evaluated dose for 6 months or greater (mean of 1 year). Most patients achieved remission at the lowest dose level for either drug. Withdrawal rates for adverse events were 14.4% with levetiracetam and 19.2% with carbamazepine. However, in this RCT, like its other predecessors, carbamazepine was again at a disadvantage in comparison with levetiracetam because of the inclusion of patients with primarily GTCSs, which favours a broad-spectrum AED (i.e. levetiracetam) over a narrow-spectrum AED (i.e. carbamazepine).

Older AEDs

Carbamazepine has been rightly considered to be the gold standard for controlling focal seizures in more than 70% of patients (around 10% of the patients develop idiosyncratic reactions). It has a narrow spectrum of efficacy and should not be used in IGEs.

Valproate, a superior drug in generalised epilepsies, has inferior efficacy in focal epilepsies and significant ADRs, particularly in women of childbearing age. Considering its adverse reactions, inferior efficacy and the introduction of some safer and more effective AEDs, valproate has a very low priority and should only be used as an adjunctive AED in focal epilepsies. It is still the first choice in generalised epilepsies.

Despite its significant implications for patient management, this view has only recently been adopted in current recommendations and expert publications. That valproate was an AED suitable for generalised and not for focal epilepsies[122,302–309] was dramatically overshadowed in the early 1990s by influential RCTs[310,311] and meta-analyses[312,313] suggesting that valproate was of similar efficacy and tolerability to carbamazepine. Thus the physicians' choice, particularly in the UK, was influenced by the indiscriminate use of valproate based on the message that this AED treats focal as well as generalised epilepsies. This promoted suboptimal treatment of focal epilepsies with valproate and suboptimal treatment of generalised epilepsies with carbamazepine.

Phenytoin is as effective as carbamazepine but its use is falling dramatically, mainly because of chronic toxicity.

Phenobarbital and primidone, which are less efficacious, have been practically eliminated in developed countries, mainly because of their adverse effects on cognition.

Clobazam is a very useful AED, both as monotherapy and polytherapy, in focal epilepsies, although it is not licensed in the USA.[314–317] It is neglected in current clinical practice mainly because tolerance to clobazam has been overemphasised. Clobazam is also erroneously considered to be of similar efficacy with regard to seizure type as clonazepam (a main anti-myoclonic AED). Clobazam should be tried in all drug-resistant focal epilepsies at 10–30 mg at night. Probably only 10% will have clinically significant improvement but this may be very dramatic and sustainable.

Newer AEDs

Of the newer AEDs, only the following are now licensed for monotherapy of focal epilepsies:

- gabapentin
- levetiracetam
- lamotrigine
- oxcarbazepine
- topiramate.

All other AEDs – eslicarbazepine acetate, lacosamide, pregabalin, tiagabine, vigabatrin and zonisamide – are licensed for adjunctive treatment only.

Monotherapy of focal epilepsies

Monotherapy is the primary aim in the treatment of all epilepsies, including the focal epilepsies (see 'Starting AED treatment in newly diagnosed epilepsy' on page 12).

Before starting AED, the following should be thoroughly considered:

- Whether the patient has definite epileptic seizures (at least a fifth of patients treated for epilepsy do not suffer from epileptic seizures).
- Whether the patient has focal and not generalised epileptic seizures (a third of patients with IGEs are misdiagnosed with focal epilepsy).
- Whether the patient needs AED medication (most of the benign childhood focal epilepsies do not need treatment).
- What is the best AED choice? This crucial question has rarely been considered in recent guidelines, which usually provide a list of AEDs efficient in focal epilepsies without prioritising them.

The best choice among AED licensed for monotherapy in focal epilepsies

AEDs licensed for monotherapy of focal epilepsies have shown a variable degree of efficacy, tolerability, safety profiles, pharmacokinetics and drug–drug interactions, which should be taken into account when choosing one drug over another. Table 15.18 compares AEDs licensed for monotherapy in the focal epilepsies in accordance with the selection-prioritising factors detailed in Table 7.3. Desirable properties are in red and these should be preferred to others.

Strength of efficacy (Table 15.8): In RCTs, all newer AEDs were found to be of almost equal efficacy to carbamazepine, phenytoin and valproate.

Spectrum of efficacy (Table 7.1): This is significant only when the differentiation between focal and generalised epileptic seizures cannot be certain. In such cases, narrow-spectrum AEDs such as carbamazepine should be avoided because they are usually ineffective or aggravate other types of seizure such as absences or myoclonic jerks.

Other factors include safety, tolerability, adverse reactions (Table 7.2), need for as little titration as possible (Table 7.10), need for less laboratory monitoring (Table 7.11), pharmacokinetic and pharmacodynamic interactions with other AEDs (Tables 7.5 and 7.6),[337–340] as well as mechanisms of actions (Table 7.9).[340–342]

As noted in Table 15.18, levetiracetam is the only AED that fulfils all the desirable properties (with the exception of cost) for a near-ideal AED in focal epilepsies. Accordingly, it challenges the concept of carbamazepine as the gold standard of AED monotherapy in focal epilepsies. Levetiracetam does not need slow titration and therefore would have an immediate advantage in RCTs with carbamazepine or lamotrigine (both of which are AEDs that require slow titration) if these are introduced rapidly.

The main advantages of carbamazepine over levetiracetam are:

- it is cheaper
- it has been exhaustively tested in clinical practice for nearly 50 years in adults, children and women.

Conversely, the main advantages of levetiracetam over carbamazepine are:

- it has a broad spectrum, which is of practical significance, particularly for clinicians who may not have special expertise in the differentiation of focal from generalised epileptic seizures
- it does not cause clinically significant idiosyncratic reactions or other serious ADRs
- it has superior pharmacokinetics (96% out of a 100% of a perfect score)
- it does not need slow titration and the starting dose is often therapeutic
- it does not need laboratory tests (such as drug monitoring or blood screening for ADRs)
- it is easier to use if polytherapy is necessitated (lack of drug–drug interactions and a novel mechanism of action)
- it does not interact with hormonal contraception and is a pregnancy category C drug.

Rational polytherapy in focal epilepsies

Rational polytherapy is often needed for the treatment of intractable focal epilepsies. Table 15.19 compares the newer AEDs licensed for adjunctive treatment of focal epilepsies in accordance with the prioritising factors detailed on Table 7.3.

If treatment with carbamazepine or levetiracetam in maximal tolerated doses fails, other pragmatic options include any other AED from the list

Comparison of licensed AEDs for monotherapy in focal seizures with and without secondarily GTCSs*

	CBZ	LEV	LTG	GBP	OXC	PB	PHT	TPM	VPA
Efficacy in add-on RCTs[318]	High	High	Low	Low	Medium	Medium	High	High	Medium
Spectrum of efficacy*,[319]	Narrow	Broad	Broad	Narrow	Narrow	Broad	Narrow	Broad	Broad
Tolerability*,[318]	Medium	Excellent	Excellent	Excellent	Medium	Poor	Poor	Poor	Poor
Pharmacokinetics[320] (% of perfect score)†,[321,322]	Inferior (50)	Superior (96)	Moderate (73)	Superior (89)	Moderate (77)	Inferior (57)	Inferior (50)	Moderate (79)	Inferior (52)
Titration[323]	Slow	Fast	Very slow	Fast	Slow	Slow	Slow	Very slow	Slow
Need for laboratory tests (1 and 2)†,‡,[323–325]	Maximal (1 and 2)	Minimal	Maximal (1 and 2)	Minimal	Maximal (1 and 2)	Maximal (1 and 2)	Maximal (1 and 2)	Maximal (1 and 2)	Maximal (1)
Main mechanisms of action[319,326–328]	⊠Na^+	Novel SV2A ligand[67]	⊠Na^+	Modifying Ca^{2+} channels	⊠Na^+	Multiple	⊠Na^+	Multiple	Multiple
Significant drug–drug interactions[322,330–332]	Yes	Not clinically significant	Yes	Not clinically significant	Yes	Yes	Yes	Yes	Yes
Interactions with hormonal contraception[333,334]	Significant	No	Significant	No	Significant	Significant	Significant	Dose related	No
Pregnancy category	D	C	From C to D?[335]	C	C	D	D	C	D
Parenteral formulation	No	Yes	No	No	No	Yes	Yes	No	Yes

*Efficacy in monotherapy	In RCTs, all newer AEDs are of approximately the same efficacy; none showed better efficacy than carbamazepine. Valproate is slightly less efficacious than carbamazepine and phenytoin and may be inappropriate for women with focal seizures.

Table 15.18 Desirable properties are in red. CBZ, carbamazepine; GBP, gabapentin; GTCS, generalised tonic–clonic seizure; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; RCT, randomised controlled trial; TPM, topiramate; VPA, valproate. *For more information, see Chapter 7, Pharmacopeia and summary of product characteristics. †The % of perfect score is based on a customised rating system of 16 parameters to evaluate the pharmacokinetic profile of AEDs.[320,321] ‡(1) Monitoring for adverse drug reactions; (2) therapeutic drug monitoring.

provided in Table 15.19 according to a rational order of priority. Combining carbamazepine and levetiracetam should be the first preference according to the evidence provided in Tables 15.18 and 15.19. Other combinations should include the AEDs listed in Tables 15.18 and 15.19.

A review of long-term open-label studies showed that after 1 year of treatment, levetiracetam had the best retention rates (60–75%) in comparison to lamotrigine and topiramate (40–60%) and gabapentin (20–25%).[349]

Lacosamide has particularly attractive properties for combined AED treatment because of proven efficacy and a high rate of retention in difficult to treat patients, an excellent pharmacokinetic profile, minimal drug to drug interactions, good safety with less sedative effects than most other AEDs and a novel mechanism of action.[349,350] Its parenteral formulation is particularly useful when oral administration is compromised; there is 1:1 dose conversion when switching between oral/parenteral lacosamide formulations with no need for dose adaptations[351,352] (Table 15.19).

Clobazam often has high and sustained efficacy and should be considered prior to other AED options in polytherapy (see page XXX).

Conclusions in the use of newer AEDs in focal epilepsies

Taking all existing evidence and all the parameters listed in Table 7.3 together, levetiracetam is far superior to other newer AEDs, either as monotherapy in newly diagnosed focal epilepsies (Table 15.18) or as adjunctive AED treatment (Table 15.19). It is the only current AED that may challenge carbamazepine.

Levetiracetam is the first-line AED fulfilling the best possible requirements with regard to strength and spectrum of efficacy, safety, pharmacokinetic and pharmacodynamic properties, and ease of use for physicians and patients.

After levetiracetam, the other newer AEDs are as follows, and are listed in order of priority:

Lamotrigine is one of the best AEDs with regard to cognitive adverse effects, but has relatively low efficacy and frequent idiosyncratic reactions, which rarely may be fatal, are a realistic threat.[353] Important drug–drug interactions, including with hormonal contraception and in pregnancy, are a significant disadvantage. Recent evidence of probable teratogenicity and interaction with pregnancy contradict its previous promotion as a women-friendly AED.

The recent proposal by the authors of SANAD that in clinical practice 'lamotrigine and possibly oxcarbazepine, rather than carbamazepine' should be the first-choice AED for epileptic seizures[304] is highly contentious and may be detrimental to patient care.

Degrading carbamazepine to a third place after lamotrigine and oxcarbazepine would be as serious an error as the promotion of valproate in focal epilepsies (see page XX), which may have resulted in suboptimal treatment of these patients with the additional risks of teratogenicity of unborn babies exposed to the drug.

Oxcarbazepine is among the first-choice AEDs for monotherapy. However, oxcarbazepine does not have high priority in co-medication with carbamazepine and phenytoin, because of drug–drug interactions and added adverse reactions.

Lacosamide appears to fulfil most optimal properties of an AED in add-on treatment of difficult to treat patients (see facing column).

Topiramate, despite its significant efficacy, has the disadvantage of frequent and sometimes serious ADRs (cognitive effects, sometimes relentless weight loss, acute angle-closure glaucoma, nephrolithiasis and others, such as hypohidrosis). It is by far the least-tolerated AED (21.5% intolerability;[354] see considerations of ADRs, page XXX). Drug–drug interactions, including with hormonal contraception, are an additional disadvantage.

Zonisamide is one of the most popular drugs in Japan, but it is associated with significant drug–drug interactions and ADRs, some of which may be severe, such hypohidrosis, hyperthermia and Stevens–Johnson syndrome. Nephrolithiasis occurs in 4% of patients.

Eslicarbazepine acetate has been developed with the intention that it should be a better AED than

Comparison of newer AEDs as adjunctive treatment in difficult to treat focal epilepsies*

	GBP	LCM	LEV	LTG	OXC	PGB	TGB	TPM	ZNS
Efficacy[318]	Low	Medium	High	Low	Medium	Low	Medium	High	Medium
Tolerability[318]	Excellent	Excellent	Excellent	Excellent	Medium	Medium	Good	Poor	Good
Serious ADR[336]	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Pharmacokinetics (% of perfect score)†,[322,343,344]	Superior (89)	Superior (96)	Superior (96)	Moderate (73)	Moderate (77)	Superior (89)	Inferior (67)	Moderate (79)	Inferior (67)
Titration[323]	Fast	Slow	Fast	Very slow	Slow	Fast	Slow	Very slow	Slow
Need for laboratory testing[323,324,345]	Minimal	Minimal	Minimal	Maximal	Maximal	Minimal	Minimal	Maximal	Maximal
Mechanism of action[346–348,328]	Modifies Ca^{2+} channels	Novel‡	Novel SV2A[66]	⊠Na^{+}	⊠Na^{+}	Modifies Ca^{2+} channels	⊠GABA	Multiple	Multiple
Significant drug–drug interactions[323,330–332]	No	Minimal	Minimal	Yes§	Yes	No	Yes§	Yes	No
Interaction with hormonal contraception	No	No	No	Yes	Yes	No	No	Yes	Yes
Parenteral formulation	No	No	Yes	Yes	No	No	No	No	No

Table 15.19 Desirable properties are highlighted in red. GBP, gabapentin; LCM, lacosamide; LTG, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; PGB pregabalin; TGB, tiagabine; TPM, topiramate; ZNS, zonisamide. *For more information, see Chapter 7, Pharmacopoeia and summary of product characteristics. †The % of perfect score is based on a customised rating system of 16 parameters to evaluate the pharmacokinetic profile of AEDs. ‡Selectively enhances slow inactivation voltage-gated sodium channels, and may be binding to collapsin response mediator protein-2 (CRMP-2). §Their plasma levels are increased or decreased depending on the concurrent AED.

carbamazepine with fewer ADRs and drug–drug interactions. However, so far this appears to be an unfulfilled promise because of its many drug–drug interactions and treatment-emergent ADRs such as rash, hyponatraemia and ECG changes.

Gabapentin has very low efficacy in RCTs and the clinical experience of most epileptologists with gabapentin[318] is disappointing.

Pregabalin has failed to gain ground as an AED probably because of similarities with gabapentin, high incidence of weight gain and treatment-emergent myoclonic jerks.

Tiagabine use is probably limited to the treatment of severe forms of focal epilepsies that have failed to respond to other AED combinations. Treatment-emergent non-convulsive status epilepticus has been reported in a significant number of patients.

Vigabatrin use in epilepsies other than West syndrome is probably prohibited because of the high risk of visual field defects, which RCTs failed to identify[355,356] even after they were reported.[357] Patients on vigabatrin should undergo formal visual field perimetric examination at least every 6 months for the duration of treatment.[358]

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Reflex seizures and related epileptic syndromes

Epileptic seizures can arise in a 'spontaneous' unpredictable fashion with no detectable precipitating factors, or they can be provoked by certain recognisable stimuli.

Factors and stimuli that contribute towards the initiation of a seizure are provided by the individual's internal and external environment. Hormones, electrolytes, state of consciousness and body temperature are examples of internal factors that alter the epileptogenic threshold. External factors may be sensory, electrical or biochemical. A complex interaction between external and internal factors may explain why the effectiveness of a well-defined seizure-precipitating stimulus may vary and why a patient may experience both 'spontaneous' and 'reflex' seizures.

Reflex seizures have a 4–7% prevalence among patients with epilepsies. Their aetiology may be idiopathic, symptomatic or cryptogenic (probably symptomatic).

Clarifications on classification

Reflex or stimulus-sensitive, or triggered or sensory evoked, epileptic seizures are synonyms denoting epileptic seizures that are consistently elicited by a specific stimulus.[1–4] 'Reflex' is the preferred name in the new ILAE diagnostic scheme[5] and report[6] (Table 16.1).

The ILAE report classifies reflex epilepsies under an unspecified category of 'special epilepsy conditions'.[6] The list of special epilepsy conditions is:

- symptomatic focal epilepsies not otherwise specified
- epilepsy with generalised tonic–clonic seizures (GTCSs) only
- reflex epilepsies
- febrile seizures plus (FS+)
- familial focal epilepsy with variable foci.

Reflex epilepsies: Although idiopathic photosensitive occipital lobe epilepsy, primary reading epilepsy and hot water epilepsy in infants are syndromes, it is unclear whether other reflex epilepsies constitute unique syndromes.[6]

Definitions

Reflex seizures are:

> Objectively and consistently demonstrated to be evoked by a specific afferent stimulus or by activity of the patient. Afferent stimuli can be: elementary, i.e. unstructured (light flashes, startle, a monotone) or elaborate i.e. structured. Activity may be *elementary*, e.g. motor (a movement); or *elaborate*, e.g. cognitive function (reading, chess playing), or both (reading aloud).[7]

Reflex epilepsy syndrome is:

> A syndrome in which *all* epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that are also associated with spontaneous seizures are listed as seizure types. Isolated reflex seizures can also occur in situations that do not necessarily require a diagnosis of epilepsy. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not reflex seizures.[5]

Reflex epilepsies are determined by the specific precipitating stimulus and the clinico-EEG response.[1,2,8]

Precipitating stimuli and reflex seizures and syndromes listed in the ILAE classification scheme[5,6]

Precipitating stimuli for reflex seizures
Visual stimuli • Flickering light – colour to be specified when possible • Patterns • Other visual stimuli
Thinking
Music
Eating
Praxis
Somatosensory
Proprioceptive
Reading
Hot water
Startle
Reflex seizures
Reflex seizures in generalised epilepsy syndromes
Reflex seizures in focal epilepsy syndromes
Reflex epilepsies*
Idiopathic photosensitive occipital lobe epilepsy (2)
Other visual-sensitive epilepsies
Primary reading epilepsy (3)
Startle epilepsy†
Hot water epilepsy in infants (2)‡
Conditions with epileptic seizures that do not require a diagnosis of epilepsy
Reflex seizures

Table 16.1 *Numbers in parenthesis indicate rating of confidence regarding the certainty with which the ILAE Core Group believed each syndrome represented a unique diagnostic entity (3 being the most clearly and reproducibly defined). †The new ILAE report[6] rightly no longer considers startle epilepsy to be an epilepsy syndrome. ‡Hot water epilepsy in infants has been newly considered an epileptic syndrome by the ILAE.[6]
Modified with permission from Engel (2001)[5] and (2006).[6]

The precipitating stimulus

The stimulus evoking an epileptic seizure is specific for a given patient and may be extrinsic, intrinsic or both.

Extrinsic stimuli are:

- simple, such as flashes of light, elimination of visual fixation and tactile stimuli
- complex, such as reading or music.

The latency from the stimulus onset to the clinical or EEG response is typically short (1–3 s) with simple stimuli or long (usually many minutes) with complex stimuli.

Intrinsic stimuli are:

- elementary, such as movements

- elaborate, such as those involving higher brain function, emotions and cognition (thinking, calculating, music or decision-making).

Author's note

In the definition of reflex epilepsy syndromes, 'all seizures are precipitated by sensory stimuli' may be too restrictive. Most patients also suffer from spontaneous seizures. Should 'all' be replaced by 'all or nearly all'?

The term 'precipitating stimulus' should be differentiated from 'facilitating stimulus'. In certain patients with idiopathic generalised epilepsy (IGE), for example, EEG discharges or seizures may increase during intermittent photic stimulation (IPS; facilitating stimulus) but these are not consistently evoked by IPS (as would be expected with precipitating stimuli).

The response to the stimulus

The response to the stimulus consists of clinical and EEG manifestations, alone or in combination. EEG activation may be electrographic (subclinical) only, i.e. without overt clinical manifestations. Conversely, ictal clinical manifestations may be triggered without conspicuous surface EEG changes.

Clinical types of reflex seizure

Reflex seizures may be:

- generalised, such as absences, myoclonic jerks or GTCSs
- focal, such as visual, motor or sensory.

Reflex generalised seizures occur either independently or within the broad framework of certain epileptic syndromes. The same patient, in response to the same specific stimulus, may have absences, myoclonic jerks and GTCSs alone, or in various combinations. Usually, absences and myoclonic jerks precede the occurrence of GTCSs. Patients may have reflex and spontaneous seizures.

Myoclonic jerks are by far the most common, and manifest in the limbs and trunk or regionally, such as in the eyelids (eyelid myoclonia with absences).

GTCSs may occur from the start, constituting the first clinical response, or more commonly they follow a cluster of absences or myoclonic jerks. Secondarily GTCSs from focal, simple or complex seizures are much less common than primarily GTCSs.

Absence seizures are common, constituting the response to a variety of specific stimuli, such as photic, pattern, fixation-off, proprioceptive, cognitive, emotional or linguistic stimuli.[9] It is recognised that absences are also common in self-induction.

Focal seizures are exclusively seen in certain types of reflex focal or lobular epilepsy, such as visual seizures of photosensitive occipital lobe epilepsy or complex focal temporal lobe seizures of musicogenic epilepsy.

Reflex-electroclinical events and the role of the EEG

The electroclinical events may be strictly limited to the stimulus-related receptive brain region only (such as photically induced EEG occipital spikes), spread to other cortical areas (such as in photosensitive focal seizures that propagate in extra-occipital areas) or become generalised (e.g. in the photoparoxysmal responses [PPRs] of an IGE). Furthermore, the electroclinical response to a specific stimulus may correspond to activation of regions other than those of the relevant receptive area, such as in primary reading epilepsy, which manifests with jaw myoclonic jerks. Conversely, reading may elicit electroclinical events strictly confined to the brain regions subserving reading, such as alexia, associated with focal ictal EEG paroxysms. There is great variability in the interindividual responses to the same stimulus.

The role of the EEG is fundamental in establishing the precipitating stimulus in reflex epilepsies, because it allows subclinical EEG reflex abnormalities, or minor clinical ictal events, to be reproduced on demand by application of the appropriate stimulus without risk to the patient. However, there are cases in which the stimulus–seizure relationship is difficult to document, as in video game-induced seizures (see page 503). Only 70% of these patients have EEG confirmation of photosensitivity with PPRs to IPS, and in the other 30% seizures may be due to a single or a variety of other precipitating or facilitating stimuli. Sleep deprivation, mental concentration,

fatigue, excitement, borderline threshold to photosensitivity, fixation-off sensitivity (FOS), proprioceptive stimuli (praxis), or more complex visual or auditory stimuli, alone or in combination, are all possibilities that are difficult to document objectively with an EEG.[10–12] There are also epileptic syndromes in which EEG 'epileptogenic activity' is consistently elicited by a specific stimulus with no apparent clinical relevance. This is exemplified by certain cases of benign focal childhood seizures in which somatosensory (tapping) or visual (elimination of fixation and central vision) stimuli consistently elicit spike activity, although these children appear to have 'unprovoked' seizures that mainly occur during sleep (see Chapter 12).[12]

Table 16.2 provides an analytical list of reflex seizures, related reflex epileptic syndromes and their precipitating stimuli. Some of these, such as photosensitivity, are well known and common, but others are extremely rare in humans, although they may be common in animals, such as audiogenic seizures.

In this chapter, common and principal forms of simple and complex reflex seizures and epilepsies are reviewed with particular emphasis on the syndromes listed in the new ILAE diagnostic scheme.[5] Classic references or reviews are cited for the remainder.

Visually induced seizures and epilepsies[1,2,8,13–16]

Seizures triggered by visual stimuli are the most common type of reflex seizure. Visual seizures are triggered by the physical characteristics of the visual stimuli and not by their cognitive effects. Photosensitivity and pattern sensitivity are the two main categories (with frequent overlap) of simple reflex epilepsies, with a short (typically within seconds) time period between stimulus and response. Photosensitivity and pattern sensitivity are genetically determined.

Video-EEG samples of many patients with photically induced seizures or other reflex epileptic seizures can be seen in the CD companion of references 57–60.

Photosensitivity, epileptic seizures and epileptic syndromes

Photosensitivity, an abnormal reflex EEG paroxysmal activation by photic stimulation (PPR), is a genetically determined trait. Reflex photic EEG activation may be asymptomatic throughout life or manifest with clinical epileptic seizures. 'Photosensitive epilepsy' is a broad term comprising numerous heterogeneous disorders in which seizures are triggered by light. It is not an epilepsy syndrome. Some recognised epileptic syndromes show a high incidence of clinically manifested epileptic seizures and, more frequently, PPRs without clinical seizures.

Clarifications on classification

Photosensitivity epilepsy was classified among the generalised epilepsies by the ILAE Commission.[4] This is for the following reasons:

- PPRs were considered to be primarily generalised,[1,13,61,62] although the initial occipital onset of the discharge was well reported[63,64] and recently appreciated.[3,13,65] The evidence is that photosensitivity in humans is mainly generated in

Reflex seizures, related reflex syndromes and the precipitating stimuli

I. Simple somatosensory stimuli

1. Exteroceptive somatosensory stimuli
   a. Tapping epilepsy and benign childhood epilepsy with somatosensory evoked spikes[17–20]
   b. Sensory (tactile) evoked idiopathic myoclonic seizures in infancy[21]
   c. Toothbrushing epilepsy[22,23]
2. Complex exteroceptive somatosensory stimuli
   a. Hot water epilepsy[24]
3. Simple proprioceptive somatosensory stimuli
   a. Seizures induced by movements[25]
   b. Seizures induced by eye closure and/or eye movements[26]
   c. Paroxysmal kinesigenic choreoathetosis (see page 96)[27]
   d. Seizures induced by micturition[28,29]
4. Complex proprioceptive stimuli
   a. Eating epilepsy[30,31]

II. Visual stimuli

1. Simple visual stimuli
   a. Photosensitive epilepsies (including self-induced photosensitive epilepsy)[13,16,32]
   b. Pattern-sensitive epilepsies[13,33,34] (including self-induced pattern-sensitive epilepsy)[35]
   c. Fixation-off sensitive epilepsies[36]
   d. Scotogenic epilepsy[36]
2. Complex visual stimuli and language processing (language-induced seizures)
   a. Reading epilepsy[37–41]
   b. Graphogenic epilepsy[42,43]

III. Auditory, vestibular, olfactory and gustatory stimuli[25,44]

   a. Seizures induced by pure sounds or words[25]
   b. Audiogenic seizures[45]
   c. Musicogenic epilepsy (and singing epilepsy)[46,47]
   d. Telephone-induced seizures[48]
   e. Olfactorhinencephalic epilepsy[1]
   f. Eating epilepsy triggered by tastes[31]
   g. Seizures triggered by vestibular and auditory stimuli[25]

IV. Seizures induced by high-level processes (cognitive, emotional, decision-making tasks and other complex stimuli)[44,49]

   a. Thinking (noogenic) epilepsy[49–51]
   b. Praxis-induced seizures[49,52]
   c. Emotional epilepsies[53–55]
   d. Startle epilepsy[56]

Table 16.2 For further details, see the literature.[1–3]
Modified with permission from Panayiotopoulos (1996).[8]

the occipital lobes and therefore it is a regional (occipital lobar) epilepsy.
- A quarter of patients with spontaneous seizures and EEG photosensitivity belong to a variety of epileptic syndromes of IGE, such as juvenile myoclonic epilepsy (JME).[8,66] A high prevalence of photosensitivity is also found in certain forms of symptomatic generalised epilepsies, such as Dravet syndrome (70%), and Unverricht disease.

Occipital photosensitivity only recently came into prominence, although it has been well known from the time of Gowers (1881).[67] This was overshadowed by the prevailing view that photosensitive epilepsies are mainly generalised. Indeed, with the application of IPS as a provocation method in EEG, it was discovered that most photosensitivity patients had generalised discharges and suffered mainly from IGEs.[68,69] That occipital spikes often preceded generalised discharges[63,64,70] was ignored. Reports of photically induced occipital seizures with or without secondary generalisation were scarce. The traditional view that occipital seizures precipitated by photic stimuli (OPSs) are rare contrasts with recent findings.[71–73] In one report alone,[74] 45 of 95 patients had occipital seizures precipitated by visual stimuli. There are two recommended, extensive reviews on OPSs.[12,75]

Demographic data[13,76,77]

The onset of photic reflex seizures can occur at any age, but they mainly start at 7–19 years with a peak at 12 or 13 years. Two-thirds are women.[13,76] PPRs occur in 1/4000 of the population and 5% of patients with epileptic seizures.[78,79] The overall annual incidence of cases with a newly presenting seizure and unequivocal photosensitivity in the UK is 1.1/100,000 (2% of all new cases with epileptic seizures). When restricted to the age range of 7–19 years, the annual incidence rises to 5.7/100,000 (10% of all new cases with epileptic seizures in this age group).[78,79] In healthy males aged between 17 and 25 years, EEG photosensitivity is very low (0.35%).[78–80]

Clinical manifestations

These vary considerably depending on syndrome and severity of photosensitivity. Of seizure patients with PPRs:
- 42% have only photically induced reflex seizures without spontaneous seizures (*pure photosensitive epilepsy*)
- 40% have spontaneous and reflex photosensitive seizures
- the remaining 18% have spontaneous seizures only.

Some recognised syndromes of IGE, such as JME, show a high incidence of clinical, but, more often, EEG photosensitivity.

Generalised seizures are much more common than occipital ones; any other focal seizures from other brain regions are exceptional at the start.

Generalised seizures

Myoclonic jerks, absences and GTCSs can occur, in this order by prevalence, in photosensitive patients. Some patients may have only one type, but most have any combination, particularly myoclonic jerks and GTCSs. That myoclonic jerks are by far the most common may appear contradictory to the ordinarily stated view that GTCSs prevail.[13] Thus, GTCSs are reported far more frequently (55–84%) than absences (6–20%), focal seizures (2.5%) and myoclonic jerks (2–8%). This prevalence is based on clinical historical evidence, which is likely to over-exaggerate GTCSs in relation to minor seizure events, even though they predominate. In 75% of patients with photosensitivity, PPRs are associated with ictal impairment of consciousness or motor symptoms (opening of the eyes, eyelid or other myoclonic jerks), although these are not reported by a third of patients.[81,82] In my personal experience with video-EEG, PPRs are commonly associated with eyelid manifestations (a blink, fluttering, flickering, myoclonia) and less often with jerks of the head, eyes, body or limbs. Absences followed in prevalence and only one patient had an accidental GTCS. Patients are often unaware of minor seizures, although some of these may be sufficiently obvious and marked. These

facts have been illustrated on many occasions in this book (see, for example, Figures 1.3 and 13.8).

Focal seizures

Photically induced occipital seizures are much more frequent than was originally appreciated before the use of IPS in EEG testing. These may occur alone or progress to symptoms from other brain locations and GTCSs. See also 'Idiopathic photosensitive occipital lobe epilepsy' (page 509).

Extra-occipital focal seizures from the onset are exceptional.[83]

Useful note

Subjective symptoms during PPRs

These are of doubtful significance; some are ictal phenomena but most are not.[14] Many people cannot tolerate the light at all, but this is not evidence of epileptic photosensitivity.

Precipitating factors

By definition all patients are sensitive to flickering lights. Many artificial or natural light sources can provoke epileptic seizures. Video games, television, visual display units of computers, stroboscopic lights in discotheques and natural flickering light are common triggers, in that order of prevalence.

Video game-induced seizures can occur not only with games using an interlaced video monitor (television) but also with small hand-held liquid crystal displays and non-interlaced 70 Hz arcade games.[10,84] Most patients (87%) are aged 7–19 years. There is a preponderance of boys, probably because more boys play video games than girls. Two-thirds of patients are photosensitive; for the other third there are other triggers such as sleep deprivation, fatigue, decision-making, excitement or frustration, and praxis, which may all operate alone or in combination.[11] A third of video game-induced seizures are occipital seizures and these occur in patients with or without photosensitivity.

Television epilepsy denotes seizures triggered by television and it is not a syndrome. Television-induced seizures mainly affect children aged 10–12 years. There is a twofold preponderance of girls. Seizures are more likely to occur when the patient is watching a faulty (i.e. flickering) television set, or is sitting very near to the television screen. Myoclonic jerks often precede the GTCSs and the history taken reveals that these may have occurred in the past without GTCSs.

> First she jerked a few times, head and hands, and then she had the convulsions. I thought she was electrocuted by an electric fault of the television.

A substantial number of these patients also have spontaneous attacks. In *pure television epilepsy*, one or a few overt television-induced seizures occur without evidence of any other type of spontaneous seizure or seizures induced by other means.

Ten per cent of patients are 'drawn like a magnet' to the screen and when they have reached a certain nearness they have a GTCS.[13] This is called 'compulsive attraction'.

> He was watching television and then suddenly, off he goes towards the set, eyes fixed in the picture, and he had the fit a few inches away from the screen.

> I do not know what happened. My eyes suddenly fixed to the picture, I could not move them away and then I passed out.

Self-induced photic reflex seizures[32,85–87]

Self-induction is a mode of seizure precipitation employed by mentally handicapped or normal photosensitive individuals. Its prevalence is debatable. Techniques include waving the outspread fingers in front of a bright light, viewing geometric patterns or slow eye closure. Absences and myoclonic jerks are the most common seizures in self-induction. Whether eyelid blinking or compulsive attraction to television or bright sun is mainly an attempt for self-induction or part of the seizure is disputed, although both may be true. In my opinion, in the majority of such cases these events are reflex seizure onsets.[85]

Aetiology

Photosensitivity is genetically determined. In particular, the genetic basis for PPRs has been

well documented. Monozygotic twin studies have shown an almost 100% concordance. Family studies indicate a sibling risk between 20% and 50%, the latter when siblings are studied between 5 and 15 years of age with one of the parents also being affected. These indicate autosomal dominant inheritance with age-related reduced penetrance in PPR-positive patients who have seizures and in non-seizure individuals. However, PPRs also occur in a number of autosomal recessive diseases.[88] In one study of 32 clinically photosensitive mothers with 67 children, 13 children (20%) had PPRs and four also had clinical photosensitive seizures. Nine other EEG-examined children did not have PPRs.[89]

In recent studies of photosensitivity, linkage was found with chromosomes 7q32 and 16p13[90,91] or 6p21.2 and 13q31.3.[92] The gene encoding NEDD4-2, a ubiquitin protein ligase, has recently been implicated in some families with photosensitive generalised epilepsy.[93]

The role of exogenous factors is indicated by the example of two monozygotic twins with PPRs. Only one developed clinical photosensitive epilepsy after a period of weekly exposures to high-intensity light flashes.[94]

A European consortium on the genetic analysis of photosensitivity and visual-sensitive epilepsies is in progress.

Diagnostic procedures

Properly applied IPS during EEG is the most important test.

IPS techniques vary significantly between publications and departments. I follow the recommendations made by Jeavons.[13] To be provocative, the IPS has to imply all potent physical characteristics of the stimulus (intensity, frequency, contrast) and combine flash with patterns, and central vision is mandatory (the patient should look at the centre of the stroboscope). IPS on eye closure should be tested.[13,95,96] Monocular stimulation is usually ineffective. Adding a quadrille pattern of small squares (2×2 mm) of fine black lines (0.33 mm) in the front of the stroboscope increases the possibility of obtaining PPRs.[97]

Warning

Prolonged photic stimulation that may expose the patient to a major convulsive seizure should be totally discouraged. There is nothing to learn or benefit from this practice. There are plenty of examples of individuals having an IPS-induced GTCS during an EEG that was performed for reasons other than epilepsy. To continue a train of photic stimulation after the appearance of EEG ictal discharges or ictal clinical manifestations is unacceptable.

The practical objective of IPS is to determine the following:

- whether seizures (of any type) are aetiologically linked with environmental photic stimuli (television, video games and others); if PPRs occur, this confirms photosensitivity
- whether PPRs are associated with ictal events; this requires video-EEG recording, otherwise minor events such as eyelid or limb jerks are likely to escape.

Useful note

The duration of PPRs and their relationship to the IPS train

Emphasis is often given to whether PPRs outlast the stimulus train or whether they are self-limited, i.e. they stop before or with the end of the IPS.[95,96] The rationale is that PPRs that outlast the stimulus train may strengthen their association with epilepsy. This may be artificial because the duration of the discharge, as a rule, depends on the duration and strength of the IPS and the time that this is stopped after the onset of PPRs.

PPRs are broadly categorised as:[13,98]

- *Generalised spike/polyspike–waves:* They are of higher amplitude in the anterior regions, but onset – particularly if patterned IPS is employed – is often with occipital spikes. They are highly associated (90%) with clinical photosensitivity, particularly if they outlast the stimulus train (Figure 16.1). Generalised PPRs often (60%) associate with clinical events such as jerks,

impairment of cognition or subjective sensations, but their detection may require video-EEG.[98]

- *Posterior (temporoparieto-occipital with occipital emphasis) spike/polyspike–waves:* This is the mildest form of PPRs and does not spread to the anterior regions. It consists of occipital spikes, polyspikes or slow waves mixed with small, larval spikes (Figures 16.1 and 16.2). Occipital spikes are often time-locked to the flash with a latency of approximately 100 ms, coinciding with the positive P_{100} of the visual evoked response (Figure 16.2).[63] Half the patients with posterior PPRs have epileptic seizures (spontaneous, photically elicited or both).[13]

Ictal clinical manifestations during PPRs may be one of the most important factors with regard to risk of seizures, but this has not been studied and emphasised in expert consensus.[95,96]

Clarification

The effectiveness of eyes open, eyes closed and eye closure during IPS

The state of the eyes during IPS is probably the most significant internal factor that modifies the response to IPS (Figures 16.1 and 16.3).[100] Eye closure (closing of the eyes while IPS continues) is by far the most potent.[13,100] Of the other two states, eyes open is more susceptible than eyes closed to patterned flickering lights. Conversely, eyes closed appears to be more susceptible than eyes open to direct unpatterned light, probably because of a diffusion effect of light by the eyelids. When light with a diffuser is applied, eyes open is again more effective than eyes closed because of an intensity loss by the closed eyelids.

The resting EEG of patients with idiopathic photic reflex seizures is usually normal or frequently (20–30%) shows eye closure-related paroxysms occurring within 1–3 s after closing of the eyes. These are usually brief EEG paroxysms lasting for 1–4 s and have similar features to those elicited by IPS for each individual patient. They disappear if eye closure occurs in total darkness.

Clinical note

Differentiation between eye-closure and eyes-closed state (Figure 16.3)

Eye closure is the transient state that immediately follows the closing of the eyes, lasts less than 3 s and does not persist in the remaining period of eyes closed. Eye closure is much more potent than 'eyes open' or 'eyes closed' in inducing abnormalities during IPS. Jeavons syndrome is a typical example of eye closure-related seizures and EEG abnormalities. In some photosensitive patients, PPRs occur only after eye closure.

Eyes closed is the state that lasts as long as the eyes remain closed. FOS is a typical example of eyes closed-related seizures and EEG abnormalities.

Prognosis

Prognosis is usually good but varies significantly in accordance with the type of photosensitivity. It may be excellent with only one clinical epileptic seizure or be severe with continuing life-long seizures.[89] Photosensitivity generally declines after the age of 30–40 years.[103]

Management[13]

Avoidance or prevention of the provocative stimulus may be the only treatment

In pure photosensitive seizures, avoidance of the provocative stimulus may be adequate, e.g. patients with television-induced seizures should be advised to view television in a well-lit room, maintain a maximum comfortable viewing distance (typically >2.5 m for a 19-inch screen), use the remote control and – if it is necessary to approach the screen – cover one eye with the palm and avoid prolonged watching, particularly if sleep deprived or tired. Occlusion of one eye is also advised when photosensitive individuals are suddenly exposed to flickering lights such as in discotheques.

Examples of photoparoxysmal responses

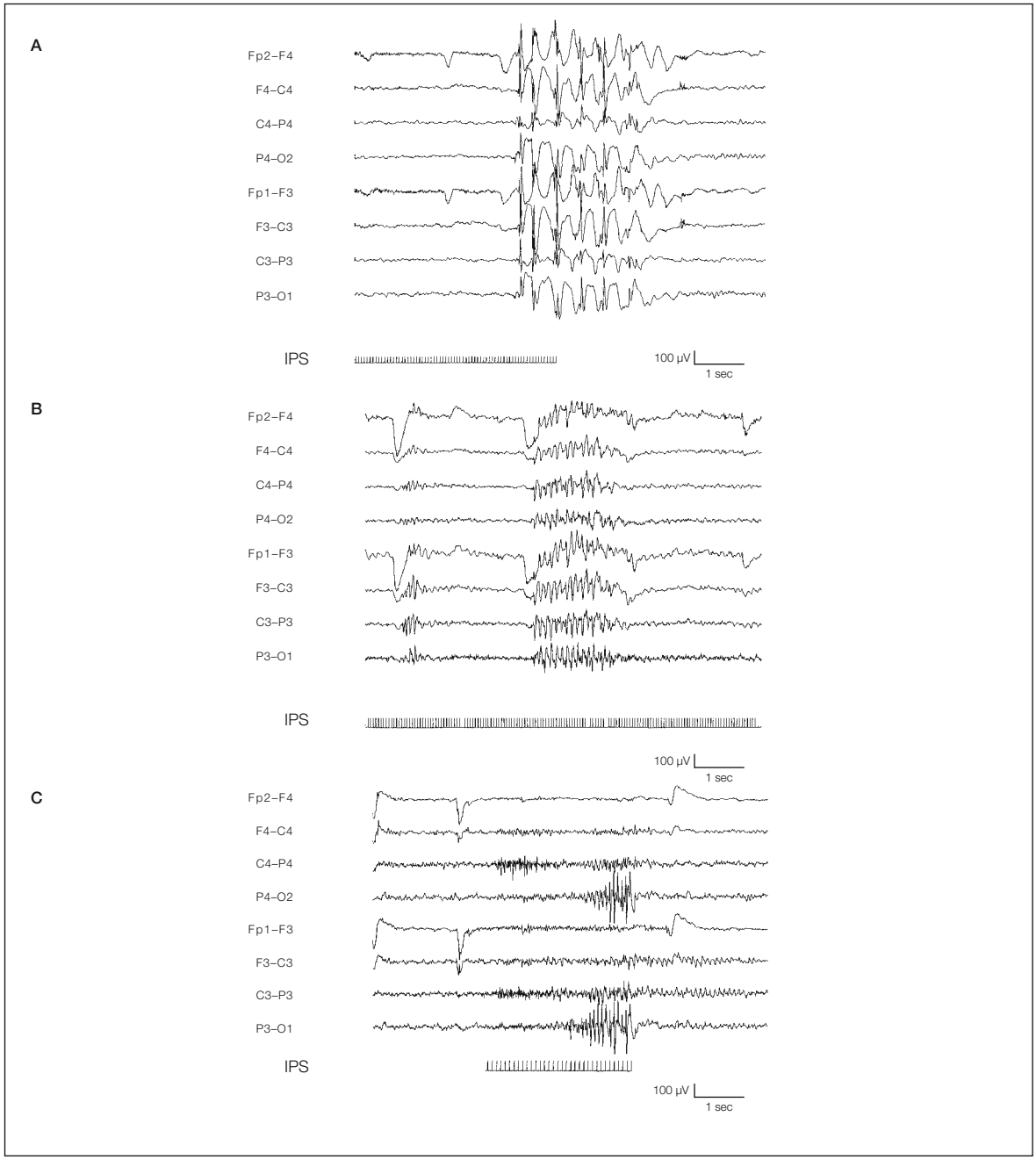

Figure 16.1 (**A**) Generalised 3–4 Hz spike/polyspike–waves associated with an absence. The discharge outlasts the duration of the stimulus. (**B**) Generalised polyspike discharge in a patient with symptomatic spontaneous and photically induced seizures, mainly GTCSs, which are resistant to appropriate anti-epileptic medication. This type of discharge is usually associated with myoclonic jerks, which did not feature in this case. Note that the discharge occurs only after eye blinks or eye closure, and does not outlast the stimulus train. (**C**) Typical occipital spikes time-locked to each flash of IPS. The patient is a woman with idiopathic occipital epilepsy (probably a variant of idiopathic childhood occipital epilepsy of Gastaut), who never had attacks precipitated by lights (case report in Agathonikou, *et al*[99]).

Occipital spikes and their relation to the P_{100} component of the visual-evoked response (VER) in photosensitive patients with generalised PPR

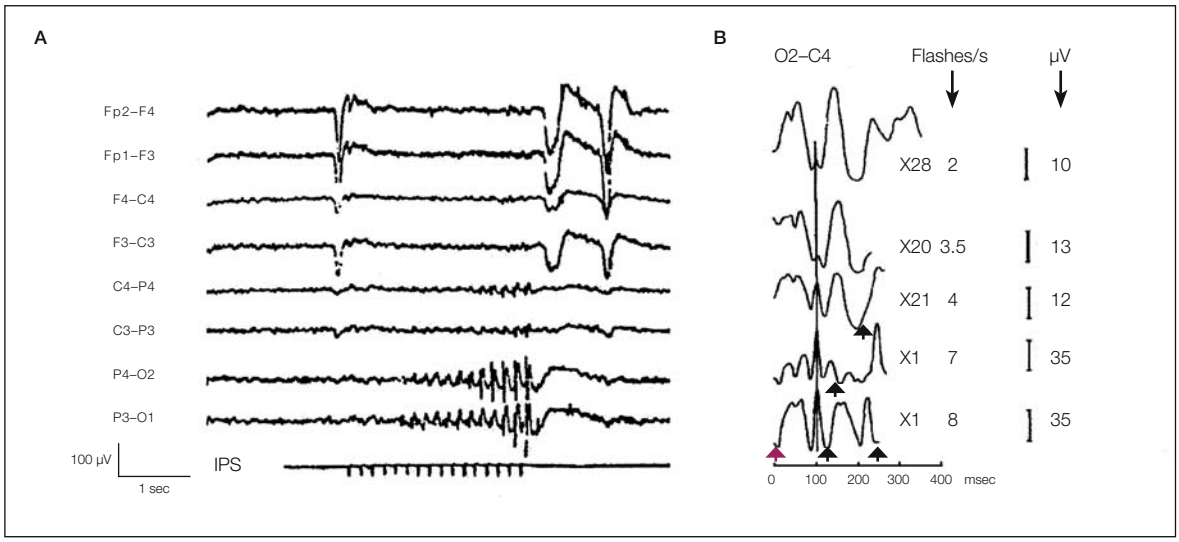

Figure 16.2 (**A**) Patterned IPS (2×2 mm graticule superimposed on the glass of the stroboscope) evoked occipital spikes, which are time-locked to flash at 6 flashes/s of a patient with spontaneous and photically elicited GTCSs. Higher flash frequencies of 9–30 Hz elicited generalised PPRs of spike–wave, briefly preceded by occipital spikes.[64] (**B**) Emergence of occipital spikes from the P_{100} VER component with increasing flash rate. The patient had spontaneous and television-induced GTCS. On the EEG, time-locked occipital spikes were apparent only at 5 flashes/s, while higher flash rates of 6–26 Hz elicited generalised discharges of spike–wave briefly preceded by occipital spikes. The three upper traces show the average VERs to 2, 3.5 and 4 flashes/s. The occipital spikes evoked at 7 and 8 flashes/s (black arrows) are shown in the two lower traces. The vertical line crosses the negative component of the occipital spikes and the Vb component of the P_{100} component of the VER. The horizontal line indicates time in ms. The red arrow indicates the onset of flash.
Modified with permission from Panayiotopoulos, et al *(1970).*[70]

Patients with video game-induced seizures should attempt to go without video games, or the time of playing should be significantly restricted and confined to periods when patients are not sleep deprived.

Conditioning treatment or wearing appropriately tinted glasses[104] has been recommended. A new commercially available blue lens, named Z1, was found to be highly effective in controlling PPRs in photosensitive epilepsy patients.[105]

AED treatment

AED prophylactic treatment is needed for patients with continuing photically induced seizures and for those who also have spontaneous epileptic seizures. The choice of an AED depends on their specific efficacy on photosensitivity, the type/types of reflex and spontaneous seizures, and the particular epileptic syndrome.

Valproate, levetiracetam, lamotrigine and clonazepam suppress photosensitivity in that order of efficacy.[106]

Valproate is effective for all types of photically or spontaneously induced seizure.

Levetiracetam is effective for all types of photically or spontaneously induced seizures. It is very much more efficacious in myoclonic and GTCS than absence seizures.

Lamotrigine is effective for all but myoclonic types of photically or spontaneously induced seizure. Its efficacy in PPRs has been studied mainly with valproate[107] and may be due to their pharmacodynamic interaction (see page 181). Lamotrigine may be particularly useful in absence seizures when valproate is ineffective or undesirable.

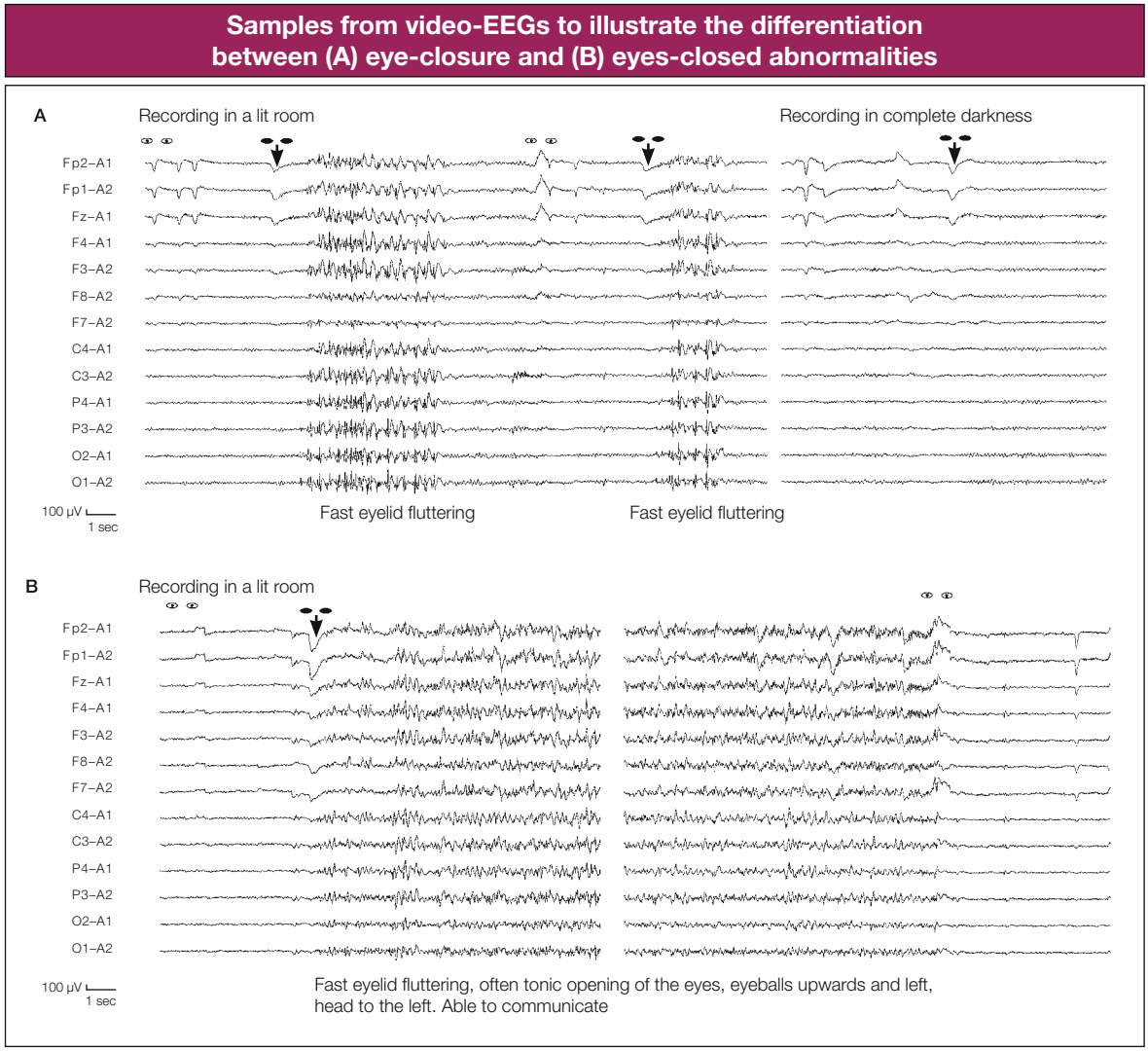

Figure 16.3 (**A**) Eye-closure-related abnormalities in a patient with Jeavons syndrome.[101] High-amplitude, generalised discharges occur within 1–3 s of closing the eyes in a lit room. These are of brief duration, do not continue in the resting period that the eyes are closed and are totally inhibited in complete darkness. (**B**) Eyes closed-related abnormalities in a woman who probably has cryptogenic epilepsy with seizures related to FOS.[36,102] The EEG paroxysms last as long as the eyes are closed. They are abruptly inhibited when the eyes are opened. The response to fixation-off and fixation-on were similar, irrespective of the means by which they were elicited (eyes closed, darkness, +10 spherical lenses, Ganzfeld stimulation). The best practical means for testing FOS is with underwater goggles covered with opaque tape.

Clonazepam is effective in photically or spontaneously induced myoclonic seizures (but is ineffective against and may exaggerate GTCSs).

Brivaracetam (UCB-34714) is a new AED that has been granted orphan medicinal designation in Europe for the treatment of progressive myoclonic epilepsies and by the FDA in the treatment of symptomatic myoclonus. It has high efficacy in PPRs, which are reduced or abolished in all tested doses (10–80 mg).[108]

Most of the other AEDs (i.e. carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin,

tiagabine and vigabatrin) are contraindicated either because:

- they are ineffective (i.e. they induce side effects without providing any therapeutic benefit in addition to depriving patients of appropriate AED treatment)
- they may worsen the seizures.

Idiopathic photosensitive occipital lobe epilepsy

Idiopathic photosensitive occipital lobe epilepsy (IPOE)[5,12,73,75,109,110] manifests with focal seizures of occipital lobe origin, which are elicited by photic stimuli.

Clarifications on classification

Occipital seizures precipitated by photic stimuli were overshadowed in the 1989 ILAE classification by the prevailing view that photosensitive epilepsies are mainly generalised (see page 502).[4] The new ILAE diagnostic scheme[5] recognised IPOE as a new syndrome of reflex epilepsy with age-related onset. This is also maintained in the new ILAE report but with less certainty; IPOE was rated 2 on a score of 1–3 (3 being the most clearly and reproducibly defined) indicating the certainty with which the ILAE Core Group believed that each syndrome represented a unique diagnostic entity.[6]

The boundaries of this syndrome of IPOE are genuinely uncertain. OPSs may start in adulthood, be part of idiopathic childhood occipital epilepsy of Gastaut (ICOE-G),[111] develop later in children with rolandic seizures or occur accidentally during IPS of normal individuals or those with migraine.[12,109] Gastaut[111] included IPOE in his syndrome:

- seven of 63 patients had IPS evoked occipital spikes, 'not seen in the resting EEG' and 'unrelated to eye opening and closing'
- seven other patients with typical occipital paroxysms had generalised PPRs, which sometimes were associated with myoclonus (see also case 11 in Gaustaut *et al*[111]).

Contrary to this is the view that 'reflex triggering of seizures have not been reported' in ICOE-G.[75]

Depending on severity, there may be three significant groups of OPSs:[12,109]

1. OPSs may occur in patients with a low occipital epileptogenic threshold to IPS that manifests with seizures only under extreme exposure to the offending stimulation. These are 'seizures that do not require a diagnosis of epilepsy'.[5] Accidental single isolated occipital seizures in normal young people[112] or patients with migraine[112] during IPS are most likely, due to a low threshold to such events, and may not happen again.
2. OPSs in patients with idiopathic occipital epileptogenicity, which probably constitute the major part of IPOE. Patients, usually children, have clinical PPRs elicited by various environmental light stimulation (video games are far more common than television).
3. OPSs occurring in patients, usually children, with idiopathic focal or generalised epilepsies other than IPOE. These are often demanding cases with regard to diagnosis and management.
4. OPSs with bizarre ictal symptomatology mimicking hysterical attacks or migraine are well reported.[12] That these symptoms, even the very prolonged and unusual ones, are ictal has been documented with ictal EEGs.[73]

Considering all of these, the data presented in this chapter may not accurately represent a single syndrome of IPOE.

Demographic data[109,113]

Onset of the first provoked seizure may range from 15 months to adulthood (peak 12–14 years). Whether females predominate[110,113] is debatable.[109] Prevalence is reported as low, at around 0.4% of all epilepsies.[109] However, OPSs reached epidemic proportions in Japan among children watching the animated cartoon television programme *Pokémon* (*Pocket Monsters*).[74]

Clinical manifestations[12,73,75,109,110]

Occipital seizures precipitated by photic stimuli are induced by video games and less often by television or other photic stimuli. These reflex seizures contain all the elements detailed in the spontaneous seizures of occipital lobe epilepsy (see Chapters 12 and 15).[73,114–116] OPSs commonly manifest with visual hallucinations, blurring of vision or blindness, alone or in combination. Less often, these visual symptoms may follow other ictal occipital manifestations, such as deviation of the eyes and head, eyelid fluttering and orbital pain.

Visual symptoms may be the only ictal manifestations, usually lasting for seconds and frequently 1–3 min. When longer (5–15 min), other ictal manifestations also occur.[73,114] Consciousness is not impaired during the phase of visual symptoms.

Progression of visual seizures to other ictal symptoms: Autonomic symptoms, such as those occurring in Panayiotopoulos syndrome (mainly retching and ictal vomiting), often follow the occipital symptoms and may end with secondarily GTCSs.[73,75]

Other type of seizures: Patients with IPOE may have exclusively OPSs. Others may also have spontaneous visual or other types of seizures. These vary from eyelid fluttering, myoclonic jerks and absences to GTCSs that occur independently of the occipital seizures.[109,113] In some cases, spontaneous secondarily GTCSs occur only during sleep.[12] Rarely, patients with rolandic seizures may later develop OPSs.[12,115]

Post-ictal symptoms: OPSs, like the spontaneous occipital seizures, are more likely than any other type of focal seizures to be followed by headache, nausea and vomiting. The headache is usually mild and diffuse, but may also be severe and throbbing, occurring 10–20 min after the end of the visual hallucinations. Post-ictal headache may also be associated with vomiting, lasting for several hours.[73]

Precipitating factors

By definition, all patients with IPOE are sensitive to flickering lights. Depending on the severity of photosensitivity in some patients, seizures may be elicited by minimal photic provocation; in others, combined pattern and photic or prolonged exposure may be responsible, whereas in others still (probably most cases of IPOE) photic stimuli are effective only if combined with other precipitating factors such as excitement or frustration, fatigue and sleep deprivation.[11]

Diagnostic procedures

All except the EEG are normal.

Electroencephalography[12,73,75,109,110]

By definition, all these patients are photosensitive and IPS elicits abnormal EEG paroxysms of spikes or polyspikes, which may be entirely confined to the occipital regions, or PPRs of generalised spike–wave discharges (GSWD), which predominate in the posterior regions (Figures 16.4 and 16.5). Spontaneous, mainly posterior, spikes often appear in the resting EEG. Centrotemporal spikes may coexist.

Occipital spikes and other posterior abnormalities induced by IPS are considered to be of much lower epileptogenic capacity than generalised PPRs. They may occur in 50% of patients who do not have seizures.[13] Occipital spikes precede generalised PPRs in 90% of photosensitive patients when light and pattern are combined during IPS.[13,117,118]

Ictal EEGs have documented the occipital origin and spreading of the discharges to the temporal regions.[75]

In my experience with video-EEG recordings, most patients with IPOE also have other types of seizure induced by IPS such as eyelid, limb, body or finger myoclonic jerks, eyelid flickering or brief absences

that are sometimes mild and may escape detection without video-EEG and if cognition is not tested (Figure 16.4).[12]

Visual evoked potentials are always of abnormally high amplitude,[75] as indeed they are in any type of photosensitive epilepsy (Figure 16.2).

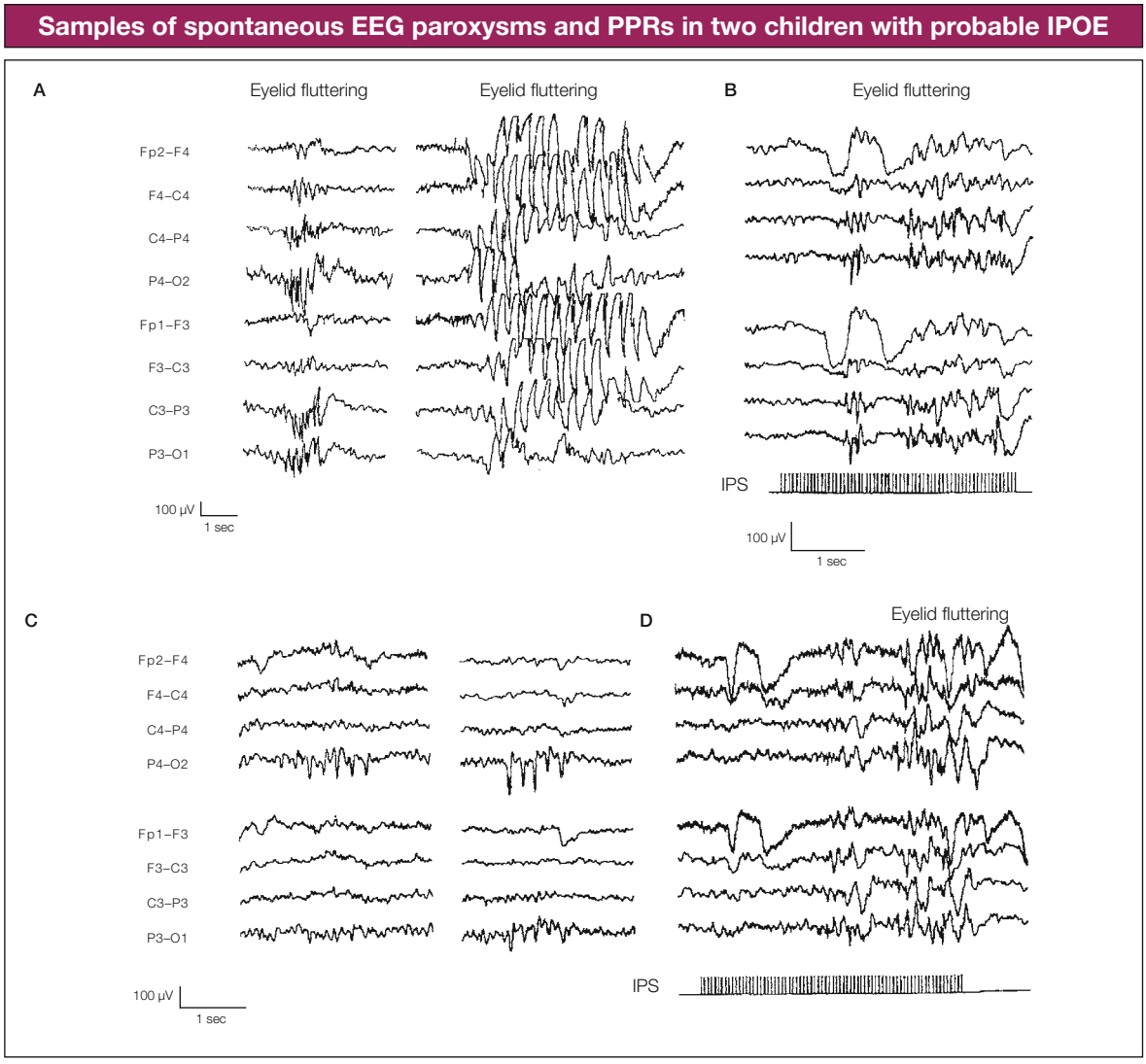

Figure 16.4 (**A**) Spontaneous occipital spikes/polyspikes and generalised discharges are associated with eyelid fluttering, which is conspicuous on video-EEG. Neither the patient nor her relatives were aware of these. (**B**) IPS consistently elicited posterior spikes, which were also associated with ictal eyelid fluttering. This patient (**A,B**) had typical multicoloured visual seizures from the age of 5 years (case 12.1 in Panayiotopoulos[12]). They were elicited by environmental lights and occasionally progressed to GTCS. She improved over the years but at 20 years of age, while on medication with valproate, she had a visual seizure with GTCS while watching television from a nearly touching distance. High-resolution MRI was normal. (**C**) Spontaneous occipital paroxysms without discernible clinical manifestations. (**D**) IPS consistently elicited PPRs with maximum posterior emphasis. These were often associated with conspicuous eyelid fluttering. This patient (**C,D**) illustrates the links between IPOE and the benign childhood seizure susceptibility syndrome (case 12.2 in Panayiotopoulos[12]). She initially had typical rolandic seizures and then developed frequent visual seizures, often with secondarily GTCSs. These were sometimes photically induced, but more often occurred during sleep. High-resolution MRI was normal.

Aetiology

By definition, idiopathic photosensitive occipital lobe epilepsy is idiopathic with genetic influences. Some patients have a family history of IPOE or IGE. Overlapping with JME has been reported.[113] Symptomatic occipital photosensitivity[119] is not part of IPOE.

Differential diagnosis

The differential diagnosis of IPOE includes migraine (rarely an actual problem if symptoms are appropriately analysed), ICOE-G, IGE (probably of management importance) and non-epileptic paroxysmal events (sometimes very difficult to differentiate).

The differential diagnosis of visual seizures from all types of migraine with visual aura has been detailed elsewhere (see Chapter 4). Some seizures of IPOE may be prolonged, also progressing from visual symptoms to nausea and vomiting with altered consciousness.[73,120] The spread of the discharge from the occipital cortex can be slow, and responsiveness may be maintained while the patient is vomiting.[73,120] These seizures may be erroneously diagnosed as migraine proper.

In children and adolescents, the differentiation of IPOE from ICOE-G may not be needed if they are the same syndrome.

Differentiation of IPOE from generalised photosensitive epilepsies should rely on clinical criteria. Occipital spikes often precede generalised discharges in photosensitive epilepsies.

In adults we have reported occipital photosensitivity in patients aged about 30 who presented with a late-onset first GTCS (often preceded by visual symptoms).[121] Of 1550 patients with seizures, three women and two men (0.3%) had EEG occipital photosensitivity and onset of solitary (three patients) or infrequent seizures in adulthood (median age 31 years, range 26–35 years). All five of these patients had generalised convulsions, which were preceded by blurring of vision or elementary visual hallucinations in four cases. Precipitation by lights, alone or in combination with other factors, was apparent in only two patients. Seizures were diurnal in all but one patient. According to the inclusion criteria, all patients had EEG occipital spikes elicited by IPS (Figure 16.5). Neurological and intellectual states, as well as brain imaging, were normal.

Prognosis[12,73,75,109,110]

Frequency of seizures and overall prognosis vary significantly among affected individuals. This depends on the severity of photosensitivity and exposure to the offending visual stimuli. There are rare case reports of normal young people[112] or patients with migraine[112,122] having an occipital seizure during IPS.

Some patients may have only one or two occipital seizures in their life despite exposure to precipitating factors and no drug treatment.[12,73,75] Others, particularly those who also have spontaneous seizures, may need medication for 1–3 years, together with strict avoidance of or cautious exposure to insulting stimuli. However, other patients may have frequent spontaneous and elicited occipital fits alone or in combination with other types of seizures, which include myoclonic jerks, often of the eyelids, infrequent absences or GTCSs.[12]

Management

Advice about avoidance of precipitating factors is essential, and is similar to that given to patients with any type of photosensitivity. Particular emphasis is needed about video games and television. Commercially available blue lenses, named Z1, that are highly effective in controlling PPRs[105] may be of value.

The effectiveness of valproate has not been tested in OPSs as it has in generalised photosensitive seizures. Patients with IPOE who are resistant to valproate became seizure free with add-on carbamazepine.[12,99] Levetiracetam or clobazam are possible alternatives.

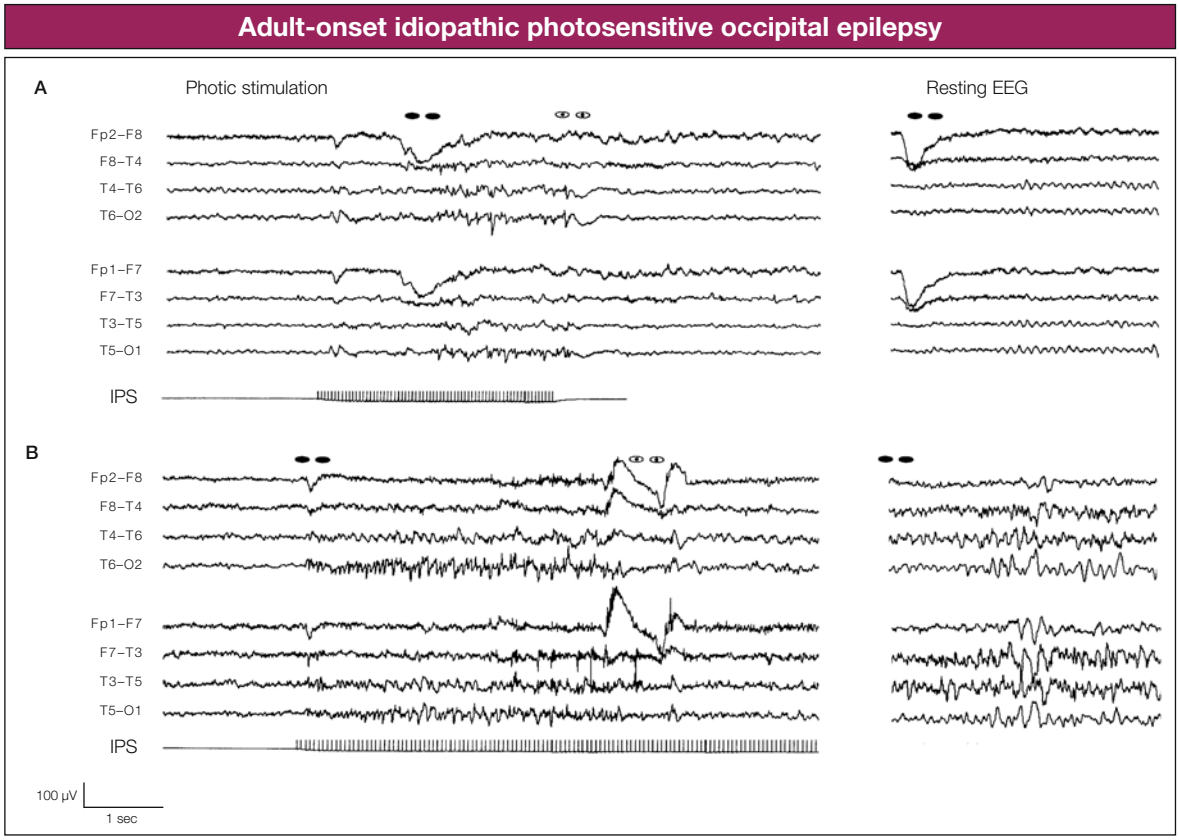

Figure 16.5 (**A**) Sample from an EEG of a man who had his first seizure at the age of 35 years while in a lift cradle at work. His vision became blurred, he felt dizzy and, within 2 min, he had a GTCS. No further seizures occurred in the next 6 months of follow-up. MRI was normal. (**B**) Sample from an EEG of a woman who had her first seizure at the age of 31 years. There was a cluster of precipitating factors; she had consumed a few alcoholic drinks, was sleep deprived, 4 months pregnant and dancing exposed to flickering discotheque lights until the early hours of the next day. She first experienced whirling lights in front of her eyes, visual perception became disturbed and within 1 min she had a GTCS. She was well during the next 4 months of follow-up. MRI was normal.

Jeavons syndrome

Synonym: eyelid myoclonia with absences.

Jeavons syndrome[101,109,123–129] is one of the most distinctive reflex IGE syndrome characterised by the triad of:

- eyelid myoclonia with and without absences
- eye closure-induced seizures, EEG paroxysms or both
- photosensitivity.

Considerations on classification

Jeavons syndrome refers to an *idiopathic reflex epilepsy*, which has unique clinical and EEG features; eyelid myoclonia is the defining seizure type. The ILAE has not yet recognised Jeavons syndrome despite overwhelming evidence.[101,109,123–129] Instead,

'eyelid myoclonia' has been accepted as a unique seizure entity with the comment that 'the degree to which these recurrent events (5 or 6 Hz) are associated with impairment of consciousness has not been adequately documented, and should be. In some patients they can be provoked by eye closure'.[6] However, it is well established that eyelid myoclonia may occur:

- with and without absences (see the clinical manifestations below)
- in many epileptic conditions of idiopathic (Jeavons syndrome), symptomatic or probably symptomatic causes.[129]

Whether or not their pathophysiology and anatomical substrates are distinct (to constitute a unique seizure diagnostic entity)[6] is unknown.

Demographic data[101,109]

Onset is typically in childhood with a peak at age 6–8 years (range 2–14 years). There is a twofold preponderance of girls. The prevalence of Jeavons syndrome is around 3% among adult patients with epileptic disorders and 13% among those with IGEs with absences.[101]

Clinical manifestations

Eyelid myoclonia, not the absences, is the hallmark of Jeavons syndrome (Figures 16.3 and 16.6).

Eyelid myoclonia consists of marked jerking of the eyelids often associated with jerky upwards deviation of the eyeballs and retropulsion of the head (eyelid myoclonia *without* absences). This may be associated with or followed by mild impairment of consciousness (eyelid myoclonia *with* absences). The seizures are brief (3–6 s), and occur mainly after eye closure and consistently many times a day. All patients are photosensitive.

GTCSs, either induced by lights or spontaneous, are probably inevitable in the long term and are provoked particularly by precipitating factors (sleep deprivation, alcohol) and inappropriate AED modifications. Typically, GTCSs are sparse and avoidable.

Myoclonic jerks of the limbs may occur, but are infrequent and random.

Eyelid myoclonic status epilepticus, either spontaneous (mainly on awakening) or photically induced, occurs in a fifth of patients. It consists of repetitive and discontinuous episodes of eyelid myoclonia with mild absence, rather than continuous non-convulsive absence status epilepticus (Figure 16.6).

Precipitating factors

The most potent precipitating factor is eye closure, whether voluntary, involuntary or reflex. Most and, in some patients, all of the seizures are induced immediately after closure of the eyes in the presence of uninterrupted (non-flickering) light. Eye closure in total darkness is ineffective.

Contrary to other forms of photosensitive epilepsies that are sensitive only to flickering lights (IPS), patients with Jeavons syndrome are also sensitive to bright, non-flickering lights. This is probably due to the enhancing effect of bright light on the sensitivity of eye closure.

Self-induction in Jeavons syndrome

Most relevant reports and the majority of epileptologists unquestionably consider the eyelid myoclonia of Jeavons syndrome as a manoeuvre used by patients to self-induce IPS and elicit seizures (see misconceptions on page 517). My view, based on numerous video-EEG recordings and interviews with 17 patients, is that eyelid myoclonia is an ictal event (15 patients) and that self-induced seizures in Jeavons syndrome are rare (possibly two patients).[85] After all, these patients do not need IPS to induce seizures. Closing the eyes (there is no need for forceful slow eye closure) in the presence of uninterrupted light may be more powerful than IPS in provoking a seizure. In physiological terms, these clinical manifestations are likely to be similar to an 'attraction movement' to light and other manifestations of the 'optic fixation reflexes', when volitional movements of the eyes are unattainable or weak.[130]

My eyes flicker as a reflex to the light.

Patients consider eyelid myoclonia as a socially embarrassing condition, they are relieved when the

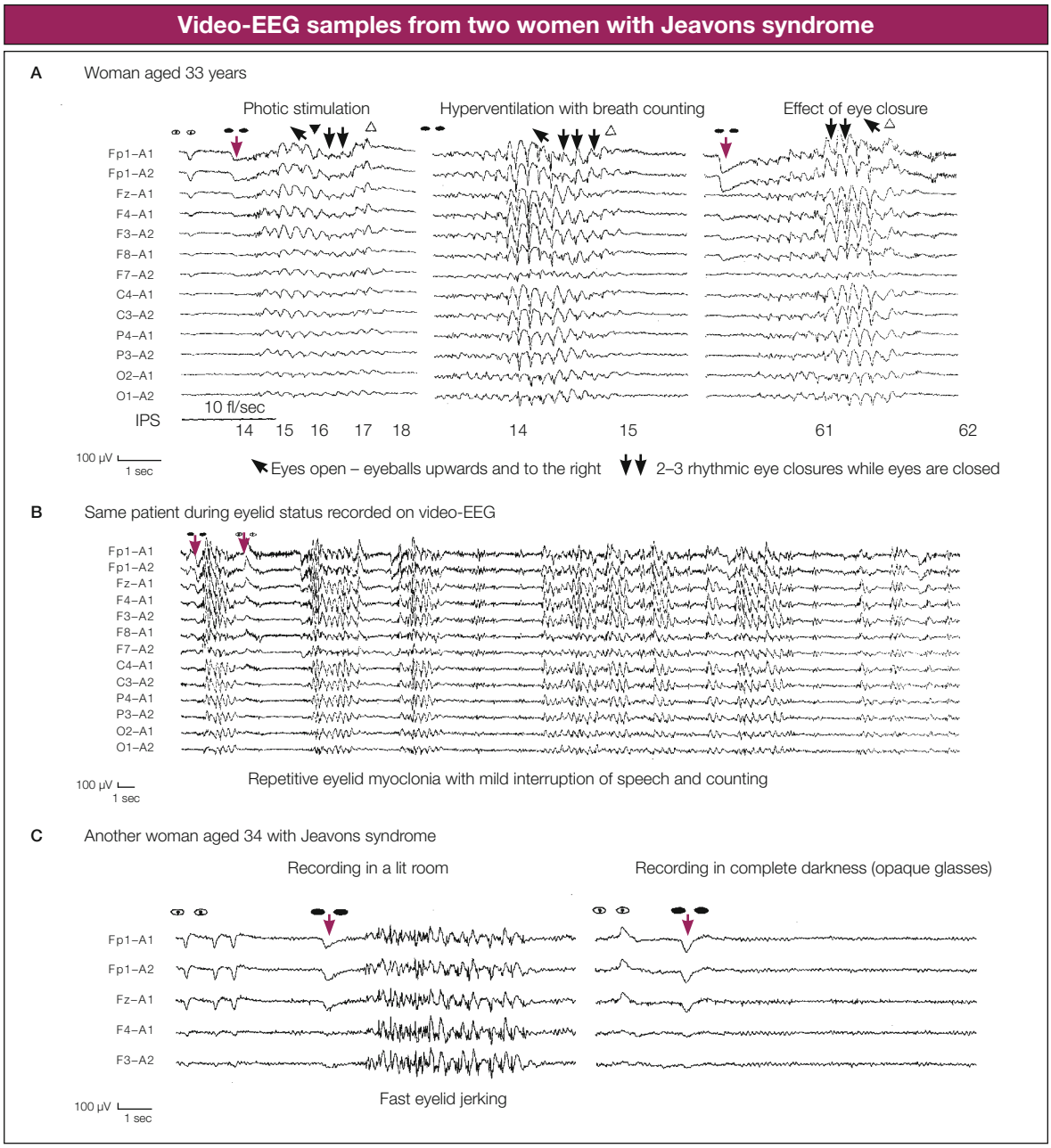

Figure 16.6 (**A**) Brief GSWD with similar characteristics are induced by IPS (left) or eye closure (right). They occasionally occur spontaneously (middle). In all illustrated occasions, these GSWD were associated with marked eyelid myoclonia denoted by the black arrows. Also note that there is no impairment of counting (numbers). (**B**) Repetitive discontinuous seizures of eyelid myoclonia occurred on awakening when the patient was erroneously treated with carbamazepine. These lasted for more than 30 min. There was only mild interruption of speech and counting during the GSWD. The patient was fully aware of her condition. (**C**) Long video-EEG of a woman with Jeavons syndrome while taking valproate. There were frequent eye-closure-related GSWD of mainly polyspikes, often associated with fast eyelid jerking, which could be mild or violent. They were totally inhibited in complete darkness (complete darkness implies that any form of possible light was totally eliminated). Symbols of eyes indicate when the eyes were open or closed.

Video-EEG samples of these and other patients with Jeavons syndrome can be seen in the CD companion of references 57–59.

seizures improve with AEDs and they show excellent compliance with their treatment.

It has been proposed that patients with Jeavons syndrome may not be deliberate 'self-inducers', but may suffer from compulsive 'self-induction' similar to the phenomenology of Tourette syndrome.[124] This is because some patients may have various compulsive or tic-like symptoms, including premonitory sensations, compulsive and difficult-to-resist urges and a sense of relief associated with the attacks.[124]

Aetiology

Jeavons syndrome is a genetically determined homogeneous syndrome, with a high prevalence of similar seizures in family members.[131,132]

Pathophysiology

It is possible that in patients with Jeavons syndrome the α-rhythm generators malfunction, and that both the magnocellular and parvocellular systems are functionally disturbed. We do not know the physiology of the epileptic phenomena and the alterations that may occur in the brain of patients with Jeavons syndrome, under the continuous bombardment from electrical discharges almost every time that they close their eyes. Age at onset may be significant.

Diagnostic procedures

All tests apart from the EEG are normal.

Electroencephalography

Video-EEG is the single most important procedure for the diagnosis of eyelid myoclonia with or without absences. It shows frequent high-amplitude 3–6 Hz GSWD of mainly polyspikes (Figures 16.3 and 16.6). Typically these are:

- related to eye closure, i.e. they occur immediately (within 0.5–2 s) on closing the eyes in an illuminated recording room and they are eliminated in total darkness
- brief (1–6 s, commonly 2 or 3 s).

GSWD are also enhanced by hyperventilation. Eyelid myoclonia of varying severity often occurs with GSWD.

PPRs are recorded in all untreated young patients, but may be absent in older patients or those on medication. Photosensitivity and FOS may coexist.

Sleep EEG patterns are normal. GSWD are more likely to increase during sleep, but may also decrease. In sleep, the GSWD are shorter and devoid of discernible clinical manifestations of any type, even in those patients who have numerous seizures during alert states.

The EEG and clinical manifestations deteriorate consistently after awakening.

A normal EEG is rare, even in well-controlled patients.

Differential diagnosis

The diagnosis of Jeavons syndrome is simple because the characteristic eyelid myoclonia, if seen once, will never be forgotten or confused with other conditions.[109] Furthermore, the EEG with the characteristic eye-closure-related discharges and photosensitivity leaves no room for diagnostic error.

As a simple rule of thumb, eyelid myoclonia is highly suggestive of Jeavons syndrome. This becomes more likely when eyelid myoclonia is combined with photosensitivity, and it is pathognomonic of the syndrome when it also occurs after eye closure.

Nevertheless, eyelid myoclonia is often misdiagnosed as facial tics, sometimes for many years. In addition, eyelid myoclonia should not be confused with either of the following:

- the rhythmic or random closing of the eyes, often seen in other forms of IGE with absences
- the eyelid jerking that may occur at the opening or initial stage of the GSWD in typical absence seizures of childhood absence epilepsy.

Persistent, frequent, non-epileptic, paroxysmal eyelid movements that occur in patients with PPRs are a source of diagnostic confusion that can be avoided with video-EEG recordings.[133]

The main diagnostic problem, which is probably iatrogenic, is self-induction. This is a diagnosis that

should not be made without taking a proper history because it is often wrong (see misconceptions below).

The symptom/seizure of eyelid myoclonia alone is not sufficient to characterise Jeavons syndrome, as it may also occur in symptomatic and cryptogenic epilepsies, which are betrayed by developmental delay, learning difficulties, neurological deficits, and abnormal MRI and background EEG.[134]

Misconceptions

A main misconception is that eyelid myoclonia (the seizure) is a self-induced attempt to induce seizures. This belief is so strong that, in almost all relevant publications, the patient described by Radovici, et al[135] is erroneously cited as the first reported case of self-induced seizures, even by hand waving.[86] No such evidence or mention of self-induced seizures can be found in the original report: 'AA… age de 20 ans, presente des troubles moteurs sous forme de mouvements involontaires de la tête et des yeux sous l'influence des rayons solaires.'[135]

Prognosis

Jeavons syndrome is a lifelong disorder, even if seizures are well controlled with AEDs. Men have a better prognosis than women. There is a tendency for photosensitivity to disappear in middle age, but eyelid myoclonia persists. It is highly resistant to treatment and occurs many times a day, often without apparent absences and even without demonstrable photosensitivity.

Management[109,129]

Based on anecdotal evidence, the drugs of choice are those used for other IGEs (see page 411).

Valproate alone, or most probably in combination with clonazepam, levetiracetam, lamotrigine or ethosuximide, appears to be the most effective regimen. The choice of the second drug depends on the main seizure type. Clonazepam is highly efficacious in eyelid myoclonia and myoclonic jerks; some patients achieve relatively good control with clonazepam monotherapy.

Of the newer AEDs, levetiracetam may be the most effective, because of its antimyoclonic and antiphotosensitive properties. Lamotrigine is very effective in absence seizures but may exaggerate myoclonic jerks.

Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin are contraindicated.

Lifestyle and avoidance of seizure precipitants are important.

Non-pharmacological treatments used for photosensitive patients (such as wearing special glasses or the newly commercially available blue Z1 lenses) should be employed in Jeavons syndrome when photosensitivity persists. [105,136]

Pattern-sensitive epilepsy

Pattern-sensitive epilepsy[13,14,33,34,77,137,138] refers to epileptic seizures induced by patterns; it is not a particular epileptic syndrome. Pattern seizure sensitivity is closely related to photosensitivity. Almost all patients with clinical pattern sensitivity epilepsy show PPRs (Figures 16.7 and 16.8). Conversely, 30% of clinically photosensitive patients are also sensitive to stationary, and 70% to appropriately vibrating, patterns of stripes. Patterns enhance the effect of photic stimulation, whether under test conditions or in real life. Pattern sensitivity without photosensitivity, sensitivity to non-geometric pat-

terns and self-induced pattern-sensitive epilepsy are all rare.

Demographic data

Pure pattern-sensitive epilepsy with clinical attacks induced only by patterns is rare;[34] it probably occurs in 0.2% of patients with onset of non-febrile seizures between birth and 15 years of age.[109] This is despite the relatively high incidence of pattern-induced EEG paroxysmal activity in photosensitive patients.

Clinical manifestations

Clinical manifestations have not been well studied in pure pattern-sensitive epilepsy.[13,34] All types of generalised seizures have been described. My impression is that absences are more common than GTCSs and myoclonic jerks, and GTCSs are more common than myoclonic jerks. I am not aware of patterns inducing occipital seizures, although they should exist considering that the visual cortex is the primary target of the pattern stimulus. Self-induced pattern-sensitive epilepsy has been reported (Figure 16.7).[35,139]

Environmental stimuli

Environmental stimuli that induce seizures in pattern-sensitive patients are those that best match the properties of the provocative patterns used in relevant EEG testing, and best suit and create the conditions of their spatial and directional presentation to the eyes. These are striped clothes, such as shirts, jackets or ties, and escalators, wallpaper and furnishings, Venetian blinds, air-conditioning grills and radiators. Any activity visually involved with these patterns, such as ironing, is likely to induce seizures. Less direct, but often very significant, is the role of patterns in more complex stimuli, such as television viewing and video games.[13,14,33]

Patients, caregivers and physicians recognise pattern as a seizure precipitant less often than environmental flicker or specific agents, such as the television, discotheque lighting or video games. Direct questioning implicates pattern as a seizure trigger in 6–30%[82,140] of photosensitive individuals.

Generalised 3 Hz spike or polyspike–wave associated with clinical absence in two patients with self-induced seizures

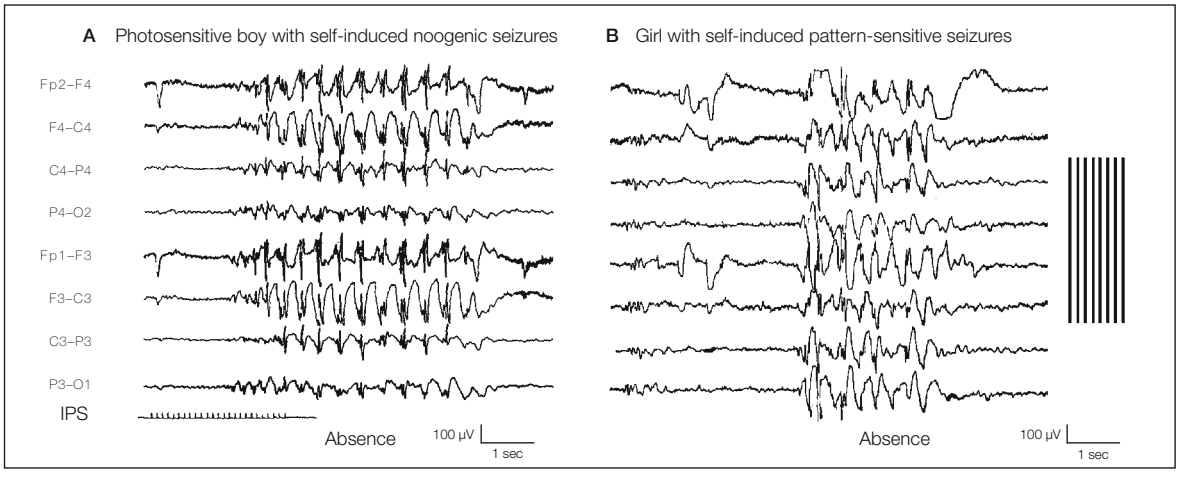

Figure 16.7 (**A**) Absence seizure induced by IPS. This patient had spontaneous, photically induced and noogenic seizures. He used noogenic processes for self-induction (see Koutroumanidis, *et al*[51]). (**B**) Absence seizure induced by a pattern with vertical lines. This patient with learning difficulties had mainly self-induced pattern-sensitive epilepsy. She was also photosensitive (see Panayiotopoulos[35]).
Modified with permission from Koutroumanidis, et al[51] *and Panayiotopoulos.*[35]

Aetiology

Pattern sensitivity, similar to photosensitive epilepsy, is a genetically determined trait.

Pathophysiology

Elaborate and intelligent methodological studies, mainly in patients with photically induced seizures, revealed many aspects of pattern seizure susceptibility and its pathophysiology:[14,33]

- seizures are triggered in the visual cortex
- synchronisation of neural activity is necessary
- the trigger involves one cerebral hemisphere or both hemispheres independently
- the trigger requires the physiological activation of a critical area of cortical tissue.

Diagnostic procedures

The EEG with appropriate pattern presentations is the key test (Figure 16.8). Pattern sensitivity depends on the spatial frequency, orientation, brightness, contrast and size of the pattern. An optimally epileptogenic pattern consists of black-and-white stripes of equal width and spacing (see the literature[14,33,109]). As in photosensitive patients, binocular is much more potent than monocular stimulation, and the patient should fixate on the presenting patterns.

Samples from a video-EEG of a child aged 14 years with pure pattern-sensitive epilepsy from the age of 7 years

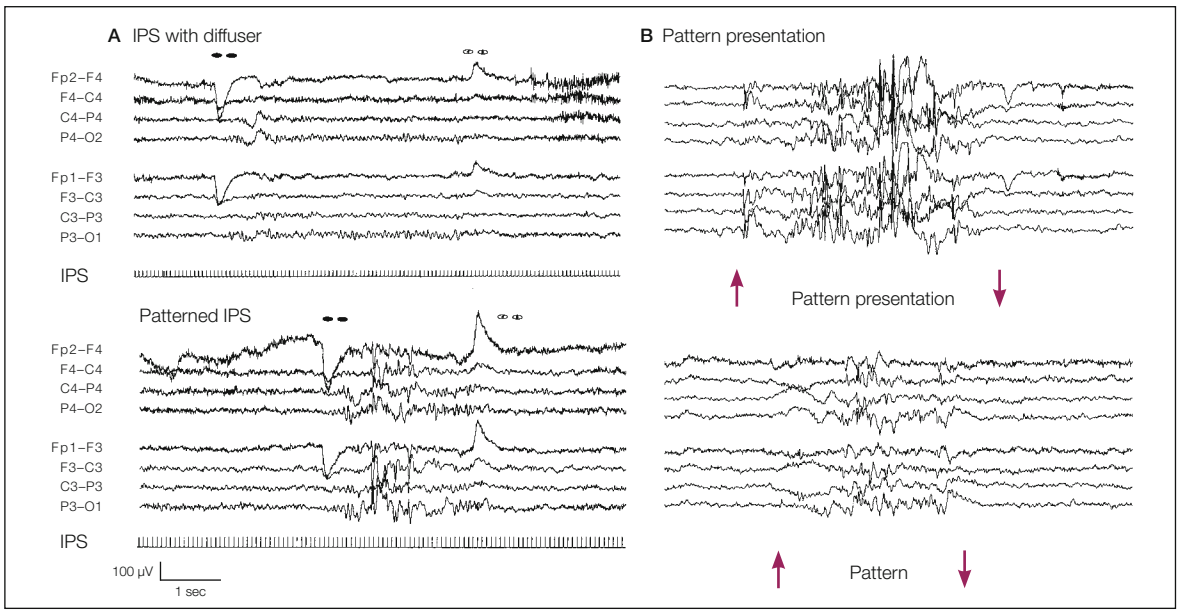

Figure 16.8 (**A**) Only patterned IPS (2×2 mm graticule superimposed on the glass of the stroboscope)[64,97] elicits PPRs. (**B**) Paroxysmal discharges were consistently elicited by various linear patterns. The child is of normal development and scholastic performance. He has brief 4–10 s absence seizures consisting of mild-to-moderate impairment of consciousness and concurrent upwards rolling of the eyeballs with eyelid flickering. The seizures are invariably elicited by patterns with grids or stripes, such as escalators, and the dotted lines of microwaves, radiators or cloths. On five occasions, the absence seizures were followed by GTCSs. He is also drawn like a magnet to the television screen, although he is not photosensitive. Spontaneous absence seizures occur only after awakening. A characteristic feature is that when patterns appear in his visual field, his eyes fixate (freeze) to them and he is unable to turn away. He says that he finds patterns 'hypnotic', but not pleasant. He would avoid patterns if he could and does not seek them out. This behaviour was considered as 'self-induction', but this was not the opinion shared by Dr A. Wilkins (a renowned expert in pattern and photosensitive epilepsies) and myself who examined him together.

Prognosis

The prognosis of pattern-sensitive epilepsy has not been systematically studied but may be worse than that of photosensitive epilepsy.

Management

Management may be similar to that of photosensitive epilepsy, but pattern-sensitive epilepsy may be much more difficult to treat.

Fixation-off sensitivity

FOS is a term that I coined to denote the form(s) of epilepsy and/or EEG abnormalities that are elicited by elimination of central vision and fixation.[36,102,109] 'Elimination of central vision and fixation' is a specific precipitating stimulus, which, even in the presence of light, induces high-amplitude occipital or generalised paroxysmal discharges.

FOS is suggested in the routine EEG by abnormalities, which consistently occur as long as the eyes are closed, but not when the eyes are opened.

Clinical and EEG correlations in patients with FOS

FOS, similar to photosensitivity, is a reflex EEG activation with some preference for certain epileptic conditions.

From clinical and video-EEG documentation, there are three types of patients with seizures and EEG abnormalities of FOS:[36]

1. *Patients with occipital paroxysms* such as those seen in EEGs of some patients with Panayiotopoulos syndrome and more frequently in patients with ICOE-G, which are the model examples of FOS. It was in these cases that FOS was first documented as a new type of activating stimulus in reflex epilepsies (Figure 12.9).

FOS-induced abnormalities are mainly localised in the occipital regions and are not associated with overt ictal clinical manifestations.

2. *A rare but 'pure' and distinct clinical form of FOS cryptogenic generalised epilepsy (Figure 16.3B).* Patients are women of borderline normal intelligence with frequent eyelid myoclonia (with or without *atypical* absences), absence status epilepticus and GTCSs. The eyelid myoclonia manifests with fast, small amplitude clonic movements of the eyelids associated with tonic spasm of the eyelids and eyes that occasionally spread to the neck muscles.[102] Absence status epilepticus is preferentially catamenial.[141]

Another of our patients also has catamenial absence status epilepticus, 'always coming with her menstruation' every month.[141] This lasts for 1–3 days when 'she is vacant, eyes rolling up, feeling slow, drowsy and depressed but also aggressive and not in control of herself'. She had four to five GTCSs in her life, probably after an absence status and indulgence in alcohol.[141]

EEG-FOS abnormalities consist mainly of diffuse α-like rhythms at 7 Hz, mixed with bisynchronous sharp and spike/polyspike components. These are often associated with clinical ictal manifestations (Figure 16.3B). Patients are not photosensitive and differ markedly from those with Jeavons syndrome (eyelid myoclonia with absences).

3. *Patients with IGEs and photosensitivity.*[109,142] The FOS abnormalities are often diffuse and not associated with overt clinical ictal manifestations.

In the second and third types, the typical abnormalities related to FOS are mainly diffuse/generalised, with 'dropout' in sleep stages simultaneous with the α-rhythm.

FOS may occur in individuals without seizures.[143] In an example of such an asymptomatic adult with FOS, continous bilateral occipital paroxysms during

elimination of central vision were associated with transitory cognitive impairment, demonstrated by neuropsychological testing.[143]

The range of EEG abnormalities and clinical manifestations associated with FOS may be extended if FOS is tested as part of routine clinical practice of EEG departments.

Pathophysiology

The underlying mechanisms of FOS are not known, but they may be related to an abnormality of the α-rhythm generators.[36]

FOS has the opposite EEG characteristics of photosensitivity epilepsies (Table 16.3), but conversion from one to the other may occur, albeit rarely.[36]

FOS paroxysms studied with functional MRI (fMRI) were correlated with activation of parieto-occipital and frontal brain areas,[143] and a significant increase of blood oxygen level-dependent signal in the extrastriate cortex.[144] Magnetoencephalography (MEG) of visual evoked fields in FOS revealed abnormal activation of the visual corticocortical pathway via the insular cortex.[145]

Scotosensitive epilepsy

Scotosensitivity (*skotos* = darkness) denotes forms of epilepsy, seizures or EEG abnormalities that are elicited by the complete elimination of retinal stimulation by light. Pure scotosensitive patients are rare.[146] Most patients described as scotosensitive probably have FOS.[36]

Techniques for documenting FOS[36]

First, it is essential to confirm that the EEG abnormalities observed in routine EEG recording are related to the eyes-closed state. The patient is asked to open and close his or her eyes every 5 s, six times consecutively. Instructing the patient to look at a fixed point, such as the tip of a pencil, ensures fixation in the eyes-opened state.

Important practical note

Complete darkness can be difficult to achieve in routine EEG departments. Even a small spot of red light on which the eyes may fixate can totally inhibit EEG abnormalities induced by complete darkness. Switching off the lights in the EEG recording room is not adequate and may explain conflicting results in the literature. Complete darkness can be produced with underwater goggles covered completely with opaque tape.

Second, FOS is evaluated by instructing the patient to perform the same sequence of eyes-opened and eyes-closed states in conditions that eliminate central vision and fixation. There are many practical ways to achieve this, such as asking the patient to wear underwater goggles covered with opaque tape (this achieves complete darkness) or semitransparent tape (which allows light in, but obscures any other visual input).

FOS versus photosensitivity

	FOS	Photosensitivity
Resting EEG in a lit recording room	Eye-closed abnormalities	Eye-closure abnormalities
Effect of darkness	Activation of abnormalities	Inhibition of abnormalities
Effect of fixation and central vision	Inhibition of abnormalities	Activation of abnormalities
Effect of patterns	Inhibition of abnormalities	Activation of abnormalities
Effect of IPS	None or inhibition	Photoparoxysmal responses

Table 16.3

Complex reflex epilepsies[1,2,65]

Seizures induced by thinking and praxis[49,52,65,147]

Thinking-induced (noogenic) seizures occur in response to high non-verbal cognitive functions such as mathematical calculations, solving problems, playing games that need mental effort (e.g. chess) and ideation, alone or more often in combination. Praxis-induced seizures are triggered by similar mental activities accompanied by execution of movement (praxis) such as drawing, and playing cards, chess, other board games or with a Rubik's cube. Decision-making, spatial tasks, and heightened attention and stress are essential elements in seizure provocation. There is significant overlap between thinking- and praxis-induced seizures and these usually occur in the context of an IGE.[147] They generally start during adolescence and manifest with myoclonic jerks, absences and GTCSs; focal seizures are rare.

Primary (idiopathic) reading epilepsy

Synonyms: idiopathic reading epilepsy (see Author's note below).

Primary (idiopathic) reading epilepsy is a distinctive form of a reflex epilepsy syndrome, which mainly manifests with myoclonic jerks of the masticatory muscles.[37,38,40,41,52]

Reading (the stimulus) is a well-documented provocative, seizure-inducing stimulus in idiopathic (primary reading epilepsy) and less often cryptogenic/symptomatic epilepsies (Figure 16.9).[37–41,148–151] In some patients with mainly symptomatic causes reading provokes focal seizures that are relatively longer than those of the primary reading epilepsy and manifest with alexia and possibly dysphasia without jaw myoclonus (Figure 16.9C).[40]

Author's note: In ILAE terminology, idiopathic has replaced the word primary and this should also apply to idiopathic (primary) reading epilepsy.

Clarifications on classification

Primary reading epilepsy is classified in the 1989 ILAE classification[4] among the 'idiopathic, age- and localisation-related (partial) epilepsies'. The new ILAE diagnostic scheme (Table 16.1) now rightly categorises 'reading epilepsy' as a syndrome of reflex epilepsy.[5]

Demographic data

Onset ranges between 12 and 19 years with a peak in the late teens, which is long after reading skills have been acquired. There is a male preponderance of 1.8/1. The prevalence may be very low (0.2% among patients with onset of non-febrile seizures between birth and 15 years of age).[109]

Clinical manifestations

Seizures are elicited by reading and consist of brief myoclonic jerks mainly restricted to the masticatory, oral and perioral muscles. They are described as clicking sensations and occur a few minutes to hours after reading. If the patient continues reading despite jaw jerks, these may become more violent, spread to the trunk and limb muscles or generate other seizure manifestations before a GTCS develops. This is usually the first and last GTCS in the patient's life, because the condition is effectively treated and the patient learns to stop reading or talking when oral/perioral jerks occur. It is extremely rare for patients with reading epilepsy to have more than one to five GTCSs or spontaneous seizures unrelated to reading. Other types of ictal manifestations (mainly visual hallucinations) rarely occur. One of my patients, a 23-year-old woman with

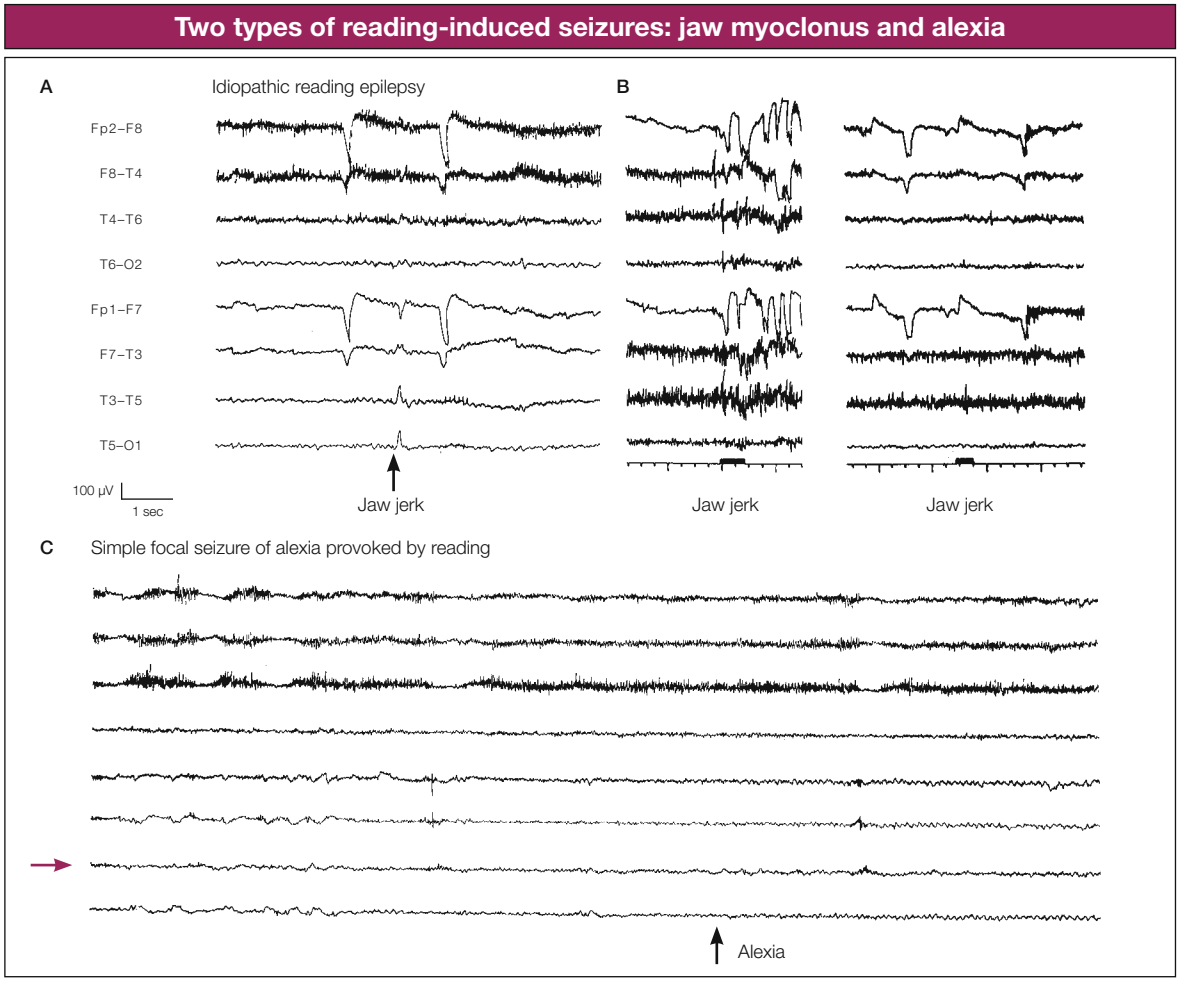

Figure 16.9 (**A**) The EEG of a woman with jaw jerks (arrow) while reading (case 8 in Koutroumanidis, *et al*[40]). She is successfully treated with clonazepam 0.5 mg at night. Her sister also suffered from jaw jerks, mainly when involved in argumentative and fast talk. (**B**) Video-EEG of another woman with jaw jerks (bars) while reading (case 10 in Koutroumanidis, *et al*[40]). The EEG shows no detectable abnormality during jaw jerks and possible changes are obscured by muscle activity. (**C**) Video-EEG of a 24-year-old man with simple focal seizures manifested with alexia (inability to understand written words) and four nocturnal GTCSs (case 17 in Koutroumanidis, *et al*[40]). The inter-ictal EEG during reading showed sharp and slow waves focused in the left posterior temporal regions (red arrow). When the patient indicated his inability to understand text (arrow), the EEG showed low-amplitude fast rhythms (around 10 or 11 Hz), which were localised in the left posterior temporal regions (red arrow). This lasted 70 s before clinical recovery. MRI and a PET scan were normal. The patient was effectively treated with carbamazepine.
Modified with permission from Panayiotopoulos (1996).[8]

primary reading epilepsy, had olfactory hallucinations after repetitive jaw myoclonus induced by prolonged reading or argumentative talking. Occasionally, absences may occur.

Hand myoclonic jerking is common among those with seizures precipitated by writing (*graphogenic epilepsy*).[43]

Precipitating factors

The stimulus is reading silently or aloud, particularly texts that are difficult to understand or are unusual. Approximately a quarter of patients may also have similar jaw jerks that are provoked by talking (particularly if this is fast or argumentative), writing, reading music or chewing. Clinically identical seizures

can also be provoked by other linguistic activities, thus justifying the term 'language-induced epilepsy'.[40,43]

Aetiology

Idiopathic reading epilepsy is probably genetically determined, and has been reported in identical twins and among first-degree relatives.[37]

Focal epileptic seizures provoked by reading that manifest with alexia without jaw jerks and last for minutes are probably of cryptogenic or symptomatic cause (Figure 16.9C).[40]

Pathophysiology

Ictogenesis in reading or language-induced epilepsy is attributed to reflex activation of a hyperexcitable network that subserves the function of speech and extends over multiple cerebral areas on both hemispheres. The parts of this network responding to the stimulus may drive the relative motor areas producing the typical regional myoclonus.[40] The main mechanism is attributed to the transformation, transcoding written linguistic symbols into phonematic, loud or silent speech.[37,150] This may be enhanced by other superimposed factors, such as proprioceptive impulses from oral, perioral and eye muscles involved in reading, and difficulty in transcoding script into speech.[37]

Brain opioid-like substances may be involved in the termination of reading-induced seizures.[148]

Diagnostic procedures

All tests apart from the EEG are normal. In symptomatic and cryptogenic forms, brain MRI may show abnormalities in the dominant posterior temporal area.[40]

An unusual gyrus branching anteriorly off the left central sulcus has been shown with fMRI.[151]

Electroencephalography[40]

The inter-ictal EEG is usually normal.

Ictal EEG manifestations are often inconspicuous because of jaw muscle artefacts. Ictal EEG changes are variable in terms of morphology and topography. Commonly, they consist of bilateral sharp waves in the temporoparietal regions with left-sided emphasis (Figure 16.9). Ictal discharges of alexia (symptomatic seizures) are prolonged and entirely focal in the language-dominant temporoparietal regions.

Prognosis

The prognosis of idiopathic reading epilepsy is good, because seizures are usually mild and related to a precipitating stimulus that can be modified.

Management

Modification of reading and talking habits may be successful.

Clonazepam 0.5–1.0 mg at night is highly effective. Some authors use valproate but this may not be needed for the majority of patients who do extremely well on clonazepam alone.

Focal seizures with alexia as a main manifestation do not usually respond to clonazepam or valproate and may also be resistant to carbamazepine.

Startle seizures

Synonym: startle-induced seizures, startle epilepsy.

Startle seizures are induced by sudden and unexpected stimuli.[56,152–158] The startle (unexpected and sudden presentation of the stimulus) is the provoking factor, although, rarely, patients may be specifically sensitive to one sensory modality. Sudden noise is the main triggering stimulus, but somatosensory and, less often, visual stimuli also effectively trigger seizures in some patients. Habituation to repetitive stimulation occurs.

Clarifications on classification

The 1989 ILAE definition for startle seizures is:

> Epileptic seizures may also be precipitated by sudden arousal (startle epilepsy); the stimulus is unexpected in nature. The seizures are usually generalized tonic but may be partial and are usually symptomatic.[4]

The ILAE diagnostic scheme considered 'startle epilepsy' to be a syndrome, although most realistically this is a type of startle-induced seizure that occurs in a heterogeneous group of patients of variable aetiologies and EEG correlates.[157] This, as was suggested in the previous editions of this book, has now been corrected in the new ILAE report, which does not include 'startle epilepsy' in the list of proposed epileptic syndromes (Table 16.1).[6]

Demographic data

Onset is in childhood or early adolescence (1–16 years). Both sexes are equally affected. The prevalence is very low.

Clinical manifestations[56,154,157]

Most patients have static neurological and intellectual handicaps. Infantile hemiplegia predominates.

The startle response is brief (up to 30 s) and consists of axial tonic posturing, frequently causing falls, which can often be traumatic. The seizures are asymmetrical in approximately a quarter of patients. In hemiparetic patients, the seizure starts with flexion and abduction of the paretic arm and extension of the ipsilateral leg, and rapidly involves the contralateral side. Concurrent symptoms, such as marked autonomic manifestations, automatisms, laughter and jerks, may occur. Less commonly, startle-induced seizures may be atonic or myoclonic, particularly in patients with cerebral anoxia. Seizures are frequent, occurring many times a day, and sometimes progress to status epilepticus.

Spontaneous seizures are common (probably all patients), but infrequent and may precede or follow the startle-induced seizures.

Aetiology

Startle-induced seizures usually occur in patients with a variety of localised or diffuse static brain pathology (*symptomatic startle seizures*). Typically, the insults are pre- or perinatal, or occur within the first 2 years of life. Startle-induced seizures appear to be common in Down syndrome.[159]

Diagnostic procedures

A variety of focal and diffuse, usually atrophic and often large, cerebral abnormalities are found. Brain MRI is necessary even in those patients with normal neurology.[154] The abnormalities are found predominantly in the lateral sensorimotor cortex.

Electroencephalography

The inter-ictal EEG shows a variety of diffuse or focal abnormalities reflecting the underlying brain structural lesions.

The ictal EEG consists of an initial vertex discharge followed by diffuse relative flattening or low-voltage rhythmic activity of about 10 Hz, which begins in the lesioned motor or premotor cortex, and spreads to mesial frontal, parietal and contralateral frontal regions.[152,154,155] On the surface EEG, this is often obscured by muscle artefacts.

Differential diagnosis

The main diagnostic confusion is with hyperekplexia (also called startle disease), which is a non-epileptic disorder (see page 113).

Seizures induced by touch, tap or sudden dousing with hot water may have a startle component, but this is not a prerequisite for their provocation. In addition, these reflex seizures are mainly myoclonic, the ictal EEG shows generalised discharges,

patients are otherwise normal and there are no structural brain abnormalities.

Prognosis

The prognosis is often poor, particularly for those with severe pre-existing encephalopathies. The mortality rate is increased compared with that of the general population. Total control of the seizures is almost impossible.

Management

There is no established drug of choice, and therapy is often unsatisfactory. Clonazepam, clobazam and carbamazepine are frequently used. The role of the newer AEDs in startle seizures has not been investigated. Lamotrigine[160] and levetiracetam[161] have been found to be very effective in small series of patients.

Hot water epilepsy

Synonyms: water immersion epilepsy, bathing epilepsy.

Hot water epilepsy is a term used to encompass a reflex epileptic condition characterised by epileptic seizures elicited by pouring hot water (40–50°C) over the head.[24,162–170] Thus, this mode of reflex epilepsy requires a specific thermal cutaneous (i.e. pouring of very hot water over the head) stimulus.

Less often, seizures may occur while using a shower, during tub bathing or exceptionally with cold water.[171] A particular type of soap and entry of water into the mouth are unusual triggering factors.

At a later stage in the natural history, 5–10% of these patients have seizures during a bath even when water is not poured over the head.[170]

Self-induction occurs in 10–20% of patients.[169,171]

Clarifications on classification

The ILAE Task Force core group has introduced 'hot water epilepsy in infants' as a new reflex epileptic syndrome with a relative confidence level of 2 (Table 16.1).[6]

Authors's note: I do not endorse 'in infants' as part of the nomenclature of this syndrome because of its wide age range at onset.

Demographic data

Age at onset of the first reflex seizure is from 2 months to 58 years with a mean of 13 years.[24,168,170]

Half of patients have their first seizure during the first decade of life but in a third, this happens after the age of 18 years. Male patients outnumber females in a ratio of 3:1. Boys are two- to three-times more frequently affected than girls. The prevalence is very low.

Hot water epilepsy has been mainly described in India and Turkey but case reports have been published from many other countries.

In India, estimated incidence is 60 per 100,000 in Bangalore and 255 per 100,000 in Yelandur.[163,170] This high incidence may be due to a racially determined genetic trait, bathing habits or both.

Clinical manifestations

Hot water-induced seizures are predominantly (80%) simple or complex focal with (25%) or without (75%) secondarily GTCSs.[24,163,168,170]

Onsets are described as staring, incomprehensible speech, déjà vu, fainting-like sensations, tinnitus, nausea, vomiting, confusion, feeling of pleasure or fear, relaxation or calmness, visual, auditory, olfactory (taste of soap) hallucinations and complex automatisms.

Primarily GTCSs are reported much less often and certainly not more than in a fourth of patients.

The seizures may occur at any time during the bathing, even at the beginning of it. Their duration is usually 30 s to 3 min.

Generally, the frequency of these seizures depends on the frequency of head bathing.[170]

One fourth to a half of patients also have spontaneous seizures (some of them are nocturnal GTCSs), which begin within 1–6 years after the onset of the reflex seizures.[24,168,170] One such patient had IPOS.[24]

Self-induced seizures: 10–20% of patients experience intense pleasure (sometimes described as sexual pleasure) during the seizures.[24,170,172] They self-induce seizures by increasing the temperature of the water and pouring more hot water over their head until they lose consciousness. Self-induction mainly occurs towards the end of the bath. Contrary to other patients with self-induced seizures, such as in photosensitive epilepsy, these patients are not embarrassed talking about their self-induced experiences (including feelings of arousal)[24] and details of the methods of self-induction.

Aetiology

Almost all cases of hot-water epilepsy are seen in otherwise healthy children with normal neurological examination and normal brain imaging.

Febrile seizures do not appear to be higher among these patients. However, almost half of them have other family members with various but non-defined types of epilepsy. Familial cases with more than one member having hot water epilepsy have been reported in 18% of the patients from India[170] and in 10% from Turkey.[168] Because of the high frequency of consanguineous marriages in these countries, autosomal recessive inheritance is likely.[169]

In a recent study[169] of a large four-generation family with autosomal dominant inheritance of hot water epilepsy, significant linkage was detected on chromosome 4q24-q28, with the highest two-point LOD score of 3.50 at recombination value (theta) of 0 for the marker D4S402. The critical genetic interval spans 22.5 cM and corresponds to about 24 megabases of DNA. Suggested candidate genes for hot water epilepsy include *NEUROG2*, *ANK2*, *UGT8* and *CAMK2D*.[169]

Pathophysiology

In a recent experimental study, kindling was demonstrated in association with hyperthermic seizures induced by repeated hot water stimulation in a male Wistar albino rat model.[173] Following 8–12 episodes of hot water stimulations there was progressive epileptic activity[173] manifested in the form of:

- a lowering of rectal temperature thresholds from 41.5°C to 40.0°C
- a drop in latency for developing seizures from 185 s to 118 s
- an increase in duration of hippocampal seizure discharge from 15 s to 140 s
- a progressive increase in complexity of EEG after discharges
- an increase in behavioural seizure severity from Grade 1 to 5 in all the rats
- neuronal sprouting observed in the supragranular molecular layer and stratum lacunosum.

Diagnostic procedures

Brain imaging is usually normal, although abnormalities have been described in a few cases.[174] One patient out of 25 had MRI findings consistent with hippocampal sclerosis.[24]

Electroencephalography[24,168,170]

The inter-ictal EEG may be normal for half of the patients. The others show mainly unilateral temporal lobe abnormalities of spikes, sharp waves or slow waves only.

The ictal EEG starts with focal, usually unilateral, rhythmic slow-wave activity of high amplitude, often intermixed with spikes.[170,175]

Differential diagnosis

The differential diagnosis includes heat-induced vagal syncopes, febrile seizures and breath-holding syncopal attacks (see Chapter 4).

Prognosis

Hot water epilepsy usually has a good prognosis and is self-limited.

Management

Altering the bathing techniques, by lowering water temperature, showering or sponging instead of pouring water over the head, and reducing the duration of the bath are usually sufficient to achieve seizure control. AEDs are only indicated when these stimulus-modifying or -preventing measures fail or when spontaneous seizures also occur. Intermittent oral administration of clobazam before a hot water bath has been found to be effective.[176] Withdrawal of medication should start upon remission of seizures.

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seventeen

Diseases frequently associated with epileptic seizures

Any functional or structural cerebral derangement is a potential cause of epileptic seizures. Axis 4 of the ILAE Diagnostic Scheme (Table 1.1)[1] is to specify the aetiology of epilepsies when known.[1,2]

The aetiology can consist of:

- a specific disease derived from a classification of diseases frequently associated with epileptic seizures or syndromes, which is the topic of this chapter
- a genetic defect, examples of which are detailed in Chapter 14 as well as this chapter
- a specific pathological substrate, as, for example, with the symptomatic focal epilepsies discussed in Chapter 15.

Definite or probably definite symptomatic focal and generalised epileptic syndromes of known aetiology are specified in the ILAE report (Table 5.2) and in various chapters of this book.

Symptomatic focal epilepsies not otherwise specified are classified among the special epilepsy conditions.[2] These are caused by epileptogenic lesions that are localised, diffuse but limited to one hemisphere or multifocal, and which do not constitute specific syndromes per se but can be defined according to their seizure type, the underlying pathophysiological disturbance, if known, and the location of the lesion(s) if they do not fit into a described syndrome.[2]

Diseases frequently associated with epileptic seizures are numerous in aetiology, manifestations, laboratory abnormalities and management; any brain disease probably has the potential to cause epileptic seizures. The ILAE diagnostic scheme provided a preliminary list of diseases which are more likely to manifest with epileptic seizures (Table 17.1) and these are:

Progressive myoclonic epilepsies: Detailed within this chapter.

Neurocutaneous disorders: Tuberous sclerosis complex, neurofibromatosis, epidermal nevus syndrome, hypomelanosis of Ito, Sturge–Weber syndrome.

Malformations due to abnormal cortical developments: Isolated lissencephaly sequence, Miller–Dieker syndrome, X-linked lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia, focal heterotopia, hemimegalencephaly, bilateral perisylvian syndrome, schizencephalies, unilateral polymicrogyria, focal or multifocal cortical dysplasia, microdysgenesis.

Other cerebral malformations: Aicardi syndrome, PEHO syndrome, acrocallosal syndrome and others.

Tumours: Dysembryoplastic neuroepithelial tumour, gangliocytoma, ganglioglioma, cavernous angiomas, astrocytomas and others. Hypothalamic hamartoma is the cause of a specific hypothalamic epilepsy (see Chapter 10).

Chromosomal abnormalities: Partial monosomy 4P or Wolf–Hirschhorn syndrome, trisomy 12p, inversion duplication 15 syndrome, ring 20 chromosome and others.

Monogenic mendelian diseases with complex pathogenetic mechanisms: Fragile X syndrome, Angelman syndrome, Rett syndrome and others.

Inherited metabolic disorders: Non-ketotic hyperglycinaemia, D-glyceric acidemia, propionic acidemia, sulphite-oxidase deficiency, fructose 1-6 diphosphatase deficiency, other organic acidurias, pyridoxine dependency, aminoacidopathies (maple syrup urine disease, phenylketonuria, other), urea cycle disorders, disorders of carbohydrate metabolism, disorders of biotin metabolism, disorders of folic acid and

Groups of syndromes frequently associated with epileptic seizures or syndromes
• Progressive myoclonic epilepsies
• Neurocutaneous disorders
• Malformations due to abnormal cortical developments
• Other cerebral malformations
• Tumours
• Chromosomal abnormalities
• Monogenic mendelian diseases with complex pathogenetic mechanisms
• Inherited metabolic disorders
• Prenatal or perinatal ischaemic or anoxic lesions or cerebral infections causing non-progressive encephalopathies
• Postnatal infections
• Other postnatal factors (i.e. head injury, alcohol and drug abuse, stroke, others)
• Miscellaneous

Table 17.1 *Modified with permission from Engel (2001).*[1]

B_{12} metabolism, glucose transport protein deficiency, Menkes' disease, glycogen-storage disorders, Krabbe disease, fumarase deficiency, peroxisomal disorders, Sanfilippo syndrome, mitochondrial diseases (pyruvate dehydrogenase deficiency, respiratory chain defects and MELAS [mitochondrial encephalomyopathy, lactic acidosis, and stroke-like symptoms]).

Prenatal or perinatal ischaemic or anoxic lesions or cerebral infections causing non-progressive encephalopathies: Porencephaly, infections causing non-progressive encephalopathies, periventricular leucomalacia, microcephaly, cerebral calcifications and other lesions due to, for example, toxoplasmosis, cerebrovascular incidents, HIV.

Postnatal infections: Cysticercosis, Herpes encephalitis, bacterial meningitis and others.

Other postnatal factors: Head injury, alcohol and drug abuse, stroke and others.

Miscellaneous: Coeliac disease (epilepsy with occipital calcifications and celiac disease), Coffin–Lowry syndrome, Alzheimer's disease, Huntington disease, Alpers' disease. Northern epilepsy syndrome is a type of neuronal ceroid lipofuscinosis (see page 542).

It should be realised that this list is endless and each group, and often each individual disease, is the subject of extensive books, monographs and reports. These can be found in text books of medicine, neurology, paediatrics and metabolic, chromosomal and genetic disorders, and most of them are also detailed and updated in very useful dedicated websites, as recommended in Chapter 4 (page 97), Chapter 14 (page 423) and on page 535 in this chapter.

Only progressive myoclonic epilepsies (PMEs) are detailed in this book.

Clarifications on classification

The 1989 ILAE classification recognised 'symptomatic generalised epilepsies of specific aetiologies' that are 'only diseases in which epileptic seizures are the presenting or a prominent feature... These diseases often have epileptic features that resemble symptomatic generalised epilepsies without specific aetiology, appearing at similar ages'.[3] These included only two main aetiological categories:

a. Malformations such as Sturge–Weber syndrome, Aicardi syndrome, lissencephaly/pachygyria and hypothalamic hamartomas.

b. Proven or suspected inborn errors of metabolism described according to the age at onset and includes non-ketotic hyperglycinaemia, phenylketonuria, Tay–Sachs disease, ceroid lipofuscinosis, infantile Huntington disease, Lafora disease, Unverricht disease and others.

The new ILAE report[1] rightly considers that these diseases are more extensive than those listed in the 1989 classification (Table 17.1)[3] and that they manifest with focal as well as symptomatic generalised epileptic seizures (see Chapter 10). However, in the 2006 ILAE report, only the PMEs were considered, and these are now listed among various other epileptic syndromes according to age at onset (Table 5.2).[2]

Progressive myoclonic epilepsies

Synonyms: progressive myoclonus epilepsies (the adjectival form 'myoclonic' is grammatically more correct than 'myoclonus' epilepsy), PMEs.

PMEs comprise a group of rare, heterogeneous genetic (mainly autosomal recessive) disorders (Figure 17.1).[4–11] PMEs are characterised by cortical myoclonus, other types of epileptic seizures and progressive neurocognitive impairment (Table 17.2).

Clarifications on nomenclature

On pathological grounds, PMEs were initially classified into three subsets:

1. Lafora disease
2. lipidoses
3. degenerative forms.

The term degenerative was used for disorders in which light microscopy of the brain revealed only neuronal loss and gliosis, without evidence of intracellular neuronal storage material. The current recognition of specific PME disorders is based on advanced pathological, biochemical and clinical analyses, and, mainly, the application of modern molecular genetics.

The ILAE classifies PMEs among 'diseases frequently associated with epileptic seizures or syndromes'.[1] In a broader classification, PMEs are classified among symptomatic myoclonus, which comprise any form of myoclonus (epileptic or non-epileptic) caused by any type of identifiable underlying disorder (see page 72).

PMEs are often encompassed under the inclusive term 'catastrophic epilepsies', which, as the name implies, are invariably associated with significant neurological morbidity and often early death. However, the catastrophic epilepsies include all severe forms of progressive epilepsy including some, but not all, epileptic encephalopathies and the PMEs.[19]

Recommended websites

See Chapter 4 (page 97) and Chapter 14 (page 423). Also see:

- Genetic Home Reference (http://ghr.nlm.nih.gov/) of the US National Library of Medicine (www.nlm.nih.gov/). This provides details of (a) all genetic disorders and related genes and chromosomes and (b) concepts and tools for understanding human genetics including a hanbook (http://ghr.nlm.nih.gov/handbook) and glossary (http://ghr.nlm.nih.gov/ghr/page/Glossary).
- GeneReviews (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests) are expert-authored, peer-reviewed, current disease descriptions that apply genetic testing to the diagnosis, management, and genetic counselling of patients and families with specific inherited conditions
- WE MOVE™, a comprehensive resource for movement disorders including myoclonus (www.wemove.org/myo/)

Other websites are cited within the discussion of the individual diseases.

The new ILAE reports[2] consider PMEs as a syndrome (although these are a group of disorders

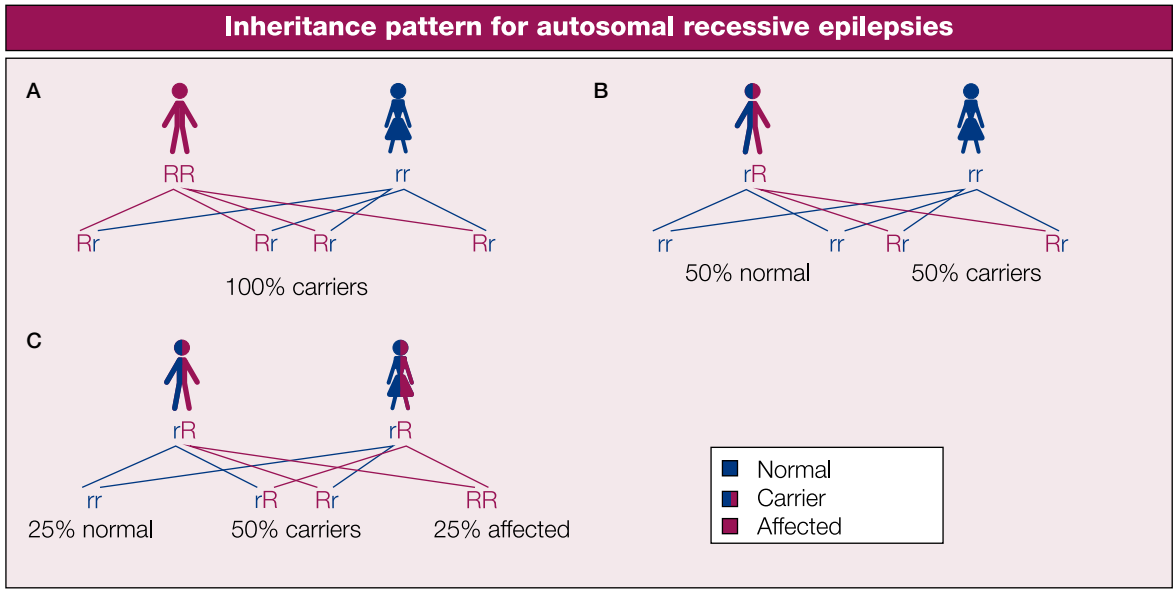

Figure 17.1 Examples of autosomal recessive inheritance where (**A**) one parent is affected (homozygous for the mutant gene) and the other is normal (homozygous for the normal gene), (**B**) one parent is an unaffected carrier (heterozygous for the mutant gene) and the other is normal (homozygous for the normal gene) and (**C**) both parents are unaffected carriers (heterozygous for the mutant gene). Autosomal recessive is a pattern of inheritance in which an individual is affected by the disease only when two copies of a mutant gene (homozygous for the gene mutation) on one of the 22 pairs of autosomes (non-sex chromosomes) are present. Carriers are individuals who have only one copy of the mutant gene (heterozygous for the gene mutation); they do not exhibit the disease because the gene is recessive to its normal counterpart gene. Note that autosomal recessive diseases are usually seen in a single generation of a pedigree and they are more likely to occur in populations with consanguineous marriages. R = autosomal recessive mutant gene; r = normal gene.

and not a syndrome) that 'is different from the others in that it consists entirely of specific diseases, and might be considered under diseases with epilepsy rather than epilepsy syndromes. However, because it is a very helpful concept for diagnostic purposes... it is still included in the list' (Table 5.2).[2]

Unverricht disease

Synonyms: Unverricht–Lundborg disease, progressive myoclonic epilepsy 1 (EPM1), Baltic myoclonus, Mediterranean myoclonus.

Unverricht disease is the most common, purest and least severe type of PME.[11,20–23]

This syndrome was first described by Unverricht in 1891. The doctoral dissertation of Herman Bernhard Lundborg in 1903 was considered a groundbreaking work in medical research, describing the disease and tracing the affected family back to the 1700s. Lundborg's view that 'the future belongs to the racially fine people'[24] and his influence on the Nazi ideology and acts overshadows his contribution to medicine.

Demographic data

In 86% of patients, myoclonic jerks first appear at 9–13 years of age (range 6–18 years). The sexes are

Progressive myoclonic epilepsies

Common and classical forms

- Unverricht disease
- Lafora disease
- Neuronal ceroid lipofuscinoses
- Sialidoses (Type I and II)
- Myoclonic epilepsy associated with ragged-red fibres (MERFF)
- Dentatorubral-pallidoluysian atrophy

Less common forms

- Alpers syndrome[12]
- Familial encephalopathy with neuroserpin inclusion bodies[13,14]
- Gaucher disease (type 3a)[15,16]
- Huntington disease (juvenile form)
- The action myoclonus–renal failure syndrome[17]

Other disorders included among the PMEs
(These are either extremely rare or epileptic myoclonus, when it occurs, is an occasional and exceptional clinical feature)

Krabbe's leucodystrophy, myoclonic encephalopathy and macular degeneration, atypical inclusion body disease, pantothenate kinase-associated neurodegeneration (formerly Hallervorden–Spatz disease), infantile neuroaxonal dystrophy (Seitelberger disease), coeliac disease, GM2 gangliosidosis (Tay–Sachs disease) and early onset Alzheimer's disease (30–40 years of age)[18]

- Autosomal dominant cortical tremor, myoclonus and epilepsy (benign adult familial myoclonic epilepsy, familial cortical tremor with epilepsy)[5]

Table 17.2

equally affected. Unverricht disease mainly occurs in Finland (incidence 4/100,000), Sweden, Mediterranean countries and North Africa.

Clinical manifestations

Unverricht disease is primarily characterised by:

- cortical myoclonus
- generalised tonic–clonic seizures (GTCSs)
- mild progressive ataxia.

Patients are initially neurologically normal and many remain so for many years after onset of the disease.

Cortical myoclonus is the first symptom in at least half of patients. The myoclonic jerks are focal and multifocal, affecting the face, body and limbs (proximal more than distal). They are small and mild, and often become violent.

GTCSs are usually infrequent and may not occur in all patients.

Myoclonus and GTCSs progressively worsen over the 3–8 years following the onset of the disease. Severe action, reflex and spontaneous myoclonus predominate and become the most incapacitating symptom. It takes the form of continuous shivering-like, small amplitude myoclonus affecting every muscle of the body, including the tongue and mouth.

Violent myoclonic jerks erupt out of this 'background myoclonic noise', causing falls and injuries.

Mild ataxia progresses slowly. Mild cognitive deterioration probably occurs.[25]

A characteristic feature of Unverricht disease is relative remissions of symptoms for days to weeks. These 'good periods' tend to shorten as the disease progresses.[11]

Disease severity may vary among affected individuals within a family who have apparently similarly sized repeat expansions.

Aetiology

Gene	Chromosomal locus	Protein
CSTB	21q22.3	Cystatin B
OMIM entries		
254800	Myoclonic epilepsy of Unverricht and Lundborg	
601145	Cystatin B (CSTB)	

Data from HUGO (genes; www.hugo-international.org/); OMIM (chromosomal locus; www.ncbi.nlm.nih.gov/omim) and Swiss-Prot (protein; http://expasy.org/sprot/).

Unverricht disease is an autosomal recessive disorder (Figure 17.1) caused by mutations of the *CSTB* gene, which is located in chromosome 21q22.3. *CSTB* encodes an inhibitor of lysosomal cysteine proteases. Nearly all patients have an unstable expansion of a 12-nucleotide (dodecamer; 5′-CCC-CGC-CCC-GCG-3′) repeat unit on at least one disease allele; most individuals have two expansions causing disease. The expanded repeat results in significantly reduced production of *CSTB* mRNA.[26] There is no apparent correlation between the mutant repeat length and disease phenotype.

Diagnostic procedures

Detection of *CSTB* gene mutations confirms the clinical suspicion of Unverricht disease.

The EEG is always abnormal (Figure 17.2).[21,22] Theta activity becomes increasingly more prominent, and alpha activity gradually disappears. Generalised spike/polyspike–wave discharges are abundant and are often associated with the myoclonic jerks. Photoparoxysmal responses occur consistently. Specific neurophysiological testing is abnormal, as with cortical myoclonus (Figure 15.12).

Biochemical abnormalities have not been demonstrated.

Differential diagnosis

At onset, Unverricht disease should be differentiated from juvenile myoclonic epilepsy (JME). Other PMEs usually manifest with relatively rapid neurocognitive impairment.

Prognosis

The prognosis of Unverricht disease improved after the toxic effect of phenytoin for these patients was realised. Withdrawal of phenytoin has led to a marked improvement.[27] It is debatable whether cognitive impairment occurs even with improved anti-epileptic drug (AED) management.[22,25]

Life expectancy may not be affected.

Management

GTCSs are relatively easy to control, but the myoclonus is usually the disabling factor. Valproate,

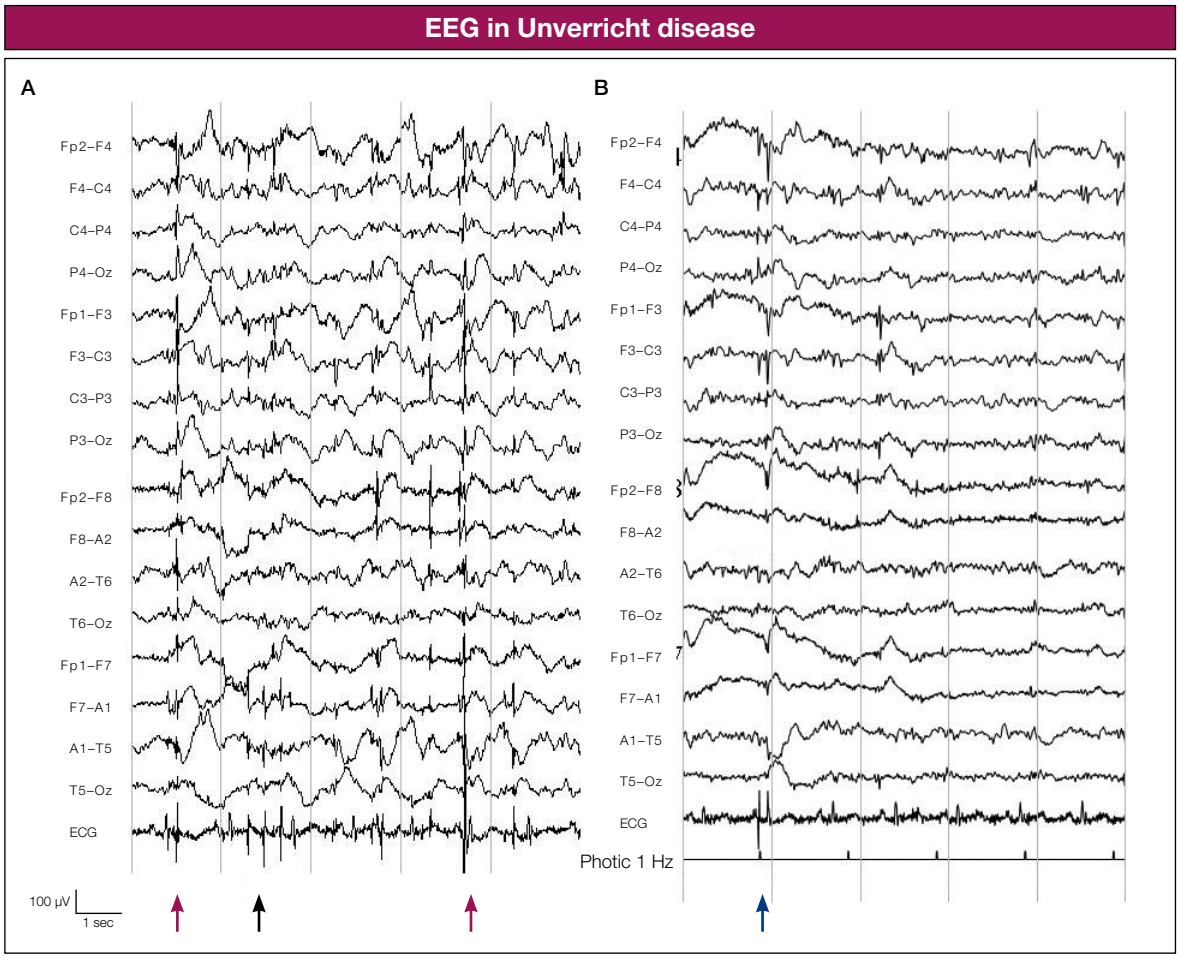

Figure 17.2 Frequent spontaneous jerks are seen following generalised bursts of spikes (red arrows), but these can also occur without EEG changes (black arrow). A generalised burst of polyspikes (blue arrow) during 0.5 Hz IPS is elicited by eye closure rather than the flash.
Courtesy of Dr Stewart G. Boyd, Great Ormond St. Hospital for Children, London.

clonazepam, piracetam and mainly levetiracetam[28,29] are the main AEDs.

> The early use of antimyoclonic drugs, such as piracetam and levetiracetam, could further reduce the final disability level of patients with Unverricht disease.[22]

Topiramate and zonisamide may be effective, but have cognitive adverse effects.

N-Acetylcysteine, a sulfhydryl antioxidant, has been beneficial in the treatment of four siblings with Unverricht disease.[30] The beneficial effect of vagal nerve stimulation in a single case is doubtful because follow-up was brief and the therapeutic effect could be explained by spontaneous remission.[31]

In Unverricht disease, the myoclonus is briefly abolished by alcohol,[32] increased by nicotine and decreased by the C6-type nicotinic antagonist mecamylamine.[33]

Avoid contraindicated AEDs, such as phenytoin, carbamazepine, gabapentin, pregabalin, lamotrigine, tiagabine and vigabatrin.[11]

Lafora disease

Synonyms: Lafora body disease, PME with polyglucosan bodies, progressive myoclonic epilepsy (EPM2A and EPM2B).

Demographic data

Lafora disease is a severe and relatively common PME.[6,10,11,34,35]

Symptoms start at 13–15 years of age (with a range of 8–18 years). A rare adult-onset form probably exists and this is associated with a more benign course. Males and females are equally affected. Lafora disease is rare but accounts for 10% of patients with PME. It is more common in Mediterranean and southern European countries, the Middle East and south-east Asia.

Clinical manifestations[6,10,11,34,35]

Disease onset is marked mainly by myoclonic and occipital seizures, and sometimes by GTCSs. Behavioural changes or cognitive decline may be the first manifestations.

Video-EEG documentation of negative myoclonus in a patient with Lafora disease

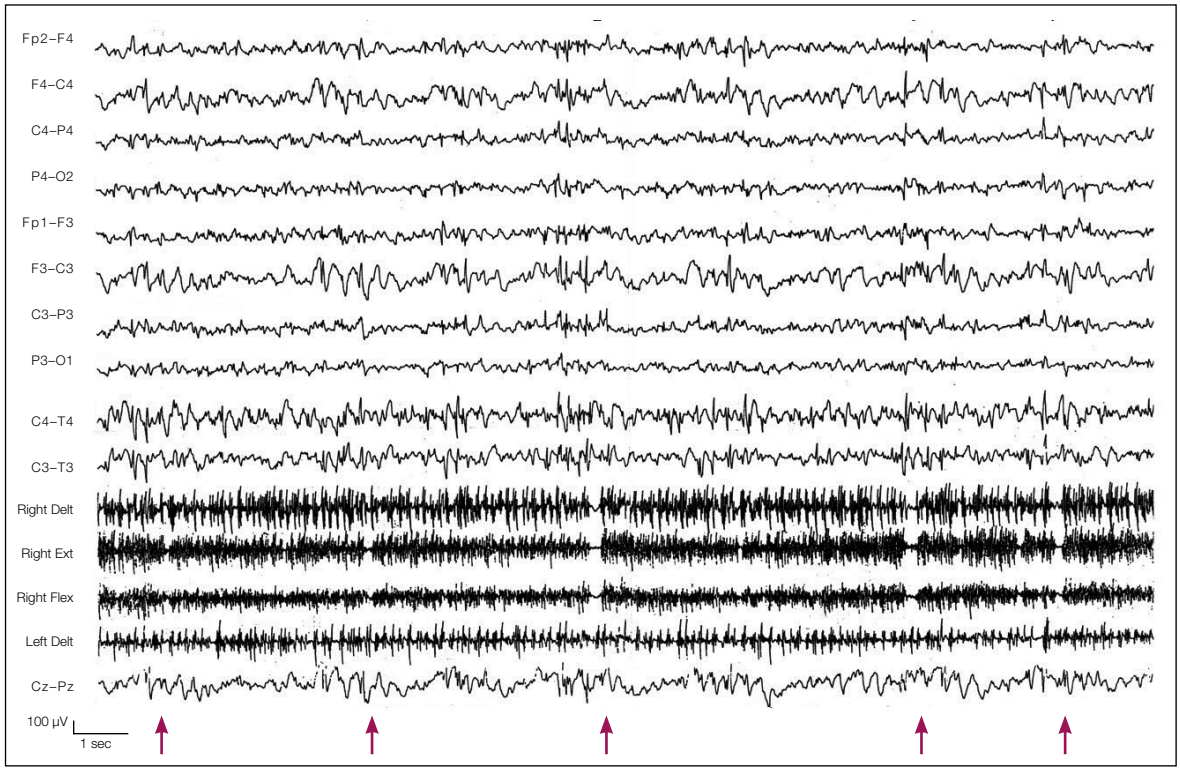

Figure 17.3 This is from a video-EEG of a 17-year-old boy while holding his hands outstretched in front of his chest. The EEG was diffusely slow with frequent, nearly continuous brief bursts of polyspikes. During the recording, the patient had negative myoclonic drops of the fingers and hands with suppression of the EMG activity (arrows) and some inconsistent association with the EEG polyspike bursts. Onset of the disease was at 14 years of age with simple focal occipital seizures of elementary visual hallucinations and generalised convulsions. Progressive and severe cognitive deterioration started soon after onset of the epileptic seizures. Valproate, piracetam and clobazam had only a transient beneficial effect on seizures. Lafora disease was confirmed with axillar biopsy, which showed Lafora bodies.
Courtesy of Professor Pierre Thomas, Hopital Pasteur, Nice, France.

Myoclonic seizures are cortical in origin. They are brief, massive, synchronous and are usually limited to one or more muscle groups. The seizures are spontaneous, reflex or action precipitated. Falls result from violent positive or negative myoclonus (Figure 17.3).

Focal visual occipital seizures occur in 30–50% of patients and may be the early presenting symptom. They may be spontaneous or photically induced, and manifest with complex and elementary visual hallucinations.

Neurocognitive decline is relentless either before or within months of the onset of the seizures. The end stages of the disease are marked by severe dementia, spastic quadriparesis and almost constant myoclonus.[36]

In some cases, Lafora disease may present predominantly as dementia with relatively infrequent seizures.

Aetiology

Gene	Chromosomal locus	Protein
EPM2A	6q24	Laforin
EPM2B (*NHLRC1*)	6p22.3	Malin
OMIM entries		
254780	Myoclonic epilepsy of Lafora	
607566	EPM2A gene; EPM2A; laforin	
608072	NHL repeat-containing 1 gene; NHLRC1; EPM2B gene; EPM2B; malin	

Data from HUGO (genes; www.hugo-international.org/); OMIM (chromosomal locus; www.ncbi.nlm.nih.gov/omim) and Swiss-Prot (protein; http://expasy.org/sprot/).

Transmission is autosomal recessive (Figure 17.1). At least three genes underlie Lafora disease, two of which have been isolated: *EPM2A* on chromosome 6q24 and *EPM2B* (*NHLRC1*) on 6p22.3.

The *EPM2A* gene product is laforin. The *EPM2B* gene product is malin.

Patients with mutations in *EPM2A* and *EPM2B* have similar clinical manifestations but the *EPM2B* mutation produces a milder course.[37,38]

Pathology

Lafora bodies are periodic acid-Schiff (PAS)-positive, diastase-resistant polyglucosan inclusions. They are found in the brain and various other tissues with some histochemical and morphological differences in the storage material between organs.

Diagnostic procedures

The diagnosis of Lafora disease is based on family history, clinical findings and primarily the detection of the characteristic Lafora bodies in tissue biopsy.

The skin biopsy appears to be consistently positive.[39] It should be deep enough to include entire sweat gland ducts. The axilla should be avoided as a biopsy site, because PAS-positive bodies may normally occur there. Cryostat sections stained with PAS are best for demonstrating the inclusions. It is advisable to confirm the diagnosis by electron microscopy.

As the biopsy may be negative due to a sampling error, the diagnosis should be confirmed by genetic testing of *EPM2A* and *EPM2B* and screening for carriers. However, the lack of mutations in *EPM2A* and *EPM2B* does not exclude Lafora disease, because mutations may occur in non-coding or non-tested regions, or at least one additional gene associated with Lafora disease may be present.

Background EEG may initially be normal, but rapidly deteriorates. Epileptiform abnormalities are generalised or focal or multifocal, and predominate in the posterior cerebral regions (Figure 17.3).

Photosensitivity is common. Fixation-off sensitivity may also occur.[40] Neurophysiological abnormalities are consistent with cortical myoclonus.

^{1}H-magnetic resonance spectroscopy is more sensitive than structural MRI to detect brain involvement. The greatest metabolic changes are seen in the frontal cortex, cerebellum and basal ganglia.[41]

Differential diagnosis

In the initial stages, Lafora disease may imitate occipital lobe epilepsy or JME. However, occipital seizures are often combined or followed by myoclonus and, with progression, the myoclonus becomes severe and multifocal. Progressive cognitive decline is relentless.

Recognition of Lafora disease in its fully developed form is not difficult. Laboratory documentation is important in cases where the disease presents mainly as dementia with relatively infrequent seizures, or when it imitates symptomatic generalised epilepsy with mild myoclonus.

Non-epileptic myoclonic disorders can also be differentiated based on clinical and pathological characteristics.

Prognosis

Lafora disease is a rapidly progressive disorder. Most patients reach the end stages of the disease and death within 1–10 years (mean of 5 years) of the onset of symptoms. The mean age at death is 20 years.

Management

Currently, Lafora disease is incurable. See page 556 for the management of PMEs.

Neuronal ceroid lipofuscinoses

Synonyms: Batten disease is the juvenile form, although the eponym is often used to encompass all forms of neuronal ceroid lipofuscinoses (NCLs).

There are many types of NCL with a number of identified human genes.[10,11,42–50]

Classically, based on the age of onset, there are four prototypical types of NCL:

1. *Infantile NCL* (Santavuori–Haltia disease) begins between 6 months and 2 years of age and progresses rapidly.
2. *Late infantile NCL* (Jansky–Bielschowsky disease) begins between 2 and 4 years of age.
3. *Juvenile NCL* (Spielmeyer–Vogt–Sjogren or Batten disease) begins between 5 and 8 years of age.
4. *Adult NCL* (Kufs disease and Parry disease) generally begins before the age of 40 years.

Several additional variant forms of NCL have been described and many NCL forms divide into distinct genetic subgroups sometimes associated with specific countries of origin.

NCLs are extensively described by Sara Mole in a continuously updated website (http://www.ucl.ac.uk/ncl/index.shtml).

Demographic data

Onset commonly occurs in infancy and childhood. Adult onset is rare. Both sexes are equally affected.

NCLs, although relatively rare, are the most common of the lysosomal storage diseases worldwide. Incidence of NCL is 1.2/100,000 live births (range 1–7/100,000 live births), with a prevalence of approximately 1/25,000 in various European countries and the USA.[51,52] In Finland, the infantile form alone has an incidence of 1/13,000 live births.[51]

Clinical manifestations

Patients are usually normal initially, but this is followed by rapid and progressive neurocognitive

deterioration. Visual loss due to retinal atrophy is a prominent feature in all but an adult form of NCL. Myoclonus and other seizures, when they develop, often become refractory and disabling.

Infantile NCL manifests with failure to thrive, myoclonus, psychomotor regression and deterioration, autistic features, acquired microcephaly and progressive retinal blindness.[53] Myoclonus and other seizure types occur early. Often children have characteristic hand movements similar to those of Rett syndrome. Spastic paraparesis worsens later in the illness. Mobility, vision and language skills are rapidly lost and children do not survive until late childhood.

Late infantile NCL manifests with massive myoclonias and myoclonic–atonic seizures, usually from onset of the disease and mainly between 2 and 4 years of age.[54] Other seizure types include focal myoclonias, GTCSs, atypical absences, and simple motor and complex focal seizures. Visual impairment occurs later. Extreme irritability is common. Limb spasticity with truncal hypotonia and loss of head control are often prominent. Death occurs around 10 years of age.

Juvenile NCL is characterised by visual impairment that progresses over 2 or 3 years to an appreciation of light and dark only. A pigmentary retinopathy occurs, which may be diagnosed as retinitis pigmentosa or cone dystrophy. Visual symptoms are followed in the early teens by myoclonus, other types of seizure, cognitive and speech impairment, ataxia or clumsiness and parkinsonian-like symptoms. Behaviour abnormalities of aggression and anxiety, mood disturbances and psychosis may become problematic at this time. As the disease progresses, myoclonus and other symptoms rapidly deteriorate to complete loss of all communication skills, mobility and self-help. Some mutations cause a mild or more protracted disease in which visual failure occurs relatively early, but other symptoms are delayed well into adulthood. This form progresses less rapidly and ends in death in the late teens or early 20s, although some individuals may live into their 30s. Patients may experience heart and circulation problems.

Adult NCL causes milder symptoms of relatively slow progressive myoclonus, ataxia and dementia. Blindness does not occur in the Kufs disease subtype. Although age of death is variable, life expectancy is shortened.

Northern epilepsy syndrome (progressive epilepsy with mental retardation) is a newly identified NCL in northern Finland.[55] GTCSs begin at 5–10 years of age, are often triggered by fever at onset and, by the time of puberty, become very frequent with many occurring each week or day. Myoclonus is not a clinical feature. A third of patients suffer from visual impairment. Patients may reach 50–60 years of age, but are significantly mentally and physically disabled.

Aetiology

Gene (locus)	Chromosomal locus	Protein
CTSD (CLN10)	11p15.5	Cathepsin D
PPT1 (CLN1)	1p32	Palmitoyl-protein thioesterase 1
TPP1 (CLN2)	11p15.5	Tripeptidyl-peptidase I
CLN3 (CLN3)	16p12.1	Protein CLN3
Unknown (CLN4)	Unknown	Unknown
CLN5 (CLN5)	13q21.1-q32	Ceroid-lipofuscinosis neuronal protein 5
CLN6 (CLN6)	15q21-q23	Ceroid-lipofuscinosis neuronal protein 6
CLN8 (CLN8)	8pter-p22	Protein CLN8

Continued overleaf

OMIM entries

204200	Ceroid lipofuscinosis, neuronal 3, juvenile; CLN3	606725	CLN6 gene; CLN6
204300	Ceroid lipofuscinosis, neuronal 4; CLN4	607042	CLN3 gene; CLN3
204500	Ceroid lipofuscinosis, neuronal 2, late infantile; CLN2	607837	CLN8 gene; CLN8
256730	ceroid lipofuscinosis, neuronal 1, infantile; CLN1	607998	CLN2 gene; CLN2
256731	Ceroid lipofuscinosis, neuronal 5; CLN5	608102	CLN5 gene; CLN5
600143	Ceroid lipofuscinosis, neuronal 8; CLN8	610127	CLN10 gene; CTSD
600722	Palmitoyl-protein thioesterase 1; PPT1		
601780	Ceroid lipofuscinosis, neuronal, late-infantile, variant		

Data from HUGO (genes; www.hugo-international.org/); OMIM (chromosomal locus; www.ncbi.nlm.nih.gov/omim) and Swiss-Prot (protein; http://expasy.org/sprot/).

NCLs are mainly autosomal recessive (Figure 17.1) lysosomal storage disorders. So far, seven human NCL gene loci have been identified. The function of most of the encoded proteins is unknown. Most mutations result in a classic morphology and disease phenotype, but some mutations are associated with disease that is of later onset, less severe or protracted in its course, or with atypical clinical presentations. Seven common mutations exist, some of which have a worldwide distribution, while others are associated with families originating from specific geographical regions.[42]

CLN1 (chromosome 1) encodes palmitoyl-protein thioesterase 1 (PPT1), an enzyme which removes palmitate residues from proteins. Mutations in this gene cause NCL with a wide clinical spectrum and typical onset in infancy, and, rarely, in adulthood.

CLN2 (chromosome 11) encodes the lysosomal enzyme tripeptidyl-peptidase I (TPP1), which is a member of a recently defined family of serine-carboxyl proteinases that remove tripeptides from the *N*-terminus of small proteins. Mutations in the *CLN2* gene cause classic late-infantile NCL and, rarely, a more protracted disease with later onset.

CLN3 (chromosome 16) accounts for cases of juvenile NCL; 73% are caused by a common intragenic deletion. The remainder are the result of other defects of the same gene, usually in combination with this common mutation. The function of CLN3 is unknown.

CLN5, CLN6, CLN8 and other, as yet unknown, genes cause variant late-infantile NCL. A specific mutation in *CLN8* (chromosome 8) also causes northern epilepsy or progressive epilepsy with mental retardation.

CTSD encodes cathepsin D. Mutations in this gene cause congenital NCL and NCL at later ages of onset.

Not all cases of NCL presenting in late infancy have been genetically defined. Rare cases of congenital NCL occur, but their cause is unknown.

Adult NCL may be inherited in an autosomal recessive (Kufs disease) or, less often, an autosomal dominant (Parry disease) pattern. In most cases of adult NCL, the gene defect has not been identified, although a few are caused by mutations in *CLN1* or *CLN2*.

Recent studies have shown a link between the juvenile form of NCL and the autoimmune system. This link is not yet fully understood, but may have some treatment implications with regard to immunosuppressant drugs.

Pathology

NCL is characterised by the intracellular accumulation of autofluorescent storage material specific to the NCL called lipopigments (*lipos* = fat). They accumulate in brain cells, eyes and other tissues.

The ultrastructural morphology of the lipopigments on electron microscopy mainly depends on the form of NCL. They can be:

- granular osmophilic deposits (resembling sand or gravel) in infantile NCL
- predominantly curvilinear bodies (like half-moons or commas) in late-infantile NCL
- fingerprint profiles in juvenile NCL.

Mixed types of inclusion are found in adult-onset NCL and in some late-infantile variant forms.

Diagnostic procedures

The diagnosis of NCL is based on clinical findings, electron microscopy of tissue biopsy and, in some instances, assays of enzyme activity and molecular genetic testing. Identification of the specific genes for most forms of NCL has led to the development of DNA diagnostics, as well as carrier and prenatal tests.

Electron microscopy – preferably of a skin biopsy – typically reveals lipopigments (see Pathology).

Enzyme assays of white blood cells, fibroblasts and chorionic villi are available only for *PPT1* (CLN1) and *TPP1* (CLN2). There is no PPT1 or TPP1 enzyme activity in patients with mutations in the relevant genes. A carrier of a mutation in *PPT1* or *TPP1* typically has 50% of normal enzymatic activity in PPT1 or TPP1, respectively.

Molecular genetic testing for the *CLN1*, *CLN2*, *CLN3*, *CLN5*, *CLN6* and *CLN8* genes is now clinically available. The identification of a mutation in both copies of an NCL gene provides a definitive diagnosis of NCL and its clinical type.

Brain imaging reveals progressive brain and cerebellar atrophy.

The EEG, electroretinogram (ERG), visual evoked potentials (VEPs) and somatosensory evoked potentials (SSEPs) are usually abnormal, but this varies according to the type of NCL:

- *In infantile NCL*, there is a progressive flattening and disappearance of biological rhythms, the so-called 'vanishing EEG activity'. The ERG is small with severe loss of the b-wave[53] and becomes unobtainable within a few months of the onset of the disease. The VEPs are also small and eventually disappear 2 or 3 years after disease onset.
- *In late-infantile NCL*, the EEG background activity progressively deteriorates with dominant slow activity and diffuse paroxysms of spike/polyspikes and waves, multifocal spikes and, less often, focal spikes predominating in posterior regions.[54] Intermittent photic stimulation (IPS) at single or low flash frequency (1–8 Hz) elicits giant (300–450 μV) polyphasic occipital spikes (Figure 17.4). The ERG is small and becomes unobtainable within a few months of the onset of the disease. VEPs are big and wide throughout the course of the disease. The SSEPs may also become large.
- *In juvenile NCL*, the EEG background activity progressively deteriorates with dominant slow activity and diffuse paroxysms of spike/polyspikes and waves that are facilitated in slow-wave sleep. There are no photoparoxysmal responses. The ERG and VEPs gradually become smaller and vanish, while the SSEPs may increase in amplitude.
- *In adult NCL*, the EEG background activity progressively deteriorates with dominant slow activity and diffuse paroxysms of spike/polyspikes and waves. There are marked photoparoxysmal responses to low frequency IPS. The ERG and VEPs are normal, while the SSEPs are often large.

Differential diagnosis

The differential diagnosis of the various types of NCL is often challenging. Onset with myoclonus occurs in many other idiopathic or symptomatic epilepsies, and developmental regression and deterioration are common in many disorders. Retinal visual impairment is also a symptom of various ophthalmological diseases. However, a combination of myoclonus, progressive developmental abnormalities and visual impairment should raise a high index of suspicion of certain types of NCL. A family history of similar disorders is the key to diagnosis.

Prognosis

NCLs are progressive and most are fatal disorders. The final stage depends on the type of NCL type; in severe forms, patients become blind, bedridden and unable to communicate soon after the onset of the disease.

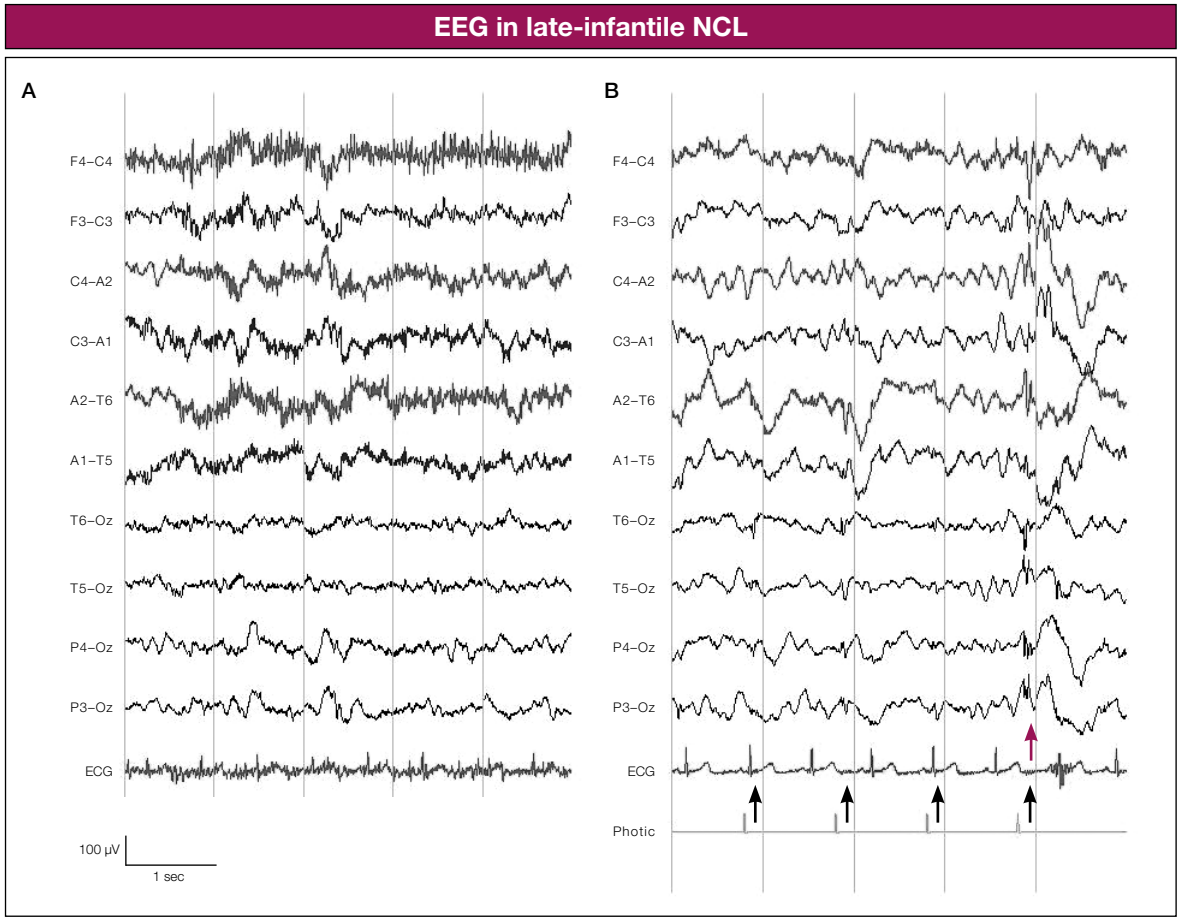

Figure 17.4 Inter-ictal EEG (**A**) in a case of late-infantile NCL compared with responses to photic stimulation at 1 Hz (**B**). Note the generalised spiking associated with the end of photic stimulation at 1 Hz (red arrow). This is preceded by a series of small occipital spikes, which appear time-locked to the flash stimulus (black arrows). Such an unusual abnormal response to photic stimulation is often more overt, but, when such a diagnosis is suspected, it must be actively sought out in the EEG. *Courtesy of Dr Stewart G. Boyd, Great Ormond St. Hospital for Children, London.*

Management

Currently, NCLs are incurable. Management is only supportive and palliative (see page 555).

The development of therapy for NCLs is challenging and still at a very early stage. The goal is to halt or delay the progress of the various types of NCL, with complete cure as the ultimate aim.

Gene trials in animal models have been started with some preliminary promising results and improvements in vectors used for delivery of the genes.

A safety trial of gene therapy in patients with mutations in *TTP1* is in its early stages.

Stem cell therapy clinical trials (Phase I) have been initiated in a small number of children.

Immunosuppressive treatments have also been tried or are under way.

Other therapeutic targets include storage material degradation and inhibition of cell death.

Sialidoses (type I and II)

Common synonyms: *sialidosis type I* – cherry-red spot myoclonus syndrome, normosomatic type of neuraminidase deficiency; *sialidosis type II* – dysmorphic type of neuraminidase deficiency.

Sialiodoses[49,56–59] are rare diseases of PME that mainly manifest with:

- visual impairment of macular degeneration
- cortical myoclonus and often with
- mild cerebellar ataxia and cognitive impairment

There are two forms of sialidosis:

- sialidosis type I – the milder form[58,60]
- sialidosis type II – the more severe form of the disease.

Demographic data

Sialidosis type I usually starts between 8 and 15 years. Sialidosis type II starts very early and sometimes before birth. Both sexes are equally affected. Sialidoses are extremely rare disorders.

Clinical manifestations

Sialidoses type I usually starts with impairment of visual acuity, myoclonus and other types of generalised epileptic seizure. Cherry-red spots in the macular region of the fundus appear early (Figure 17.5).[61] The myoclonus is predominantly facial, affecting mainly the perioral muscles. It persists in sleep and becomes progressively worse and debilitating. Cerebellar ataxia, cataracts and colour and/or night-blindness may develop. Vision gradually deteriorates into blindness.[61] Cognition is either mildly or not affected.

Sialidosis type II manifests with all the symptoms of sialidosis type 1 but in a more severe and more progressive manner. Additional manifestations include *dysmorphic features* (distinctive coarse facial features, increased head size, short trunk with relatively long legs and arms) and *skeletal malformations* (dysostosis multiplex). Ascites, hepatosplenomegaly and hernias are common. Sensorineural hearing loss, cataracts and joint stiffness are other associated symptoms. Patients may also have dyspnoea. Cardiac problems and dilated coronary arteries may occur in congenital sialidosis type II. Nearly all patients show progressive mild-to-severe mental deterioration.

Aetiology

Gene	Chromosomal locus	Protein
NEU1	6p21.3	Neuraminidase
OMIM entries		
256550	Neuraminidase deficiency	
608272	Neuraminidase 1; NEU1	

Data from HUGO (genes; www.hugo-international.org/); OMIM (chromosomal locus; www.ncbi.nlm.nih.gov/omim) and Swiss-Prot (protein; http://expasy.org/sprot/).

Sialidoses result from inherited deficiencies of the lysosomal enzyme α-*N*-acetylneuraminidase (neuraminidase or sialidase) due to mutations in the gene *NEU1*, which is located on chromosome 6p21.3. Several different mutations significantly reduce or almost completely eradicate lysosomal neuraminidase activity. The clinical phenotype and its severity depend on the specific mutations in the gene.

Cherry-red spot in a patient with (A) sialidosis and (B) Tay–Sachs disease

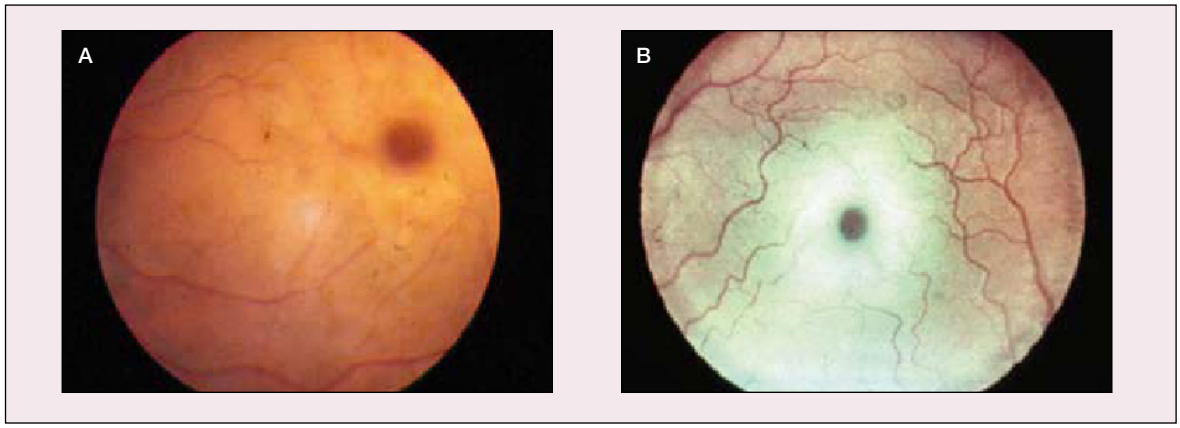

Figure 17.5 *Figure A courtesy of Professor Antonio Federico, Department of Neurological Sciences, University of Siena, Italy. Figure B courtesy of Dr John H. Livingston, Leeds General Infirmary, Leeds, UK.*

Diagnostic procedures

The detection of the cherry-red spot (Figure 17.5) is essential when sialidosis is suspected clinically.[61] The diagnosis is confirmed by the detection of high levels of sialyloligosaccharides in the urine and lysosomal enzyme deficiency in leucocytes or cultured fibroblasts.[57]

Brain MRI is normal in the early stages but, as the disease progresses, cerebellar, pontine and cerebral atrophy become apparent.[62]

Radiographic changes in sialidosis type II are similar to those seen in the mucopolysaccharidoses, with beaking of the lumbar vertebrae, broadening of the ribs and thickening of the skull.

The EEG background activity initially shows low-voltage fast activity, but slow waves gradually predominate with progress of the disease. Massive myoclonus is associated with trains of 10–20 Hz, small, vertex-positive spikes preceding the electromyographic artefact.

The amplitude of VEPs becomes smaller, whereas that of the SSEPs is high.

Differential diagnosis

The triad of myoclonus, macular degeneration and ataxia occurs in other PMEs and different metabolic storage disorders (GM1, GM2 gangliosidosis, Niemann-Pick type C).[59]

Differentiating between the two types of sialidosis is easy, because the skeletal and facial abnormalities and cognitive impairment do not feature in the type I form of the disease.

Prognosis[63]

Sialidosis type II has a poor prognosis; the earlier the onset, the shorter the life expectancy.

In sialidosis type I, the course of the disease may be long and most patients have a near-normal life expectancy. However, there is progressive visual impairment and the myoclonus may be progressively debilitating; falls induced by myoclonic seizures can be fatal.

Management

Currently, the sialidoses are incurable. Therefore, management can only be supportive and palliative (see page 555).

Enzyme replacement therapy may be a possible approach in the near future.[64]

Myoclonic epilepsy associated with ragged-red fibres

Synonym: MERRF syndrome.

MERRF is a multisystem disorder[18,65–67] characterised by:

- cortical myoclonus
- ataxia
- mild myopathy
- cognitive impairment.

Demographic data

MERRF usually starts at 3–10 years of age, but adult onset in the late 50s has been reported. The age of onset varies considerably, even in the same family. Both sexes are equally affected.

MERRF is a rare disorder that is found worldwide. The prevalence of the main A8344G mutation in northern Europe is less than 1.5 per 100,000 of the population.

Clinical manifestations

Early development is normal.

Cortical myoclonus affects the head, limbs and body, and may be spontaneous, reflex or action-induced. Focal seizures may occur. Progressive ataxia and other cerebellar symptoms may be mild or the main cause of disability. Cognitive impairment occurs with the progression of MERRF. Myopathy is usually mild. Exercise intolerance is sometimes prominent.

> Any kind of exertion brings on fatigue. Sometimes I get up in the morning and I just have no energy at all... It's hard to explain. Just simple daily functions are very tiring.

Other common manifestations include sensorineural hearing loss, peripheral neuropathy, short stature, lactic acidosis and optic atrophy. Less common clinical signs include cardiomyopathy with Wolff–Parkinson–White syndrome, pigmentary retinopathy, pyramidal signs, ophthalmoplegia, pes cavus and multiple lipomas in the neck and shoulders.

Occasionally, young patients with MERRF also have strokes as in MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke). Spinocerebellar degeneration and Leigh disease are unusual manifestations in MERRF families.

Patterns, sequence and severity of symptoms show marked variations even among affected members of the same family, because they often inherit different percentages of mutant mitochondrial DNA (mtDNA). The phenotype of an individual with an mtDNA mutation results from a combination of factors such as severity of the mutation, the percentage of mutant mitochondria (mutational load) and the organs and tissues in which they are found (tissue distribution).

Aetiology

Gene	Chromosomal locus	Protein
MT-TK	Mitochondrial DNA	Mitochondrial tRNA lysine
OMIM entries		
545000	Myoclonic epilepsy associated with ragged-red fibres (MERRF)	
590060	Transfer RNA, mitochondrial, lysine; MT-TK	

Data from HUGO (genes; www.hugo-international.org/); OMIM (chromosomal locus; www.ncbi.nlm.nih.gov/omim) and Swiss-Prot (protein; http://expasy.org/sprot/).

MERRF is caused by mutations in mtDNA and is transmitted by maternal inheritance. Clinical severity is not proportional to the degree of mutation in muscle. However, the latter might not reflect the degree of mutation in the central nervous system.

Diagnostic procedures

At presentation patients should have complete neurological, cognitive, ophthalmological, audiological and cardiological evaluations.

Muscle biopsy is the best diagnostic test to confirm MERRF diagnosis. Ragged-red fibres on modified Gomori trichrome stain are the defining histological feature. In over 90% of MERRF patients, a modified Gomori trichrome stain shows ragged-red fibres in the skeletal muscle biopsy. Increased numbers of morphologically abnormal mitochondria are found on electron microscopy.

Biochemical analysis of respiratory chain enzymes in muscle extracts usually demonstrates decreased activity of respiratory chain complexes containing mtDNA-encoded subunits, especially cytochrome *c* oxidase deficiency. The muscle mtDNA should be screened for mutations associated with MERRF.

Lactate and pyruvate at rest are commonly elevated and may increase dramatically after moderate exercise. Renal or liver dysfunction may be found.

Mutations are usually present in all tissues. Blood leucocytes should first be screened for the mtDNA point mutation. However, the occurrence of 'heteroplasmy' in disorders of mtDNA can result in varying tissue distribution of mutated mtDNA. Hence, in individuals having few symptoms consistent with MERRF or in asymptomatic maternal relatives of an affected individual, the pathogenic mutation may be undetectable in mtDNA from leucocytes and may only be detected in other tissues, such as cultured skin fibroblasts, urinary sediment, oral mucosa (from mouthwash), hair follicles or, most reliably, skeletal muscle.

Brain MRI often shows brain atrophy and basal ganglia calcification.[68]

ECG may reveal pre-excitation, but heart block has not been noted.

Cerebrospinal fluid protein may be mildly elevated to no more than 100 mg/dl.

Electromyography and nerve conduction studies may show signs of myopathy, axonal neuropathy or both.

EEG background activity is slow with generalised polyspike–wave discharges. Focal epileptiform discharges are common. A quarter of patients show photoparoxysmal discharges.

SSEPs and other neurophysiological tests relevant to cortical myoclonus are abnormal (Figure 15.12).

Differential diagnosis

The differential diagnosis depends on the clinical presentation of MERRF. Cortical myoclonus, other epileptic seizures and ataxia should be differentiated from other types of PME. The multisystem involvement, lactic acidosis, maternal inheritance and the muscle biopsy with ragged red fibres are characteristic of MERRF.

Prognosis

MERRF is gradually progressive but prognosis is extremely variable. Patients may have a normal life span but others may, for example, die in middle childhood. The major complications are seizures and, less commonly, ataxia, blindness and cardiac failure.

Management

Currently, there is no curative treatment for the genetic defect. Therefore, management is only supportive and palliative.

Coenzyme Q_{10} (50–100 mg three times a day) and L-carnitine (1000 mg three times a day) have been used, although probably unsuccessfully, to improve mitochondrial function.

For myoclonus, most authors use valproate, even though it should be used with caution in MERRF because of its interaction with mitochondrial respiration and metabolism.[69] Conversely, levetiracetam is highly beneficial for myoclonus without altering mitochondrial function.[69–70]

Aerobic exercise has been recommended by some authors in MERRF and other mitochondrial diseases.[71]

Dentatorubral-pallidoluysian atrophy

Synonym: DRPLA, Naito–Oyanagi disease.

DRPLA[72–76] is an autosomal dominant disorder (Figure 14.1) associated with myoclonus, other epileptic seizures, ataxia, choreoathetosis and cognitive deterioration progressing to dementia.

Demographic data

Age at onset varies from 1–62 years of age with a peak at 30 years. The age at onset and disease manifestations are closely correlated (see clinical manifestations). DRPLA demonstrates *anticipation*, which means that in each successive generation the disease starts at a younger age and presents with more severe symptoms.[77] Both sexes are equally affected.

DRPLA mostly affects the Japanese with a prevalence of 2–7 per million population. Haw River syndrome, seen in the USA, is genetically the same as DRPLA but the phenotype does not manifest with myoclonus.[78]

Clinical manifestations

The patients are normal before the onset of the disease and the clinical manifestations vary considerably according to the age at onset. However, cerebellar ataxia and dementia are principal features irrespective of the age at onset.[79]

Early onset of DRPLA (before the age of 20 years) manifests with cortical myoclonus and other epileptic seizures, cerebellar ataxia, progressive intellectual deterioration and behavioural changes.[79,80] Myoclonus is severe and progressive. Other forms of generalised seizures include tonic, clonic, tonic–clonic, atonic and absence seizures.

The later onset DRPLA is a relatively milder and non-PME phenotype. It manifests with cerebellar ataxia, choreoathetosis, cognitive and psychiatric disturbances. Seizures are less frequent in individuals with disease onset between 20 and 40 years of age, and extremely rare in individuals with onset after the age of 40 years. In some patients, involuntary movements and severe cognitive deficits mask the presence of ataxia. Psychosis may sometimes be a presenting feature.[81] Cervical dystonia and corneal endothelial degeneration have been reported.

Aetiology

Gene symbol	Chromosomal locus	Protein
ATN1	12p13.3	Atrophin-1
OMIM entries		
125370	Dentatorubral-pallidoluysian atrophy; DRPLA	
140340	Haw River syndrome	
607462	DRPLA gene; DRPLA	

Data from HUGO (genes; www.hugo-international.org/); OMIM (chromosomal locus; www.ncbi.nlm.nih.gov/omim) and Swiss-Prot (protein; http://expasy.org/sprot/).

The DRPLA gene *ATN1* is located on the short arm of chromosome 12. The molecular defect consists of an expansion of the trinucleotide CAG repeats to over 49 (normal = 6–35).

The number of repeats increases from one generation to the next, and their length depends on the length of the parent's repeat and the sex of the transmitting parent.[77] Paternal transmissions result in a more severe increase in CAG repeats than maternal transmission. Early onset and severe symptoms become more marked as the number of CAG repeats increases.

Pathology

Brain autopsy reveals a uniform pattern consisting of combined degeneration of the dentatorubral and pallidoluysian systems.

Diagnostic procedures

The diagnosis of DRPLA is based on a positive family history, characteristic clinical findings and DNA-based testing, which is 100% sensitive and is widely available. Polymerase chain reaction (PCR) analysis of the CAG/polyglutamine repeat expansion seen in *ATN1* is performed on a small blood sample.

A CAG repeat length of 17 or higher (usually 20–35) is more common in healthy Japanese individuals than Caucasians.

On MRI, the degree of atrophy is related to the patient's age and the length of the expanded CAG repeat.[82]

Inter-ictal EEG depends on the type, severity and stage of DRPLA. Early onset DRPLA usually manifests with generalised atypical spike–wave complexes, and a third of patients have photoparoxysmal responses. The background EEG activity becomes progressively slower.[83]

Differential diagnosis

DRPLA is easy to diagnose because of a positive family history of the disease, characteristic clinical findings and an expansion in the CAG repeat of the DRPLA gene on DNA testing. Both parents of affected individuals should be thoroughly evaluated because, in so-called sporadic cases, asymptomatic fathers have a mildly expanded CAG repeat length.

Early onset DRPLA with myoclonus should be differentiated from other forms of PME.[8] Adult-onset DRPLA without myoclonus should be differentiated from Huntington disease and the various forms of autosomal dominant ataxia. The presence of cerebellar ataxia provides evidence against Huntington disease, but in some patients with DRPLA choreoathetosis may mask the presence of ataxia. On MRI, atrophy of the caudate nucleus favours the diagnosis of Huntington disease. It is often necessary to perform DNA tests for both Huntington disease and DRPLA in individuals with unexplained progressive dementia and involuntary movements.

Prognosis

The earlier the onset of DRPLA, the worse the prognosis.

Management

Currently, management is only supportive and palliative (see page 555).

Angelman syndrome

Synonyms: happy puppet syndrome, marionette joyeuse, pantin hilare.

Angelman syndrome[84–90] is presented here because it is a common non-progressive genetic disorder frequently manifesting with myoclonic jerks and myoclonic status epilepticus. It is not a PME, although some authors consider it as one.[5]

The salient features of Angelman syndrome have best been summarised in a recent expert consensus statement.[84]

Demographic data

Developmental regression and delays appear at about 6 months of age. Other clinical features start later, at 1–3 years of age. Both sexes are equally affected. The prevalence of Angelman syndrome is high. It is estimated to occur in 1 per 12,000–20,000 of the population and 1 per 15,000 births.

Clinical manifestations[84]

Development is usually normal before the onset of the disease.

Angelman syndrome is characterised by:

- severe developmental delay with mental retardation
- severe speech impairment, gait ataxia, tremulousness
- myoclonic jerks
- other epileptic seizures
- a happy demeanour with excessive chortling or paroxysms of laughter.

Patients are hyperactive and constantly keep their hands or toys in their mouth and move from one object to another.

The first symptoms may be sucking difficulties, delayed gross motor milestones, hypotonia or speech delay. The children have 'flat heads, jerky movements, protruding tongues, and bouts of laughter', as was first described by Angelman in 1965.[91]

More than two-thirds of patients have focal and generalised epileptic seizures, of various types, which may become intractable.[86–88,92–94] Quasi-continuous rhythmic myoclonus mainly involving the hands and face, with spontaneous, rhythmic, fast-bursts of cortical myoclonus is a prominent feature.[93] Some patients also have seizures with ictal vomiting. Of those patients with myoclonic status epilepticus in non-progressive encephalopathies (Chapters 3 and 10), 50% have Angelman syndrome.[95]

Sleep disorders are common with a decreased need for sleep, frequent night waking and early awakening.

Microcephaly develops in 50% of children by 12 months of age. Strabismus may also occur.

Aetiology

Gene symbol	Chromosomal locus	Protein
UBE3A	15q11-q13	Ubiquitin-protein ligase E3A
OMIM entries		
105830	Angelman syndrome; AS	
601623	Ubiquitin-protein ligase E3A; UBE3A	

Data from HUGO (genes; www.hugo-international.org/); OMIM (chromosomal locus; www.ncbi.nlm.nih.gov/omim) and Swiss-Prot (protein; http://expasy.org/sprot/).

Angelman syndrome was the first recognised single-gene disorder of the ubiquitination pathway. The syndrome is caused by the failure of the expression of the *maternal* copy of the imprinted *UBE3A* gene on chromosome 15q11-q13, which arises as a result of one of at least five different known genetic mechanisms.[85,96–100] The *UBE3A* gene encodes E6-AP ubiquitin-protein ligase (also known as ubiquitin ligase 3A).

Most cases of Angelman syndrome result from the lack of a maternal contribution to this same region by maternal *de novo* deletion (approximately 70% of cases). Paternal unipaternal disomy with maternal deficiency for 15q11-q13 and normal parental chromosomes is much less common (3–5%). Thus, although the genetic mechanisms of Angelman syndrome vary in their aetiology and inheritance risk, they all cause a lack of proper expression of the *UBE3A* gene.[101]

Prader-Willi syndrome is a clinically distinct disorder resulting from paternal deletion of the same 15q11-q13 region.[99,100]

Diagnostic procedures[85]

The clinical features of Angelman syndrome are often characteristic.[84] Genetic testing identifies alterations in 85–90% of patients (78% by analysis of parent-specific DNA methylation imprints in the 15q11.2-q13 chromosome region and 11% by *UBE3A* sequence analysis). In 10–15% of suspected cases of Angelman syndrome, a genetic abnormality cannot be identified, which leaves clinicians and families with an uncertain diagnosis and inheritance risk. Diagnostic yield may improve with the introduction of new methods.[85,97,99]

Brain MRI may show mild atrophy and mild demyelination, but no structural lesions.

The EEG shows prolonged runs of high-amplitude delta waves with superimposed spike and slow-wave discharges, which predominate in the anterior regions, and high-amplitude, rhythmic 4–6 Hz activity with spikes, which are prominent in the occipital regions and are facilitated when eyes are closed (Figure 17.6).[93,94,102,103] SSEPs and C-reflexes are normal.

Differential diagnosis

The differential diagnosis encompasses such entities as cerebral palsy, static encephalopathy, PMEs and syndromes of severe epilepsies, Rett syndrome (in infant girls), Prader-Willi syndrome, Mowat syndrome, autism spectrum disorder and pervasive developmental delay.

EEG samples of a 2-year-old girl with Angelman syndrome

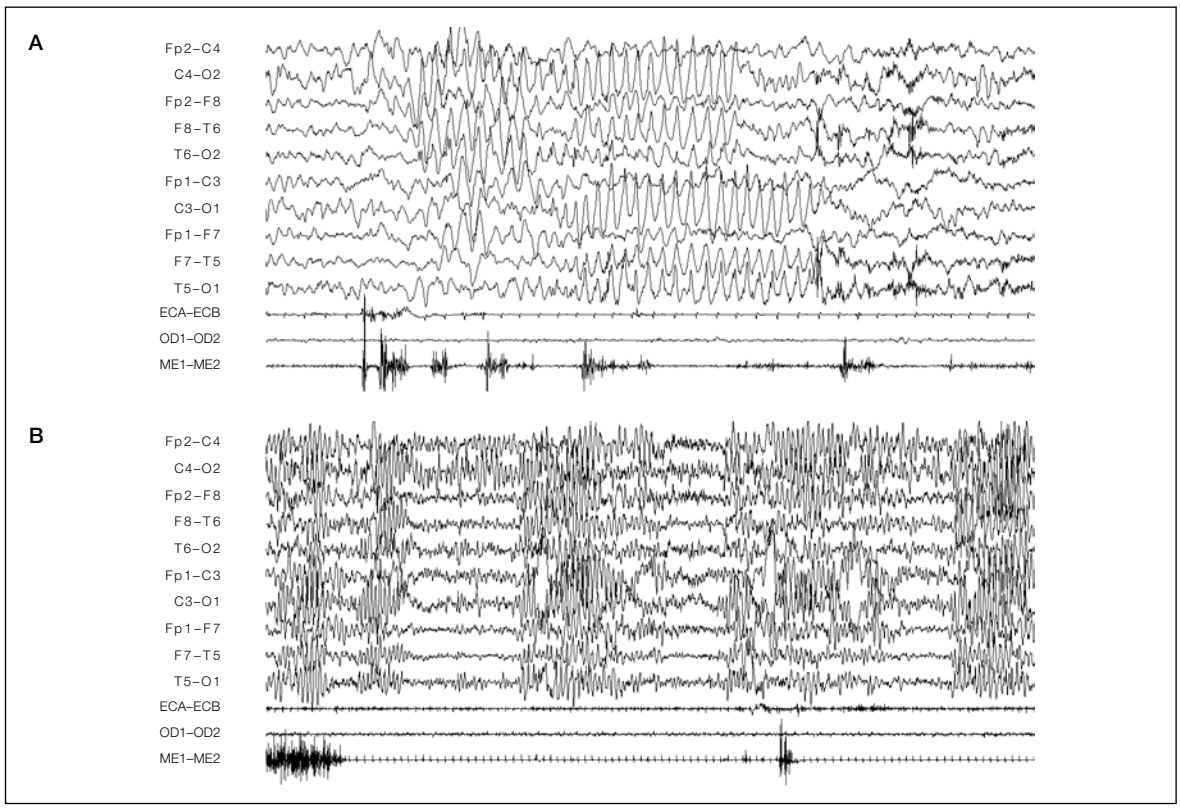

Figure 17.6 (**A**) Runs of slow waves mixed with spikes occur asynchronously between the two hemispheres. Note that the background activity lacks physiological rhythms. (**B**) Same EEG in slow speed.
Courtesy of Dr Perrine M. Plouin, Hopital Necker Enfants Malade, Paris, France.

Prognosis

Most patients with Angelman syndrome have severe physical (10% are unable to walk) and mental disabilities. Epileptic seizures are often intractable, but frequently improve during late childhood and puberty. Adult patients are incapable of independent living. Life expectancy appears to be nearly normal.

Management[88]

Management is only supportive and palliative (see below).

Valproate alone or in combination with clonazepam is commonly used. Piracetam significantly improved myoclonus in five patients.[88] Levetiracetam is a favourable option.[104]

Clinical trials involving the use of high-dose, orally administered folate and betaine are ongoing. The therapeutic rationale is to augment DNA methylation pathways and possibly increase *UBE3A* expression of the paternal allele in the central nervous system.

AEDs that are contraindicated include phenytoin, carbamazepine, gabapentin, pregabalin, tiagabine and vigabatrin.

Management of myoclonus

Good management of myoclonus demands a thorough clinical and investigative approach in order to identify its cause and the needs of the patient.[105–111] Myoclonus will usually resolve if the offending agent is withdrawn (drug- or toxin-induced myoclonus), if the metabolic disturbance is corrected (e.g. hyponatraemia or non-ketotic hyperglycaemia) or the treatment of the underlying disease is effective (e.g. bacterial or viral encephalitis). For myoclonus of other aetiologies, management depends on whether it is epileptic or non-epileptic, severe or mild, static or progressive, or occurs alone or in combination with other types of seizure (focal or generalised, convulsive or non-convulsive). Current management also includes measures to achieve optimal health-related quality of life with regard to the physical, mental and psychological functioning of the patient within his/her family, and educational and social environment.[112]

Epileptic myoclonus

AEDs are the basis of the symptomatic treatment of epileptic myoclonus. However, the selection of an AED and its dosage is demanding:

- the AED chosen should possess true antimyoclonic efficacy and should also be beneficial for any other types of coexisting seizure
- the AED safety and adverse drug reaction (ADR) profile is of paramount importance and may vary significantly depending on the neurocognitive stage, age and sex of the patient
- monotherapy is preferred, but polytherapy is often unavoidable, particularly in patients with PME either because of worsening myoclonus with the progression of the disease or the presence of multiple types of seizure
- more than half of the current AEDs make myoclonus worse or do not treat it effectively.

Drugs with antimyoclonic efficacy: Clonazepam, valproate, levetiracetam, topiramate and zonisamide are AEDs with antimyoclonic efficacy. Piracetam is specifically effective against cortical myoclonus of PME and myoclonus of hypoxic encephalopathy. Ethosuximide is mainly effective in negative myoclonus. Clobazam and phenobarbital are second options. Lamotrigine monotherapy may worsen myoclonus, but it can be used in combination with another antimyoclonic AED for the control of other types of coexisting seizure.

AEDs licensed (FDA, EMEA or both) for the prophylactic (sole or adjunctive) treatment of myoclonus*

Drug	Efficacy	ADRs in children	Use in PMEs
Clobazam	Not as efficacious as clonazepam	Sedation, fatigue, behavioural and cognitive impairment; tolerance and withdrawal syndrome	Best used when focal seizures are also a problem. Avoid in inerted children
Clonazepam	Excellent	Sedation, fatigue, behavioural and cognitive impairment; tolerance and withdrawal syndrome	Probably the best antimyoclonic AED choice for myoclonus but not for other seizures. Avoid in inerted children
Ethosuximide†	Excellent for negative myoclonus but uncertain for positive myoclonus	Idiosyncratic and anticonvulsant hypersensitivity syndrome	Best used for negative myoclonus and when absences are also a problem
Levetiracetam	Excellent	Behavioural	Best used also when other seizures of any type are a problem
Phenobarbital	Moderate	Agitation, hyperkinesias, sedation, fatigue, behavioural and cognitive impairment; withdrawal syndrome	Useful, but practically impossible to use in some children because of marked agitation and a lack of concentration
Piracetam‡	Excellent, but only in PMEs	Relatively safe	Only as an adjunctive drug
Valproate	Excellent	Hepatic and pancreatic failure	Probably the first-choice AED, particularly when other types of seizure occur. The risk for ADRs is increased in babies and younger children, particularly on polytherapy

Table 17.3 *See the pharmacopoeia (Chapter 18) for exact indications and for specified aged groups, ADRs (which are also shown in Table 7.2) and a recommended published volume of reference.[128] †Mainly for negative myoclonus. ‡Not for any other types of seizure.

Fast-acting benzodiazepines are used for temporary relief of myoclonus during social events and the treatment of myoclonic status epilepticus (Chapter 3).[116] Chloral hydrate can be used to control daytime myoclonic exacerbations.[113]

Ketogenic diet should be considered for patients with severe myoclonic epilepsies such as Dravet syndrome.[114]

Contraindicated drugs: Carbamazepine, oxcarbazepine, phenytoin, gabapentin, pregabalin, tiagabine and vigabatrin may worsen myoclonus and should be avoided.

Table 17.3 lists drugs licensed (FDA, EMEA or both) for the prophylactic (sole or adjunctive) treatment of epileptic myoclonus and their best application in PMEs.

Progressive myoclonic epilepsies[11]

Currently, there is no preventative or curative treatment for most PMEs (see the individual diseases for further details). Despite significant recent advances in the management of some aspects of

PMEs, the neurological manifestations are resistant to any treatment. For example, bone marrow transplantation may be curative for Gaucher disease type 1 and enzyme replacement therapy may be successful in reversing systemic manifestations, but neither of these has proved to be beneficial in preventing the neurodevelopment deterioration of Gaucher disease type 3 or myoclonus.

Management of PME is therefore often only supportive and palliative. It includes:

- symptomatic treatment of myoclonus and other epileptic seizures with appropriate AEDs
- appropriate management of psychiatric problems, including treatment with psychotropic medications (which sometimes exacerbate or induce myoclonus and other epileptic seizures)
- adaptation of educational programmes and physical therapy to the patient's physical and cognitive abilities
- supporting the family
- genetic counselling.

Medical therapeutic support is important, but alone is not sufficient to achieve an acceptable quality of life.

Symptomatic treatment of myoclonus usually starts with a single appropriate antimyoclonic AED, but this is often effective only in the initial stages of the disease. Subsequently, the myoclonus becomes relentlessly worse and requires multiple combinations and high doses of AEDs. This may, in turn, increase the number of adverse effects, and worsen the already disturbed neurological and mental state of the patient.

Valproate, clonazepam and piracetam are established antimyoclonic drugs in PMEs. Levetiracetam is increasingly reported to be of particular value because of its high efficacy in myoclonus, its broad-spectrum of efficacy in all types of seizure and its excellent safety profile (see page 587). Apart from the drugs mentioned above, most AEDs are contraindicated and their prescription may constitute a medical error.

Antimyoclonic pharmacological agents

Older antimyoclonic AEDs[115]

The indications and contraindications for older antimyoclonic AEDs have been established through numerous prospective and retrospective studies, and clinical experience over many years of use.[108,115–117]

Valproate has been recognised as the most effective drug for treating generalised epileptic seizures of all types and causes. In JME, for example, valproate monotherapy controls absence seizures and myoclonic jerks in about 75% and GTCSs in 70% of patients.

The major problem with valproate is that it is unsuitable for use in women (see page 206). Hepatic failure resulting in fatalities occurs mainly in children receiving polypharmacy and with organic brain disease; the risk is 1/600 before the age of 3 years. Acute haemorrhagic pancreatitis is another rare, but serious, adverse effect of valproate in children and is seen particularly with polytherapy (see valproate in the pharmacopoeia [Chapter 18]).

Clonazepam is probably the most effective antimyoclonic drug for any type of epileptic myoclonus of any cause.[115] However, it has a narrow spectrum of efficacy and, for this reason, is usually prescribed in polytherapy. Clonazepam monotherapy may be the first choice in myoclonic epilepsies in which other types of seizure do not occur or emerge from clusters of myoclonic jerks, such as reading epilepsy, myoclonic epilepsy in infancy and mild forms of JME. Clonazepam alone may not suppress GTCSs. Furthermore, clonazepam may deprive patients of the warning of an impending GTCS provided by the myoclonic jerks.

Small doses of clonazepam (0.5–2 mg at night), are usually sufficient in most patients with myoclonic jerks of idiopathic generalised epilepsy (IGE). However, in PME, doses of 20–30 mg/day are often required with the worsening of the disease or the development of tolerance to the drug.

Clobazam is an extremely useful AED in focal epilepsies. It is, however, far inferior to clonazepam in controlling myoclonic jerks or other types of generalised seizures.[115]

Ethosuximide is probably as effective as valproate in the treatment of absence seizures. It is also a useful adjunct for the treatment of negative myoclonus,[118] certain types of myoclonic epilepsy[119] and drop attacks. It does not control GTCSs.

Phenobarbital has moderate efficacy in controlling GTCSs and myoclonic jerks, but may exacerbate absences.[115] It is the AED of choice for JME when cost is of concern. Its use is humbled by serious sedation and age-related, mainly cognitive and behavioural ADRs in children. Therefore, the use of phenobarbital in children with learning difficulties is significantly problematic. In adults with JME, a single dose of 100–200 mg of phenobarbital before going to sleep is often sufficient. Some patients may be controlled with 60–90 mg at night.

Piracetam[120] has been widely used for 30 years as a 'nootropic drug' with the debatable promise of enhancing learning and memory, and providing neuroprotection without sedation or behavioural changes. Its antimyoclonic efficacy has been documented in many open studies and controlled trials, particularly in cortical myoclonus and PME.[121–124] Piracetam has also been found to be effective in the myoclonus of IGEs, opsoclonus–myoclonus, and palatal and other types of myoclonus. In PMEs, high doses of up to 35 g/day are often used and are remarkably well tolerated.[120–124]

Piracetam is licensed in many countries both as a nootropic and antimyoclonic drug. It is not licensed in the USA.

Newer antimyoclonic AEDs

Levetiracetam[125–130] fulfils all expectations as probably the best new AED for the treatment of myoclonus. It is the likely candidate to replace valproate in the treatment of epileptic myoclonic disorders, because of its high and sustained efficacy, fast action, good safety profile and lack of clinically meaningful interactions with other drugs. Levetiracetam has a potent antimyoclonic effect,[70,106,125–132] even in severe myoclonic epilepsies, such as Unverricht disease,[28,29,133] MERRF[69] and other PMEs.[70] Levetiracetam is effective in cortical[127] and negative,[134] as well as non-epileptic myoclonus.[135–137] Also, levetiracetam is the only newer AED with well-established efficacy in clinical photosensitivity and the photoparoxysmal EEG discharges.[138,139]

The results of treatment with levetiracetam in JME are very impressive (see page 400). Levetiracetam is the only one of the newer AEDs with FDA and EMEA approved indications for adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with JME.[140] It is available in oral and intravenous formulations.

Topiramate[141–143] is another broad-spectrum AED that is highly effective in focal epilepsies. It also has significant benefit in primarily GTCSs,[144,145] but has a weak action in absence seizures.[146] In a small number of open studies, topiramate was found to be useful in myoclonic epilepsies, mainly Dravet syndrome.[147–150] Irrespective of efficacy, the major problem with topiramate is the high incidence of ADRs, some of which are very serious and include significant cognitive disturbances (see page 602).[151–153]

Zonisamide[143,154–156] is a broad-spectrum AED and is often effective in PMEs.[157–160]

Lamotrigine is a very useful AED because of its efficacy in controlling GTCSs, and absence and focal seizures. However, lamotrigine is often a promyoclonic AED that may exaggerate myoclonic jerks.[128,161–168] Its role in the treatment of myoclonic epilepsies may only be as an adjunct to antimyoclonic drugs, particularly valproate.[115] Furthermore, recent evidence documents significant problems with lamotrigine in women of childbearing age and during pregnancy (see page 205).

Antimyoclonic AEDs in development

The antimyoclonic AEDs currently being developed include: the levetiracetam analogue; the valproate-like agents valrocemide, valnoctamide, propylisopropyl acetamide and isovaleramide; and the felbamate analogue flurofelbamate, a dicarbamate.[169]

Brivaracetam (UCB-34714) has been granted orphan medicinal designation in Europe for the treatment of PMEs and in the USA for the treatment of symptomatic myoclonus.[170]

Other pharmacological agents[105,111]

There is considerable doubt about the efficacy of other pharmacological agents apart from AEDs in

myoclonus and, in fact, some may worsen myoclonic symptoms or cause unwanted and occasionally serious ADRs.

Serotonergic drugs include 5-hydroxy-L-tryptophan (L-5-HTP), sumatriptan and fluoxetine. Treatment of myoclonus with the serotonin precursor L-5-HTP (often administered with carbidopa in order to reduce ADRs, such as cramps) has been reported to be beneficial in some cases of mainly progressive myoclonus, posthypoxic myoclonus and photosensitive cortical reflex myoclonus.[105] However, other patients have deteriorated and the drug may, in susceptible individuals, induce the eosinophilia–myalgia syndrome, which is a serious and sometimes fatal condition.

Anticholinergic drugs, such as trihexyphenidyl, are mainly used to treat myoclonic dystonia syndrome.

Dopamine agonists, such as apomorphine, are used to treat photosensitive cortical reflex myoclonus.

Dopamine antagonists, such as tetrabenazine, are useful in dystonia, chorea, tic disorders and spinal myoclonus.

GABA agonists, such as baclofen, are used in spinal myoclonus and occasionally PME.

Lisuride has both serotonergic and dopaminergic properties and is used in PME.[171,172]

Dextromethorphan has been used for non-ketotic hyperglycinaemia[173] but with disappointing results.[174]

Melatonin has been used in Dravet syndrome and non-epileptic myoclonus.[175,176]

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Pharmacopoeia

This pharmacopoeia is mainly based on information provided by the package insert (PI) in accordance with the US FDA approval, and the Summary of Product Characteristics (SmPC) of the EMEA for each drug used in prophylactic treatment of recurrent epileptic seizures. This is supplemented with extensively cited, recent published reports and expert clinical advice . It is not a substitute of the PI or SmPC, which are the legal and most complete single sources of information on a drug. Rather, it is a concise guide for the properties and clinical applications of each AED in a friendly-use template that physicians may consult in their wish to best treat patients with epileptic seizures.

The authorised indications in the SmPC and PI discussed in this revised edition have been updated to November 2009. In many cases they differ from those that formed the basis of the original 2nd edition of this book in 2007.

This is a pharmacopoeia of all antiepileptic drugs (AEDs) currently used in the prophylactic treatment of epileptic seizures around the world. It includes older and newest generation AEDs. Most of these AEDs have authorised indications in the USA (FDA-PI) and Europe (EMEA-SmPC), which may be different and in fact some AEDs are licensed in Europe but not USA (for example vigabatrin) and vice versa (for example felbamate). Further, in Europe, some AEDs, such as valproate, phenytoin and lamotrigine, do not have a centrally approved license by the European Commission and each country in which an AED is licensed within Europe may have slightly different licensed indications. In these cases, the information provided is from the UK-SmPC. In addition, some AEDs, such as sulthiame, are licensed in some countries through local regulatory authorities but do not have an EMEA or FDA approval. There is a constant flow of information relating to AED therapy, especially for adverse drug reactions (ADRs), interactions with other drugs, and warnings and precautions that may impact labelling. Therefore, physicians should consult the authorised indications and product information found in the approved prescribing information for the country in which they practice medicine before making a decision as to whether a particular AED is appropriate for their patients.

Note: Brivaracetam, carisbamate, and retigabine are newest AEDs that may be soon licensed for adjunctive therapy of focal epileptic seizures. However, it is beyond the remits of this pharmacopoeia to detail them until their approval by the FDA or EMEA.

Recommended sources of information

For information regarding the PI and SmPC of AEDs, some suggestions have been made in Chapter 7 (page XXX). The package insert (PI) can be obtained from http://dailymed.nlm.nih.gov/dailymed/about.cfm. The summary of package characteristics (SmPC) can be obtained in any European language from http://www.emea.europa.eu/htms/human/epar/a.htm. In the UK these are also available from http://emc.medicines.org.uk.

Information about clinical trials (purpose, who may participate, locations, and phone numbers for more details) may be searched for in http://www.clinicaltrials.gov/. ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world.

The *Handbook of Epilepsy Treatment*[1] by Simon Shorvon is highly recommended. The synonymously titled books, *Treatment of Epilepsy*,[2,3] and *Pediatric Epilepsy: Diagnosis and Treatment*[4] are other recommended sources that provide more detailed AED information.

AEDs in development and updates on newer AEDs have been recently detailed by the Ninth Eilat conference held in June, 2008.[5]

Acetazolamide

Acetazolamide, an heterocyclic sulfonamide, is a carbonic anhydrase-inhibiting drug used predominantly for the treatment of glaucoma.

Authorised indications

UK-SmPC: second-line drug for both tonic–clonic and focal seizures. It is occasionally helpful in atypical absence, atonic and tonic seizures.
FDA-PI: adjunctive treatment of centrencephalic epilepsies (petit mal, unlocalised seizures).

Clinical applications

Acetazolamide has limited use as an adjunctive therapy for a variety of seizures, but mainly absences.[6] However, it also controls myoclonic jerks, generalised tonic–clonic seizures (GTCSs) and focal seizures. It is particularly used for intermittent administration in catamenial epilepsy (5 days before the expected onset of menses and continued until termination of bleeding);[7] it is not recommended if there is a likelihood of pregnancy.

Dosage and titration

Adults: start treatment with 250 mg and increase to 500–750 mg.
Children: 10–20 mg/day.
Dosing: two or three times daily.
Therapeutic drug monitoring (TDM): not needed.
Reference range: 10–14 mg/l (400–700 µmol/l).

Main ADRs

Frequent and/or/or important: flushing, lethargy, anorexia, nausea, vomiting, paraesthesiae and increased diuresis.
Serious: idiosyncratic reactions, as with other sulfonamides (rash, aplastic anaemia, Stevens–Johnson syndrome), renal failure; nephrolithiasis in chronic treatment and metabolic acidosis, as with other carbonic anhydrase inhibitors (see also topiramate).

Mechanism of action

Acetazolamide is a carbonic anhydrase-inhibiting drug that reversibly catalyses the hydration of CO_2 and the dehydration of carbonic acid. It blocks the action of brain carbonic anhydrase, resulting in an elevation of intracellular CO_2, a decrease of intracellular pH and depression of neuronal activity.

Pharmacokinetics

Oral bioavailability: >90%.

Protein binding: 90–95%.
Metabolism: does not undergo metabolic alteration.
Excretion: renal.
Elimination half-life: 12–14 hours.

Drug interactions

Not significant: reduces carbamazepine levels; salicylates increase levels of acetazolamide due to competition at the renal tubule for secretion.

Main disadvantages

Unpredictable seizure efficacy, development of tolerance and idiosyncratic reactions that exceptionally may be fatal.

Useful clinical notes

- Risk of withdrawal seizures.
- Combination with carbamazepine or oxcarbazepine increases the risk of hyponatraemia.
- Avoid concurrent use with other carbonic anhydrase inhibitors (i.e. sulthiame, topiramate, zonisamide).
- It should be withdrawn prior to starting a ketogenic diet.
- Concurrent use with aspirin can lead to high plasma concentrations of acetazolamide and toxicity.

Benzodiazepines

Benzodiazepines are a group of two-ring heterocyclic compounds consisting of a benzene ring fused to a diazepine ring. The first benzodiazepine, chlordiazepoxide, was introduced in clinical practice as anxiolytic and hypnotic in 1960 under the brand name Librium. Diazepam (Valium) followed in 1963. There are today over 30 benzodiazenines (15 are marketed in the USA) used for anxiety, panic, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures.

In epilepsies:[8,9]

- clonazepam (see page XXX) and clobazam (see page XXX) are the most useful of all benzodiazepines for preventing recurrent seizures; clonazepam is the main drug used for myoclonic jerks, whereas clobazam is more effective in focal seizures.
- Nitrazepam is another long-acting benzodiazepine which has been used as an AED, mainly in epileptic encephalopathies and particularly in West syndrome. Its usefulness is very limited because of severe sedative ADRs, sialorroeia, hypotonia, development of tolerance and its low efficacy in relation to other more appropriate AEDs. Nitrazepam is not discussed further in this book.
- diazepam, lorazepam and midazolam are exclusively used in the treatment of status epilepticus (Chapter 3).

Main ADRs

Sedation (sometimes intolerably severe), drowsiness, fatigue, hypersalivation, behavioural and cognitive impairment, restlessness, aggressiveness and coordination disturbances.

Tolerance, dependence and withdrawal syndrome

Benzodiazepines are addictive and regulated in schedule IV of the Substance Controlled Act. Long term use is associated with benzodiazepine tolerance, dependence and withdrawal syndrome. Benzodiazepine tolerance manifests with decreasing efficacy over time so that larger doses are required to achieve the same effect as with the original dose. In benzodiazepine dependence a person becomes dependent on benzodiazepines physically, psychologically or both. Benzodiazepine withdrawal is similar to the barbiturate or alcohol withdrawal syndrome. Administration of therapeutic doses of benzodiazepines for 6 weeks or longer can result in physical dependence, characterised by a

Useful note

GABAergic AEDs

GABA is the main inhibitory neurotransmitter in the brain. It is synthesised in the presynaptic terminals of inhibitory neurones and degraded by GABA transaminase (GABA-T). Of the GABA receptors, $GABA_A$ and $GABA_C$ are ligand-gated ion channels, whereas $GABA_B$ receptors are G-protein-coupled receptors.

The action of GABAergic AEDs is mainly through the $GABA_A$ (inhibition of most types of epileptic seizure) and $GABA_B$ (activation of absence seizures) receptors.

When GABA binds to $GABA_A$ receptors, chloride (Cl^-) channels open and allow increased entry to Cl^- ions, which ultimately cause hyperpolarisation of the neurone or inhibition. There are three basic binding sites to this complex $GABA_A$ receptor; the GABA site, the benzodiazepine site and a barbiturate site within the ion channel. Most drugs affecting the $GABA_A$ receptor act to modulate it rather than to directly excite or inhibit it. This modulation generally acts to increase the probability of the channel opening for a given concentration of GABA, or to increase the time that the receptor remains open. $GABA_A$ receptors are the main binding sites for benzodiazepines and barbiturates. Benzodiazepine derivatives (e.g. clobazam, clonazepam and diazepam) increase the frequency of the Cl^- channel openings, whereas barbiturates (e.g. phenobarbital) prolong the opening time of the Cl^- channel. Both the benzodiazepines and barbiturates also enhance the affinity of the $GABA_A$ receptors for GABA.

The $GABA_B$ receptors are metabotrophic transmembrane receptors for GABA that are linked via G-proteins to potassium channels. Thalamic $GABA_B$ receptors modulate absence seizures. Baclofen, a $GABA_B$ receptor agonist, promotes absence seizures.

Tiagabine and vigabatrin increase GABA and cause non-specific activation of the $GABA_A$ (thus inhibiting seizures) and $GABA_B$ (thus aggravating absences) receptors. The anti-epileptic effect of most other AEDs with GABA-ergic activity (e.g. gabapentin, pregabalin and valproate) is probably in combination with other anti-epileptic properties.

withdrawal syndrome when the drug is discontinued. With larger doses, the physical dependence develops more rapidly.

Main mechanism of action

$GABA_A$-receptor agonists (see useful note above).

Carbamazepine

Carbamazepine is an iminodibenzyl derivative designated chemically as 5H-dibenzo[b,f]azepine-5-carboxamide. It is structurally related to the tricyclic antidepressants. It was first introduced into clinical practice in 1962, mainly for the treatment of trigeminal neuralgia prior to becoming the main AED for focal epilepsies.

Authorised indications

UK-SmPC: Epilepsy – generalised tonic-clonic and partial seizures. Carbamazepine Retard is indicated in newly diagnosed patients with epilepsy and in those patients who are uncontrolled or unable to tolerate their current anti-convulsant therapy.

Note: Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences.

FDA-PI: Carbamazepine is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1 Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2 Generalized tonic-clonic seizures (grand mal).

3 Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by carbamazepine.

Clinical applications

Carbamazepine is the superior drug for the treatment of focal epilepsies of any type (idiopathic or symptomatic) with or without secondarily GTCS. It is also licensed for the treatment of primarily GTCSs. In numerous comparative studies, no other drug showed better efficacy than carbamazepine in focal seizures. However, carbamazepine is ineffective and contraindicated in idiopathic generalised epilepsies (IGEs) and epileptic encephalopathies. It is probably ineffective in neonatal and febrile seizures.

Dosage and titration

'Start low and go slow' is important when initiating carbamazepine treatment in order to minimise ADRs.

Adults and children over 12 years of age: start treatment with 200 mg/day in two equally divided doses and increase at weekly intervals in increments of 200 mg/day up to a total of 800–1200 mg/day. Rarely, higher doses of up to 1800 mg/day are needed.

Children 6–12 years old: start with 100 mg/day in two equally divided doses and increase at weekly intervals in increments of 100 mg/day up to a total of 600–1000 mg/day.

Children under 6 years: start with 10–20 mg/kg/day in two or three divided doses and increase at weekly intervals in increments of 10–20 mg/kg/day up to a maintenance dose of no more than 35 mg/kg/day.

There is a significant difference between the carbamazepine dose given as monotherapy and that used in combination with other AEDs. Higher doses may be necessary in polytherapy with enzyme-inducing AEDs, which increase the metabolism of carbamazepine.

Dosing: two or three times daily.

Fluctuations in the levels of carbamazepine can be reduced by the use of sustained-release preparations.

The clearance of carbamazepine in children is faster than in adults and therefore three- and, sometimes, four-times daily dosing may be required.

TDM: useful but substantial diurnal variation in plasma concentrations is common and symptoms of toxicity due to carbamazepine epoxide may occur without increases in carbamazepine levels.

Reference range: 3–12 mg/l (12–50 µmol/l). Carbamazepine epoxide: up to 9 µmol/l.

Developing diplopia may be a good indicator of maximum tolerated carbamazepine levels or epoxide toxicity when carbamazepine levels are within the target range.

Main ADRs

Frequent and/or important: sedation, headache, diplopia, blurred vision, rash, gastrointestinal disturbances, ataxia, tremor, impotence, hyponatraemia and neutropenia. CNS-related ADRs are usually dose related and appear on initiation of treatment.

Dose-related reduction in neutrophil count occurs in 10–20% of patients treated with carbamazepine, but it rarely drops below 1.2×10^9 The vast majority of cases of leucopenia have not progressed to the more serious conditions of aplastic anaemia or agranulocytosis. Nonetheless, complete pretreatment haematological testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence for significant bone marrow depression develops.

Hyponatraemia occurs in around 5% of treated patients (see oxcarbazepine). Most physicians advise obtaining blood counts at baseline and every 6–8 weeks for the first 6 months of carbamazepine treatment.

Other: Carbamazepine has shown mild anticholinergic activity; patients with increased intraocular pressure should therefore be warned and advised regarding possible hazards.

Serious: allergic skin rash is the most common idiosyncratic ADR that occurs in 5–10% of patients (probably reduced by half with slow titration of controlled-release carbamazepine). This is usually mild and develops within the first 2–6 weeks of treatment. Carbamazepine should immediately be withdrawn if a skin rash develops in order to prevent serious and sometimes life-threatening conditions, such as anticonvulsant hypersensitivity syndrome. Hepatotoxicity usually occurs in the setting of a generalised hypersensitivity response.

HLA-B*1502[10–13] in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome when treated with carbamazepine. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine. If these individuals test positive, carbamazepine should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of Stevens-Johnson syndrome, although the reactions may still very rarely occur. It is not definitely known whether all individuals of south east-Asian ancestry are at risk due to lack of data. The allele HLA-B*1502 has been shown not to be associated with Stevens-Johnson syndrome in the Caucasian population.

The risk for aplastic anaemia and agranulocytosis is five- to eight-times greater than in the general population, which is very low.

Cardiac conduction disturbances are rare and mainly occur in susceptible patients (those with pre-existing cardiac abnormalities and the elderly). These are re-assessed[14,15] in view of cardiac conduction abnormalities now highlighted with newer AEDs (see cardiac ADRs in chapter 7 page xxx).

FDA warning: All patients who are currently taking or starting on carbamazepine for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category D. Contrary to previous studies, recent pregnancy registries are consistent in the finding that risk of teratogenicity with carbamazepine is relatively small.[16] In a recent study the major congenital malformation (MCM) rate for pregnancies exposed only to carbamazepine was 2.2% (1.4–3.4%), which is less than the MCM rate for women with epilepsy who had not taken AEDs during pregnancy (3.5% [1.8–6.8%]; n=239).[17] See Table 7.15.

Main mechanisms of action

Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. Its main mechanism of action appears to be the prevention of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels.

Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be responsible for the antimanic properties of carbamazepine.

Pharmacokinetics

Oral bioavailability: 75–85%. It is unaffected by food intake. Bioavailability may be reduced by up to 50% when stored in hot humid conditions. The slow release formulation shows about 15% lower bioavailability than standard preparations. After oral administration, absorption is relatively slow and often erratic, reaching peak plasma concentrations within 4–24 hours; 75–85% of orally ingested carbamazepine is absorbed. Absorption and bioavailability vary among different carbamazepine formulations. Slow-release formulations show about 15% lower bioavailability than standard preparations and have a prolonged absorption phase. Syrup formulations reach maximum plasma concentration faster than chewable or plain tablets.

There are significant diurnal variations in the plasma concentrations of carbamazepine. This is greater in children than in adults, which can result in intermittent ADRs that demand adjustments to the daily dosing.

Protein binding: 66–89%.

Metabolism: carbamazepine is extensively metabolised in the liver. The predominant elimination pathway leads to the formation of carbamazepine 10,11-epoxide, which is a stable and pharmacologically active agent with its own anti-epileptic activity and ADRs.

Carbamazepine epoxide makes a greater contribution to the pharmacological effects (both beneficial and toxic) of carbamazepine in children than in adults. This is because children metabolise carbamazepine more rapidly than adults and this results in carbamazepine epoxide concentrations approaching those of carbamazepine.

Carbamazepine is a potent enzyme inducer. It also induces its own metabolism (autoinduction) by simulating the activity of the cytochrome P450

(CYP) subenzyme 3A4. Autoinduction is usually completed within 3–5 weeks. The half-life of carbamazepine decreases considerably from 18–55 hours to 6–18 hours as autoinduction takes place. In practical terms, this means that carbamazepine levels fall significantly (by about 50%) after several weeks of treatment, which may result in seizure recurrence within this period of autoinduction.

Elimination half-life: 5–26 hours. In combination treatment, the elimination half-life of carbamazepine is reduced by enzyme inducers and increased by enzyme inhibitors.

Drug interactions[18–20]

With other AEDs

Carbamazepine metabolism is highly inducible by certain AEDs.

Enzyme-inducing AEDs, such as phenobarbital, phenytoin and primidone, cause significant reductions in plasma concentrations of carbamazepine. Furthermore, AEDs exacerbate and often double the diurnal variation of plasma carbamazepine concentrations, thus increasing the risk of transient ADRs.

Valproate markedly increases carbamazepine epoxide levels (sometimes fourfold) without concurrent changes in carbamazepine plasma concentration.

Co-medication with lamotrigine may cause neurotoxic symptoms of headache, nausea, diplopia and ataxia, probably as the result of a pharmacodynamic interaction and not by increasing carbamazepine epoxide (as originally suggested). Conversely, carmabazepine decreases plasma levels of lamotrigine.

Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity.

With non-AEDs

Major: carbamazepine increases the metabolism and therefore decreases the efficacy of a wide variety of drugs, such as oral contraceptives, theophylline, oral anticoagulants and beta-blockers.

Macrolide antibiotics, such as erythromycin, inhibit carbamazepine metabolism and have been associated with carbamazepine toxicity. Carbamazepine toxicity is observed shortly after starting erythromycin therapy, is rapidly reversed on withdrawal of the antibiotic, but can be severe if not recognised early.

Combination therapy with monoamine oxidase inhibitors should be avoided, because carbamazepine has structural similarities with tricyclic antidepressants.

Potential: additive cardiotoxicity with calcium channel blockers and beta-blockers.

Main disadvantages

Idiosyncratic and other ADRs, drug–drug interactions, the need for laboratory testing and relatively narrow spectrum of anti-epileptic efficacy.

Although carbamazepine is the best AED in the treatment of focal seizures and secondarily GTCSs, it offers no benefit in most other epilepsies, where it is either ineffective or seizure exacerbating. It exaggerates myoclonic jerks, absences and atonic seizures.[21–23] Exceptionally, carbamazepine may exaggerate seizures in Panayiotopoulos syndrome and rolandic epilepsy and may induce non-convulsive status and features of serious atypical evolutions.[24]

Clobazam

Clobazam was the first 1,5-benzodiazepine and was designed to have a chemical structure with a different pharmacological profile from that of the 1,4-benzodiazepines.

Authorised indications

UK-SmPC: adjunctive therapy in epilepsy.

FDA-PI: not licensed.

Clinical applications

Clobazam is a very useful AED, both as polytherapy and monotherapy.[25–35] It is neglected in current clinical practice, mainly because it is erroneously considered to (1) induce high dependence/tolerance

and (2) be of similar effectiveness regarding seizure type to clonazepam.

The main clinical applications of clobazam are:

- Adjunctive medication in all forms of drug-resistant epilepsy in adults and children. It is particularly effective in focal rather than generalised seizures. Clobazam was found to have equivalent efficacy to carbamazepine and phenytoin monotherapy in childhood epilepsies.[25,34]
- Intermittent administration 5 days prior and during the menses in catamenial epilepsy[35] is the most popular textbook recommendation.

The CYP2C19 genotype had an impact on the metabolism, efficacy and ADRs of clobazam.[35,36]

Dosage and titration

Adults and children over 12 years: start treatment with 5–10 mg/day at night and increase at weekly intervals in increments of 5 mg/day up to a total of 40 mg/day. In my experience 10 mg taken before sleep is often therapeutic in focal seizures. I do not use a dose of more than 20 mg in children.

Children under 12 years: start with 0.1–0.2 mg/kg/day and slowly increase at weekly intervals in increments of 0.1 mg/kg/day up to a total of 0.8 mg/kg/day.

Dosing: once or twice daily; a smaller dose in the day time and a larger dose prior to sleep.

TDM: not useful except when unusual ADRs appear.[36]

Reference range: norclobazam (active metabolite) 60–200 µg/l (200–670 nmol/l).

Main ADRs

As for all benzodiazepines (see page XXX), but much milder than with most. Somnolence may be partly prevented by administering the drug in small doses 1 hour prior to going to sleep. The cognitive and behavioural effects of clobazam appear to be similar to those of standard monotherapy with carbamazepine or phenytoin.[25]

Severe aggressive outbursts, hyperactivity, insomnia and depression with suicidal ideation may occur, particularly in children.

Tolerance may develop, but this aspect has been largely overemphasised, as documented in many studies.[37–39] More than a third of patients do not develop tolerance. When clobazam is effective, most patients continue to benefit for years without drug dependence or unwanted ADRs.

Main mechanism of action

$GABA_A$-receptor agonist (see note on page XXX).

Pharmacokinetics

Oral bioavailability: 90%.

Protein binding: 85%.

Metabolism: hepatic oxidation and then conjugation. *N*-desmethyl clobazam (norclobazam) is its principal and active metabolite.

Elimination half-life: 20 hours, but this is about 50 hours of its principal metabolite, norclobazam.

Drug interactions

Minor and not clinically significant. Potentiates the effect of CNS depressants such as alcohol, barbiturates and neuroleptics.

Main disadvantages

Sedation and development of tolerance (though the latter may have been exaggerated).

Useful clinical notes

Clobazam should be tried as adjunctive medication in all drug-resistant epilepsies at a dose of 10–30 mg nocte (half this dose in children >5 years old). It is more effective in focal than generalised epilepsies and can also be used as monotherapy. Probably only one out of ten patients will have a clinically significant improvement, but this may be very dramatic and render the patient seizure-free.

Unlike clonazepam, clobazam is much less effective in myoclonic jerks and absences.

Avoid overmedication. Small doses 10–20 mg given 1 hour prior to going to sleep may be therapeutic and well tolerated.

Withdrawal should be very slow, occurring over months. Rapid discontinuation may lead to withdrawal symptoms, seizures and status epilepticus.

Clonazepam

Clonazepam is a 1,4-benzodiazepine.

Authorised indications

UK-SmPC: all clinical forms of epileptic disease and seizures in infants, children, and adults, especially absence seizures, including atypical absences; primarily or secondarily generalised tonic–clonic, tonic or clonic seizures; focal seizures; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

FDA-PI: alone or as an adjunct in the treatment of the Lennox–Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. In patients with absence seizures (petit mal) who have failed to respond to succinimides, clonazepam may be useful. Lower age limit is not specified.

Clinical applications

Clonazepam[8,40] is the most effective AED in the treatment of myoclonic jerks (superior to valproate), and is also effective in absences (although much more inferior to valproate and ethosuximide)[6] and focal seizures (it is much more inferior to carbamazepine and any other appropriate drug for this type of seizures). Opinions about its effectiveness in GTCSs are conflicting and range from beneficial[41] to aggrevation.[42]

> Clonazepam is the main AED for myoclonic jerks in all forms of idiopathic or symptomatic and progressive epilepsies (monotherapy, but mainly adjunctive therapy).

Clonazepam monotherapy is probably the first choice in reading epilepsy (better than valproate). It is particularly effective in juvenile myoclonic epilepsy (JME) if myoclonic jerks are not controlled by other drugs. Adding small doses of clonazepam (0.5–2 mg prior to going to sleep) to valproate, levetiracetam or lamotrigine is highly beneficial and may prevent an unnecessary increase of the main concomitant drug. It is widely used in epileptic encephalopathies, but may also be responsible for benzodiazepine-related ADRs (e.g. sialorrhoea and lethargy).

Dosage and titration

'Start low and go slow' is essential, both in adults and children.

Adults: start treatment with 0.25 mg/day at night and increase at weekly intervals in increments of 0.25 mg/day up to a total of 8–10 mg/day. In my experience, 0.5–2 mg of clonazepam taken before sleep is often highly effective in controlling myoclonic jerks either as monotherapy or as adjunctive therapy in resistant cases.

Children: start with 0.01–0.02 mg/kg/day and slowly increase up to 0.1–0.2 mg/kg/day.

Dosing: once or twice daily; a smaller dose in the day time and a larger dose prior to going to sleep.

TDM: not needed.

Reference range: 20–80 µg/l (80–250 nmol/l).

Main ADRs

Frequent and/or important: sedation, drowsiness, hypersalivation, hyperactivity, lack of concentration and incoordination. Sedation is more serious than with clobazam. This may be partly prevented by administering the drug in small doses 1 hour prior to going to sleep.

Serious: withdrawal syndrome after chronic use.

See also benzodiazepines.

Main mechanism of action

$GABA_A$-receptor agonist (see useful note on page XXX).

Pharmacokinetics

Oral bioavailability: >80%.

Protein binding: 85%.

Metabolism: hepatic.

Elimination half-life: 20–80 hours.

Drug interactions

Minor and not clinically significant. Potentiates the effect of CNS depressants such as alcohol, barbiturates and neuroleptics.

Main disadvantages

Sedation and development of tolerance.

Useful clinical notes

- Clonazepam is the first-choice drug for the control of myoclonic jerks (either as monotherapy if this is the only seizure type, as in reading epilepsy, or mainly as adjunctive medication).
- Avoid overmedication. Small doses 1 hour prior to sleep may be effective and well tolerated.
- Withdrawal should be very slow, occuring over months. A rapid discontinuation often leads to withdrawal symptoms, seizures and status epilepticus.

Eslicarbazepine acetate[43–45]

Eslicarbazepine acetate [(S)-(--)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide] is a prodrug of eslicarbazepine (S-9-(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide) and shares with carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitute, but is structurally different at the 10,11-position. Eslicarbazepine acetate is the latest AED to be licensed in Europe (April 2009) with the brand names Exalief and Zebinix (it will trade in USA as Stedesa).

Authorized indications

SmPC. Adjunctive therapy in adults (≥ 18 years of age) within the treatment of focal seizures with or without secondary generalisation.
FDA. Not yet licensed.

Clinical applications

Eslicarbazepine acetate is the newest AED licensed for adjunctive treatment of focal seizures. Considering its similarities with carbamazepine, eslicarbazepine acetate may be contra-indicated in generalised seizures, though this has not been assessed.

Dosage and titration.

Adults. The recommended starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. Based on individual response, the dose may be increased to 1200 mg once daily.
Dosing. Once daily.
Therapeutic drug monitoring. Unknown.
Reference range. Unknown.

Main ADRs

Frequent and/or important. Dizziness, somnolence, headache, ataxia, inattention, diplopia, tremor, nausea, vomiting.
Serious. Rash in 1.1% and hyponatraemia in 1% of total treated population.
The use of eslicarbazepine acetate is associated with increase in the PR interval. Adverse reactions associated with PR interval prolongation that include atrioventricular block, syncope and bradycardia may occur. No second or higher degree atrioventricular block was seen.

Considerations in women

Pregnancy. Category C. Studies in animals have shown reproductive toxicity.
Breastfeeding. Unknown but possibly excreted in breast milk (animal data).
Interactions with hormonal contraception. Significantly decreases the effectiveness of hormonal contraception by decreasing levonorgestrel and ethinyloestradiol levels, most likely by inducing CYP3A4.

Main mechanisms of action

Probably similar to carbamazepine – that is, inhibition of voltage-gated sodium channels. Both eslicarbazepine acetate and its metabolites stabilise the inactivated state of voltage-gated sodium channels, preventing their return to the activated state and thereby sustaining repetitive neuronal firing.

Pharmacokinetics

Oral bioavailability: high – the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose.

Protein binding: 30%

Metabolism: Eslicarbazepine acetate is rapidly and extensively biotransformed to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism. Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. Minor active metabolites in plasma are R-licarbazepine and oxcarbazepine. Eslicarbazepine acetate does not affect its own metabolism or clearance.

Elimination half-life: 12–20 hours.

Drug interactions

Drug interactions may be significant. Eslicarbazepine acetate may have an inducing effect on the metabolism of drugs which are mainly eliminated by metabolism through CYP3A4 (carbamazepine, phenytoin, phenobarbital, topiramate) or conjugation through the UDP-glucuronyltransferases (lamotrigine).

When initiating or discontinuing treatment with eslicarbazepine acetate or changing the dose, it may take 2 to 3 weeks to reach the new level of enzyme activity. This time delay must be taken into account when eslicarbazepine acetate is being used just prior to or in combination with other drugs that require dose adjustment when co-administered with eslicarbazepine acetate.

Also, eslicarbazepine has inhibiting properties with respect to CYP2C19 and therefore interacts in co-medication with drugs that are mainly metabolised by CYP2C19.

Concomitant administration of eslicarbazepine acetate with

- phenytoin significantly decreases exposure to eslicarbazepine (most likely caused by an induction of glucuronidation) and increases exposure to phenytoin (most likely caused by CYP2C19 inhibition)
- lamotrigine is expected to lead to interactions because glucuronidation is the major metabolic pathway for both of these drugs. However, their co-administration in healthy subjects showed a minor average pharmacokinetic interaction (exposure of lamotrigine decreased 15%)
- topiramate mildly decreases exposure to topiramate (most likely caused by a reduced bioavailability of topiramate)
- carbamazepine significantly increases the risk of diplopia, ataxia and dizziness. Carbamazepine increases eslicarbazepine clearance and vice versa.

Concomitant administration with valproate or levetiracetam appeared not to affect the exposure to eslicarbazepine.

Main disadvantages

Eslicarbazepine acetate has been developed with the intention that it should have less interaction potential with other drugs than its parent drug carbamazepine and no auto-induction by preventing the formation of toxic epoxide metabolites such as carbamazepine-10,11 epoxide. However, this appears to be an unfulfilled promise because eslicarbazepine acetate has many drug interactions. Whether it will match the success of carbamazepine is too early to assess.

Ethosuximide

Ethosuximide (α-ethyl-α-methyl-succinimide) is the main survivor of the succinimides.[46–48] It was first introduced in clinical practice in the early 1950s for the treatment of 'petit mal'.[49]

Authorised indications

UK-SmPC: primarily useful in absence seizures. When GTCSs and other forms of epilepsy co-exist with absence seizures, ethosuximide may be administered in combination with other AEDs.
FDA-PI: control of absence (petit mal) epilepsy.

Clinical applications

Ethosuximide is still a valuable AED for the treatment of typical absence seizures and has a 70% seizure-free success rate as monotherapy.[6] It is recommended in childhood absence epilepsy (monotherapy) and IGEs with intractable absence seizures (adjunctive therapy).

Ethosuximide is also useful as adjunctive treatment in negative myoclonus,[50] drop attacks[51] and certain types of myoclonic epilepsy.[52] An anecdotal view that ethosuximide does not control GTCS has recently been challenged.[53]

Dosage and titration

Titrate slowly to avoid ADRs, mainly gastrointestinal disturbances.
Adults and children over 12 years: start treatment with 250 mg/day and increase slowly in 250 mg increments every 4–7 days, to up to 750–1500 mg.
Children under 12 years: start with 5–10 mg/kg/day and increase slowly to 20–35 mg/kg/day.
Dosing: two or three times daily.
TDM: mostly not needed.
Reference range: 40–100 mg/l (300–700 µmol/l).

Main ADRs

Common and/or serious: gastrointestinal symptoms include anorexia, vague gastric upset, nausea and vomiting, cramps, epigastric and abdominal pain and diarrhoea. Drowsiness, weight loss photophobia, euphoria, hiccups, headache and, less often, behavioural and psychotic disturbances may occur.
Severe: haemopoietic complications (aplastic anaemia), Stevens–Johnson syndrome, renal and hepatic impairment, and systemic lupus erythematosus.

Considerations in women

Pregnancy: category C.
Interaction with hormonal contraception: none.

Main mechanisms of action

Ethosuximide exerts its anti-absence effect by either reducing thalamic low threshold calcium currents, probably by a direct channel-blocking action that is voltage dependent,[54] or through a potent inhibitory effect in the perioral region of the primary somatosensory cortex.[55]

Pharmacokinetics

Oral bioavailability: 90–100%.
Protein binding: 85%.
Metabolism: hepatic oxidation and then conjugation.
Elimination half-life: 30–60 hours.

Drug interactions

Commonly, there are no clinically significant drug–drug interactions. Ethosuximide may raise the plasma concentration of phenytoin. Valproate has been reported to both increase and decrease ethosuximide levels.

Main disadvantages

- Narrow spectrum of anti-epileptic activity.
- It sometimes exhibits severe adverse idiosyncratic reactions.
- Abrupt withdrawal in patients with absences may precipitate absence status epilepticus.

Other available succinimides

Methsuximide is a broader spectrum drug than ethosuximide (but with a weaker action) and is also effective in focal seizures. ADRs are more frequent and may be more serious than with ethosuximide.
Phensuximide is rarely used because its effect is inferior to other succinimides.

Felbamate[56–59]

In 1993, felbamate, a 2-phenyl-1,3-propanediol dicarbamate, became the first AED since 1978 to be approved by the FDA with the brand name Felbatol. Unlike its dicarbamate analog meprobamate, it has minimal anxiolytic and sedative-hypnotic effects in therapeutic doses.

Authorised indications

UK-SmPC: not licensed.

FDA-PI: alone or as an adjunct in the treatment of focal seizures in adults and as an adjunct in focal and generalised seizures of Lennox–Gastaut syndrome in children.

Warnings apply: felbamate should only be used in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anaemia and/ or liver failure is deemed acceptable in light of the benefits conferred by its use.

Clinical applications

The clinical use of felbamate as an AED practically ended 1 year after its FDA approval, when it became apparent that felbamate is associated with a high incidence of aplastic anaemia and hepatic failure, and also with some fatalities. [60–63] In addition, felbamate is difficult to use because of its narrow therapeutic range and significant drug– drug interactions. Currently, the use of felbamate as an AED is cautiously limited to severe cases of Lennox–Gastaut syndrome, mainly with atonic/astatic seizures, and with bi-monthly follow-up of transaminases and blood cell counts. Possibly, the risk of using felbamate in Lennox–Gastaut syndrome outweighs any benefits, which, even if they occur, are short lived.

However, an expert panel concluded in 2006 that "although felbamate is not indicated as first-line AED, its utility in treating seizures that are refractory to other AEDs is undisputed, as shown by the number of patients who continue to use it. New exposures to felbamate number approximately 3200–4200 patients annually, and it is estimated that over the past 10 years, approximately 35,000 new starts have occurred."[57]

Author's note: The stated numbers in the above quotation cannot be used as evidence of effectiveness because they are influenced by factors other than efficacy.

Dosage and titration

Adults (14 years of age and older): start felbamate at 1200 mg/day in three or four divided doses while reducing present AEDs by 20% in order to control plasma levels of concurrent phenytoin, valproate, phenobarbital, and carbamazepine and its metabolites. Further reductions of the concomitant AEDs dosage may be necessary to minimise side effects due to drug interactions. Titrate in increments of 1200 mg /day at weekly intervals to a maintenance dose of 3600 mg/day. Higher doses of 5000–6000 mg/day may be used. If the patient is not taking enzyme-inducing AED, then a slower titration is recommended.

Children with Lennox-Gastaut Syndrome (2–14 years of age): start felbamate at 15 mg/kg/day in three or four divided doses while reducing present AEDs by 20% in order to control plasma levels of concurrent phenytoin, valproic acid, phenobarbital, and carbamazepine and its metabolites. Further reductions of the concomitant AEDs dosage may be necessary to minimise side effects due to drug interactions. Titrate in increments of 15 mg/kg/day at weekly intervals to a maintenance dose of 45 mg/kg/day.

Dosing: Three to four-times daily.

TDM: It is mandatory because of its many interactions with other AEDs.

Reference range: 50–110 mg/l (300- 750 umol/l)

Main ADRs

It is because of serious ADRs that felbamate has been downgraded in its license indications and clinical practice.

Frequent and/or important: insomnia, anorexia, nausea, dizziness, headache, vomiting, weight loss, irritability, hyperactivity and behavioural disturbances.

Serious: Aplastic anaemia and hepatic failure which are usually seen during the first 6–12 months of felbamate therapy.

Aplastic anaemia: Aplastic anaemia (pancytopenia in the presence of a bone marrow largely depleted of

hematopoietic precursors) occurs with felbamate at an incidence that may be more than a 100 fold greater than that seen in the untreated population (i.e., 2 to 5 per million persons per year). The risk of death in patients with aplastic anaemia generally varies as a function of its severity and aetiology; current estimates of the overall case fatality rate are in the range of 20–30%, but rates as high as 70% have been reported in the past. There are too few felbamate-associated cases, and too little known about them, to provide a reliable estimate of the syndrome's incidence or its case fatality rate or to identify the factors, if any, that might conceivably be used to predict who is at greater or lesser risk. Most of the cases of aplastic anaemia with felbamate occurred in women over the age of 17 years with a history of idiosyncratic reactions to other AEDs or a history of cytopenia, allergy and underlying autoimmune disease previous to felbamate use.[57] It was not reported in children younger than 13 years.

In managing patients on felbamate, it should be borne in mind that the clinical manifestation of aplastic anaemia may not be seen until after a patient has been on this drug from 5–30 weeks. However, the injury to bone marrow stem cells that is held to be ultimately responsible for the anaemia may occur weeks to months earlier. It is not known whether or not the risk of developing aplastic anaemia changes with duration of exposure. Consequently, it is not safe to assume that a patient who has been on felbamate without signs of haematologic abnormality for long periods of time is without risk.

It is not known whether or not the dose of felbamate or concomitant use of AEDs and/or other drugs affects the incidence of aplastic anaemia.

Aplastic anaemia typically develops without premonitory clinical or laboratory signs, the full blown syndrome presenting with signs of infection, bleeding, or anaemia. Accordingly, routine blood testing cannot be reliably used to reduce the incidence of aplastic anaemia, but it will, in some cases, allow the detection of the haematologic changes before the syndrome declares itself clinically.

Hepatic failure: this has mainly occurred in young children. The reported rate of hepatic failure with felbamate in the US has been about 6 cases leading to death or transplant per 75,000 patient years of use. This rate may be an underestimate because of underreporting. Of the cases reported, about 67% resulted in death or liver transplantation, usually within 5 weeks of the onset of signs and symptoms of liver failure. The earliest onset of severe hepatic dysfunction followed subsequently by liver failure was 3 weeks after initiation of felbamate. Some reports described dark urine and nonspecific prodromal symptoms (e.g., anorexia, malaise, and gastrointestinal symptoms) but in other reports it was not clear if any prodromal symptoms preceded the onset of jaundice. It is not known whether or not the risk of developing hepatic failure changes with duration of exposure. It is also not known whether or not the dosage of felbamate or concomitant use of other drugs affects the incidence of hepatic failure.

It has not been proved that periodic serum transaminase testing will prevent serious hepatic injury but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. There is no information available that documents how rapidly patients can progress from normal liver function to liver failure, but other drugs known to be hepatotoxins can cause liver failure rapidly (e.g., from normal enzymes to liver failure in 2-4 weeks). Accordingly, monitoring of serum transaminase levels is recommended at baseline and periodically thereafter. Felbamate should be discontinued if either serum alanine or aspartate transaminase levels become increased ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure.

FDA warning: All patients who are currently taking or starting on felbamate for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category C.

Breastfeeding: unknown but excreted in human breast milk.

Interactions with hormonal contraception: Significant reduction of the efficacy of hormonal contraception.

Main mechanisms of action

These are unknown and but are likely to be multiple. The most probable mechanisms are (a) potentiation of GABA responses via its interaction with a site on the $GABA_A$ receptor that is distinct from the benzodiazepine recognition site and (b) inhibition of N-methyl-D-aspartate (NMDA) receptors via a channel-blocking action and also possibly by distinct effects on channel gating.

Felbamate has weak inhibitory effects on GABA receptor binding and benzodiazepine receptor binding and is devoid of activity at the MK-801 receptor binding site of the NMDA receptor-ionophore complex. However, felbamate does interact as an antagonist at the strychnine-insensitive glycine recognition site of the NMDA receptor-ionophore complex.

Pharmacokinetics

Oral bioavailability: 90%

Protein binding: 22% to 25%

Metabolism: Felbamate is metabolised by the hepatic CYP3A4 system and it is an enzyme inhibitor. Following oral administration, about 40–50% of absorbed dose appears unchanged in urine, and an additional 40% is present as unidentified metabolites and conjugates. About 15% is present as parahydroxyfelbamate, 2-hydroxyfelbamate, and felbamate monocarbamate, none of which have significant antiepileptic activity.

Elimination half life: 20 hours (without enzyme-inducing drugs).

Drug interactions

These are numerous. Felbamate significantly increases the plasma levels of phenytoin, valproate, carbamazepine epoxide (but decreases carbamazepine) and phenobarbital. Conversely, phenytoin, carbamazepine and phenobarbital approximately double the clearance of felbamate and, therefore, their addition causes a significant decrease in the plasma levels of felbamate. Valproate probably does not affect felbamate. Felbamate's interaction with newer AEDs is not well studied, but the elimination of felbamate is strikingly reduced in co-medication with gabapentin.[64]

Main disadvantages

Probably more disadvantages than advantages.

Gabapentin

Gabapentin (1-[aminomethyl]-cyclohexaneacetic acid) first received marketing approval as an adjunctive AED for the treatment of focal epilepsies in 1993.[65,66]

Authorised indications

UK-SmPC: (1) monotherapy in the treatment of focal seizures with and without secondary generalization in adults and adolescents aged 12 years and above and (2) adjunctive therapy of focal seizures with and without secondary generalisation in patients ⩾6 years of age.

FDA-PI: (1) adjunctive therapy of focal seizures with and without secondary generalisation in patients over 12 years of age; (2) adjunctive therapy of focal seizures in children aged 3–12 years.

Clinical applications

Recommendations for gabapentin as an AED are limited to focal seizures. It is the least effective of all the other newer AEDs, even at higher doses of around 3000 mg/day.[67] However, it is considered relatively safe with few ADRs. It is mainly used for non-epileptic disorders such as neuropathic pain.

It is contraindicated for generalised-onset seizures of any type (absences, myoclonic jerks, GTCSs) because it is either ineffective or may exaggerate them.[68–70]

Dosage and titration

Adults: start with 300 mg/day and increase rapidly in increments of 300 mg/day up to a typical adult maintenance dose of 900–1800 mg/day given in three divided doses. Doses of up to 3600 mg/day have been used.

Children: start treatment with 15 mg/kg/day and increase to 30 mg/kg/day within a few days. The recommended maintenance dose is 50–100 mg/day. Children require relatively higher doses than adults, because clearance of gabapentin is greater in children than in adults.

Dosing: three times daily.

TDM: usually not needed; its dose-dependent absorption increases its pharmacokinetic variability.[71,72]

Reference range: 2–20 mg/l (12–120 µmol/l).

Main ADRs

Gabapentin has a relatively good adverse reaction profile.

Frequent and/or important: increased appetite and weight gain is a problem. Other reactions include dizziness, ataxia, nystagmus, headache, tremor, fatigue, diplopia, rhinitis and nausea. Significant behavioural disturbances, such as aggression, hyperexcitability and tantrums, have been reported, mainly in children.[73] Caution is recommended in patients with a history of psychotic illness.

Serious: rarely, rash (0.5%), leucopenia (0.2%) and ECG changes and angina (0.05%).

Gabapentin may unmask myasthenia gravis.[74]

FDA warning: All patients who are currently taking or starting on gabapentin for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category C but with teratogenic effects in animal exposure.[75]

Breastfeeding: it is excreted in breast milk, but the effect on the nursing infant is unknown.

Interaction with hormonal contraception: none.

Others: weight gain may be of particular importance to women because of the associated risk for polycystic ovary syndrome.

Main mechanisms of action

The mechanism of action is uncertain. Gabapentin was developed because of its structural similarity to GABA and its ability to cross the blood–brain barrier. However, it does not appear to be a GABA agonist.

The mechanism responsible for its anti-epileptic activity and the relief of neuropathic pain is probably due to a modulating action of gabapentin on voltage-gated calcium channels and neurotransmitter release.

Pharmacokinetics

Oral bioavailability: low <60%. Gabapentin is rapidly absorbed and reaches peak plasma levels within 2–4 hours after oral ingestion. Bioavailability is less than 60%, but is dose-dependent; absorption is progressively reduced with an increasing dosage. Food intake does not influence absorption.

Protein binding: none.

Metabolism: gabapentin is not metabolised and is excreted by the kidneys in unchanged form. Renal impairment reduces drug clearance and raises plasma gabapentin concentrations.

Elimination half-life: 5–9 hours.

Drug interactions

There are no significant interactions with other AEDs. However, see the note on renally eliminated drugs below.

Cimetidine reduces the renal clearance of gabapentin and antacids reduce the absorption of gabapentin by 20%.

Main disadvantages

A narrow-spectrum and low-efficiency AED that is limited to the treatment of focal seizures.

Therapeutic efficacy is weak in relation to other AEDs, the number of responders is disappointingly low even when higher doses are used and it is unusual for patients with severe focal epilepsies to derive much benefit.

Lacosamide[76–84]

Lacosamide is a functionalized amino acid (R)-2-acetamido-N-benzyl-3-methoxypropionamide. It is one of the latest AEDs to be licensed (at the end of 2008), under the brand name Vimpat.

Authorised indications

SmPC: adjunctive therapy in the treatment of focal seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. Solution for infusion is an alternative for patients for whom oral administration is temporarily not feasible.
FDA: (1) tablets are indicated as adjunctive therapy in the treatment of focal seizures in patients with epilepsy aged 17 years and older and (2) injection for intravenous use is indicated as adjunctive therapy in the treatment of focal seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible

Clinical applications

Based on RCTs, lacosamide is a useful addition to our armamentarium in the treatment of epilepsy. This is also supported by experience since its introduction in clinical practice.

Lacosamide has proven efficacy and a high retention rate (77% in a year) in difficult to treat patients. It is particularly important in adjunctive AED therapy because of its excellent pharmacokinetic profile, minimal drug to drug interactions, good safety and novel mechanism/s of action, which is different than any other AED co-medication. It is considered as having less sedative effects than most other AEDs. Intravenous solution is important when oral drug administration is impossible.

Dosage and titration

"Start low and go slow"
Adults: Start with 50 mg twice daily (100 mg/day). Increase at weekly intervals by 100 mg/day to 200–400 mg/day.

The maximum recommended dose of lacosamide is 400 mg/day because higher doses may be associated with CNS and gastrointestinal ADRs.

A maximum dose of 300 mg/day is recommended by the FDA for patients with mild or moderate hepatic impairment; no such upper limits are recommended by the EMEA.

Lacosamide injection (without further dilution or mixed in compatible diluents) should be administered intravenously over 15–60 minutes. When switching from oral lacosamide, the initial total daily intravenous dosage should be equivalent to the total daily dosage and frequency of oral lacosamide. When used as short-term replacement for oral lacosamide, intravenous lacosamide was well tolerated when administered as a 15-, 30- or 60-minute infusion.
Dosing: twice daily
TDM: unknown.
Reference range: unknown.

Main ADRs

Frequent and/or important: Dizziness, headache, diplopia, nausea, vomiting and blurred vision.
Serious: A small, asymptomatic, dose-related increase in the PR interval measured on ECG has been observed in clinical studies (see also eslicarbazepine and Chapter 7, page XXX). However, atrioventricular block is uncommon, with an occurrrence of 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree atrioventricular block was seen in lacosamide patients. Also, the incidence rate for syncope did not differ between lacosamide (0.1%) and placebo treated epilepsy patients (0.3%). However, caution is needed in patients with known conduction problems or severe cardiac disease, in the elderly and in comedication with drugs known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, pregabalin, eslicarbazepine or class I antiarrhythmic drugs), though an increased magnitude of PR prolongation has not been found so far in comedication with carbamazepine or lamotrigine.

Considerations in women

Pregnancy: category C.
Breastfeeding: unknown but possibly excreted in breast milk (animal data).
Interactions with hormonal contraception: none.

Main mechanisms of action

Not fully elucidated but two mechanisms are possible: (a) lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing (Figure 7.1) and (b) lacosamide may bind to collapsin response mediator protein–2 (CRMP–2), a phosphoprotein which is mainly expressed in the nervous system and is involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown.

Pharmacokinetics

Lacosamide has near-ideal pharmacokinetics (score 96 out of maximal best 100).

Oral bioavailability: 100%.

Protein binding: <15%

Metabolism: Primarily eliminated by renal excretion and biotransformation. Its metabolism has not been fully elucidated but CYP-2C19 is involved in the demethylation of lacosamide. Lacosamide showed no potential to induce or inhibit the activity of CYP isoforms 1A1, 1A2, 2A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 in human hepatocytes at therapeutic concentrations, although inhibition of the CYP2C19 iso-enzyme was noted at concentrations 15-times higher than therapeutic concentrations.

Elimination half-life: 13 hours.

Drug interactions

These are minimal and probably of no clinical significance. From available evidence, lacosamide does not affect plasma levels of carbamazepine or its epoxide metabolite, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, valproate and zonisamide or the oral contraceptive levonorgestrel/ethinylestradiol, metformin and digoxin.[76] Carbamazepine, phenytoin and phenobarbital may decrease plasma levels of lacosamide by 15–20%. Omeprazole (a CYP2C19 inhibitor) did not produce any clinically significant changes in lacosamide plasma concentrations.

Main disadvantages

Not yet exposed to lengthy clinical practice but its use so far has met with favourable results.

Lamotrigine

Lamotrigine is a 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine of the phenyltriazine class. It was first licensed for clinical practice in 1991. Lamotrigine is one of the best newer AEDs, although there are now concerns for its use in women and myoclonic epilepsies.

Authorised indications

UK-SmPC: (1) Adults and adolescents aged 13 years and above: (a) adjunctive or monotherapy treatment of focal seizures and generalised seizures, including tonic clonic seizures and (b) seizures associated with Lennox Gastaut syndrome. Lamotrigine is given as adjunctive therapy but may be the initial antiepileptic drug to start with in Lennox Gastaut syndrome. (2) Children and adolescents aged 2 to 12 years: (a) adjunctive treatment of partial seizures and generalised seizures, including tonic clonic seizures and the seizures associated with Lennox Gastaut syndrome and (b) monotherapy of typical absence seizures.

FDA-PI: (1) adjunctive therapy for focal seizures and primarily GTSC in patients ⩾2 years of age; (2) adjunctive therapy for the generalised seizures of Lennox–Gastaut syndrome; and (3) conversion to monotherapy in adults (⩾16 years of age) with focal seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone or valproate as the single AED.

Safety and effectiveness of lamotrigine have not been established (1) as initial monotherapy; (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate; or (3) for simultaneous conversion to monotherapy from two or more concomitant AEDs.

Clinical applications

Lamotrigine is an effective broad-spectrum AED for the treatment of all types of seizures except myoclonic jerks.[85–92] It has been recommended for all focal or generalised, idiopathic or symptomatic epileptic syndromes of adults,[88–90] children[85,86] and neonates.[93] Exceptions to this are syndromes with predominantly myoclonic jerks.

In monotherapy of focal seizures and primarily GTCSs, lamotrigine has less efficacy than carbamazepine but it is better tolerated.[94,95] The conclusions of a recent meta-analysis[94] and the SANAD report[65] comparing lamotrigine and carbamazepine have been debated,[96–99] as detailed on page XXX.

In polytherapy, lamotrigine is at its best efficacy when combined with valproate, because of beneficial pharmacodynamic interactions (increased therapeutic efficacy),[100] although it may also be detrimental (increased risk of ADRs and teratogenicity). This combination may be ideal for drug-resistant generalised epilepsies including those with myoclonic seizures.[101] Usually, small doses of lamotrigine added to valproate may render previously uncontrolled patients seizure-free.[6,100,102,103]

Other major advantages are that it lacks significant cognitive and behavioural ADRs and it is non-sedating with improved global functioning, which includes increased attention and alertness, which has been reported in both paediatric and adult trials.[87,104,105] Adjunctive lamotrigine significantly improved anger-hostility subscale scores relative to adjunctive levetiracetam in patients with focal seizures at the end of 20 weeks and similar improvement with lamotrigine versus levetiracetam was observed for other mood symptoms.[106] Idiosyncratic reactions, mainly rash, that can become very serious are a significant disadvantage.[107–109]

Exacerbation of seizures: increase in seizure frequency, mainly myoclonic jerks, has been reported in JME and Dravet syndrome.

Dosage and titration

'Start very low and go very slow' is essential in both adults and children.

Dosage and titration vary considerably between monotherapy, co-medication with valproate and co-medication with enzyme-inducing AEDs. For this reason the manufacturers have provided detailed tables to be followed in each of these circumstances in children and adults. The following are some examples:

Adults and children over 12 years (monotherapy): start with 25 mg once daily for 2 weeks, followed by 50 mg once daily for 2 weeks. Thereafter, the dose should be increased by a maximum of 50–100 mg every 1 or 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100–200 mg/day given once daily or as two divided doses. Some patients have required 500 mg/day to achieve the desired response.

Adults and children over 12 years (add-on therapy with valproate): start with 25 mg every alternate day for 2 weeks, followed by 25 mg once daily for 2 weeks. Thereafter, the dose should be increased by a maximum of 25–50 mg every 1 or 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100–200 mg/day given once daily or in two divided doses.

Adults and children over 12 years (add-on therapy with enzyme-inducing AEDs): start with 50 mg once daily for 2 weeks, followed by 100 mg/day given in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1 or 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200–400 mg/day given in two divided doses. Some patients have required 700 mg/day to achieve the desired response.

Children aged 2–12 years (with valproate co-medication): start treatment with 0.15 mg/kg given once daily for 2 weeks, followed by 0.3 mg/kg given once daily for 2 weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1 or 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1–5 mg/kg given once daily or in two divided doses.

Children aged 2–12 years (co-medication with enzyme-inducing AEDs): start with 0.6 mg/kg/day given in two divided doses for 2 weeks, followed by 1.2 mg/kg/day for 2 weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1 or 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5–15 mg/kg/day in two divided doses.

Cautionary note

A slower dosage titration probably reduces the risk of skin rash and possibly reduces the risk of generalised hypersensitivity reactions.[108] Therefore, it is mandatory to follow the recommendations of the manufacturers regarding initial dose and subsequent slow-dose escalation of lamotrigine.

Conversion to monotherapy from polytherapy with valproate or with enzyme-inducing AEDs should follow appropriate guidelines provided by the manufacturers of lamotrigine.

If lamotrigine has to be replaced by valproate, a satisfying outcome has been found after suddenly and completely withdrawing lamotrigine and introducing the valproate maintenance dosage rapidly.[110]

Useful note

TDM of newer AEDS that are metabolised[71,72]

For newer AEDs that are metabolised (felbamate, lamotrigine, oxcarbazepine, tiagabine and zonisamide), pharmacokinetic variability is just as relevant as for many of the older AEDs, mainly because of pronounced inter-individual variability in their pharmacokinetics.

TDM: it was not recommended initially for lamotrigine and other newer AEDs, but this has now been revised (see useful note).[71,72,111] More specifically, TDM for lamotrigine is particularly useful in pregnancy,[112–114] in conjunction with hormonal contraception[115] and post-operatively.[116]
Reference range: 1–15 mg/l (10–60 µmol/l).

Main ADRs

Common and/or important: skin rash, headache, nausea, diplopia, dizziness, ataxia, tremor, asthenia, anxiety, aggression, irritability, insomnia, somnolence, vomiting, diarrhoea, confusion, hallucinations and movement disorders.

Serious: an allergic skin rash is the most common and probably the most dangerous ADR, prompting withdrawal of lamotrigine.[108,109] Skin rash occurs in approximately 10% of patients, but serious rashes leading to hospitalisation, including Stevens–Johnson syndrome and anticonvulsant hypersensitivity syndrome, occur in approximately 1 out of 300 adults and 1 out of 100 children (<16 years of age) treated with lamotrigine.[108]

Nearly all cases of life-threatening rashes associated with lamotrigine have occurred within 2–8 weeks of treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g. 6 months). Accordingly, duration of therapy cannot be relied on as a means to predict the potential risk heralded by the first appearance of a rash.

There are suggestions, still to be proven, that the risk of rash may also be increased by: (1) the co-administration of lamotrigine with valproate; (2) exceeding the recommended initial dose of lamotrigine; or (3) exceeding the recommended dose escalation for lamotrigine. However, cases have been reported in the absence of these factors. The incidence of skin rash can probably be reduced by starting treatment with a low dose spread over longer intervals, particularly in patients receiving concomitant valproate, which inhibits lamotrigine metabolism.

Although benign rashes also occur with lamotrigine, it is not possible to predict reliably which rashes will prove to be serious or life threatening. Accordingly, lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not

drug related. Discontinuation of treatment may not prevent a rash from becoming life threatening, or permanently disabling or disfiguring.

Patients should be advised to immediately report any symptoms of skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, because these symptoms may be the first signs of a serious reaction.

Cardiac arrhythmia and sudden unexpected death (SUDEP): a recent report described SUDEP of four women with IGE treated with lamotrigine monotherapy.[117] Lamotrigine inhibits the cardiac rapid delayed rectifier potassium ion current (I_{Kr}). I_{Kr}-blocking drugs may increase the risk of cardiac arrhythmia and SUDEP. The authors of the report called for a systematic study to assess whether lamotrigine may increase the risk of SUDEP in certain groups of patients[117], which generated an interesting exchange of views.[118,119] In the SANAD study, four of ten deaths related to epilepsy occurred in patients treated with lamotrigine, three with oxcarbazepine, two with gabapentin, one with carbamazepine and none with topiramate.[95] A recent study found that therapeutic doses of lamotrigine (100–400 mg daily) were not associated with QT prolongation in healthy subjects.[120] Also, clinically significant ECG changes were not common during treatment with either lamotrigine or carbamazepine in elderly patients with no pre-existing significant AV conduction defects.[121] See cardiac ADRs in chapter 7.

Other potentially serious ADRs: there have been reports of haematological abnormalities, which may or may not be associated with anticonvulsant hypersensitivity syndrome. These have included neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia and, very rarely, aplastic anaemia and agranulocytosis. Elevations of liver function tests and rare reports of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions, but isolated cases have been reported without overt signs of hypersensitivity.

Very rarely, lupus-like reactions have been reported.

FDA warning: All patients who are currently taking or starting on lamotrigine for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category C. However, there is recent evidence of teratogenicity that resulted in lamotrigine being downgraded to category D in the Australian PI (see page XX in chapter 7). For example, an increased risk for non-syndromic cleft palate among infants exposed to lamotrigine during pregnancy[122] (not replicated in other pregnancy registries)[123] and a dose-related effect with MCMs have been reported.[17] The risk for MCMs in women on a combination of lamotrigine with valproate is around 10%.[17,124]

Breastfeeding: significant amounts of lamotrigine (40–60%) are excreted in breast milk. In breast-fed infants, plasma concentrations of lamotrigine reached levels at which pharmacological effects may occur.

Interactions with oral hormonal contraception and pregnancy: oral contraceptives are not affected by lamotrigine. However, pregnancy[112–114,125] and hormonal contraception[115,126] significantly lower lamotrigine levels (by more than half). Patients may suffer breakthrough seizures, mainly during the first trimester of pregnancy (if lamotrigine levels are not corrected) or toxic effects postpartum (if lamotrigine levels are adjusted during pregnancy, but not after delivery). Gradual transient increases in lamotrigine levels will occur during the week of no active hormone preparation (pill-free week).

Liver function tests should probably be monitored in infants of lamotrigine-treated mothers, as γ-glutamyl transpeptidase enzyme elevation might suggest liver damage.[127]

Main mechanisms of action

The precise mechanisms by which lamotrigine exerts its anti-epileptic action are unknown. The most likely mechanism is inhibition of voltage-gated sodium channels, thereby stabilising neuronal membranes and consequently modulating pre-

synaptic transmitter release of excitatory amino acids (e.g. glutamate and aspartate).

Pharmacokinetics

Oral bioavailability: <100%. Lamotrigine is rapidly and completely absorbed from the gut with no significant first-pass metabolism.

Protein binding: 55%.

Metabolism: lamotrigine is predominantly metabolised in the liver by glucuronic acid conjugation. UGT1A4 is the main enzyme responsible for N-glucuronidation of lamotrigine. The major metabolite is an inactive 2-*N*-glucuronide conjugate. Lamotrigine is a weak UGT enzyme inducer.

Elimination half-life: 29 hours, but this is greatly affected by concomitant medication. Mean half-life is reduced to approximately 14 hours when given with enzyme-inducing drugs and is increased to a mean of approximately 70 hours when co-administered with valproate alone. Valproate is a potent inhibitor of UGT-dependent metabolism of lamotrigine, while enzyme-inducer AEDs are potent inducers of UGT-dependent metabolism of lamotrigine, which is the reason for different schemes of lamotrigine dosage and titration when combined with these AEDs.

Furthermore, the half-life of lamotrigine is generally shorter in children than in adults, with a mean value of approximately 7 hours when given with enzyme-inducing drugs and increasing to mean values of 45–50 hours when co-administered with valproate alone.

Drug interactions

The metabolism of lamotrigine is badly affected by concomitant AEDs, which makes its use in polytherapy problematic:

- Valproate inhibits the metabolism of lamotrigine, doubling or tripling its half-life,[107] whether given with or without carbamazepine, phenytoin, phenobarbital or primidone. Also, valproate seems to reduce the induction of lamotrigine metabolism associated with pregnancy or use of contraceptives.[125]
- Enzyme inducers, such as carbamazepine, phenytoin and phenobarbital, accelerate its elimination, but lamotrigine itself has no effect on hepatic metabolic processes.[128]

When lamotrigine is added to carbamazepine, symptoms of carbamazepine neurotoxicity (headache, diplopia, ataxia) may occur (probably because of pharmacodynamic interactions rather than elevated carbamazepine epoxide levels); this necessitates a reduction in the carbamazepine dose when lamotrigine is introduced.

Oxcarbazepine and levetiracetam do not affect the clearance of lamotrigine.

Main disadvantages

- High incidence of idiosyncratic ADRs, which, exceptionally, may be fatal.
- Very slow titration.
- Significant interactions with other AEDs requiring complex schemes of dosage and titration.
- Frequent TDM and dosage adjustments before, during and after pregnancy[112–114,125] and hormonal contraception.[115,125,129] Risk for seizure deterioration in pregnancy.
- Pro-myoclonic effect in syndromes with predominant myoclonic jerks, such as JME,[130–132] Dravet syndrome[133,134] and progressive myoclonic epilepsies.[135]

Useful clinical notes

- Recent evidence of teratogenicity and interaction with pregnancy and hormonal contraception contradict the previous promotion of lamotrigine as a female-friendly AED.
- Lamotrigine demands significant clinical attention in polytherapy, hormonal contraception and pregnancy.
- Lamotrigine also has significant pharmacodynamic interactions with valproate.
- The use of lamotrigine should follow the manufacturer's recommendations regarding titration and include a proper warning to the patient or guardians for immediate medical attention if suspicious rashes appear, unless the rash is clearly not drug related.

Levetiracetam

Levetiracetam is a single enantiomer, (*S*)-α-ethyl-2-oxo-pyrrolidine acetamide. Levetiracetam, licensed in 1999, is probably the best of all the newer AEDs.[136–144] It is chemically unrelated to any of the other current AEDs.

Authorised indications

EMEA-SmPC: (1) monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy; (2) adjunctive therapy (a) in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy (the concentrate for solution for infusion is indicated for adults, adolescents and children from 4 years of age), (b) in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with JME, and (c) in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with IGE.

Levetiracetam concentrate is an alternative for patients when oral administration is temporarily not feasible.

FDA-PI: (1) adjunctive therapy in the treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy; (2) adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy; and (3) adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.

Levetiracetam injection is an alternative for adult patients (16 years and older) when oral administration is temporarily not feasible.

Clinical applications

Levetiracetam is probably a major breakthrough in the treatment of epilepsies, similar to that of carbamazepine and valproate in the 1960s. It is a highly effective, broad-spectrum, newer class of AED with a unique mechanism of action, and can be used to treat all focal or generalised, idiopathic or symptomatic epileptic syndromes in all age groups.

Levetiracetam is the first-choice AED in monotherapy and polytherapy of focal epilepsies (see page XXX), where it is the main challenger of carbamazepine. It is also the likely candidate to replace valproate in the treatment of JME and IGEs in general (pages XXX and XXX).

The main advantages of levetiracetam include the following:

- it is broad spectrum, which is of practical significance, particularly for clinicians who may not have special expertise in differentiating between focal and generalised epileptic seizures
- it has a relatively good safety profile[145–147] and does not cause significant idiosyncratic reactions or other serious ADRs
- it has superior pharmacokinetics (96% versus 100% of perfect score)[148]
- it does not need slow titration, the starting dose is often therapeutic for all forms of seizures and epilepsies (including the difficult-to-treat myoclonic seizures);[149] its action starts 2 days after drug initiation[150]
- it does not need laboratory tests (such as routine TDM or blood screening for ADRs)
- it is easier to use if polytherapy is necessitated (a lack of clinically significant drug–drug interactions[18,151] and a novel mechanism of action)
- it does not interact with hormonal contraception and is a pregnancy category C drug
- it does not interfere with liver function (a major problem with most other AEDs that are metabolised in the liver).

Levetiracetam has a significant and sustained proven efficacy for newly diagnosed or intractable focal seizures with or without secondarily generalisation.[152–162] Addition of levetiracetam to standard medication seems to have a positive impact on health-related quality of life.[145]

Its effectiveness in generalised epileptic seizures and at any age has been documented in experimental and observational studies, postmarketing experience and RCTs. This includes IGE, JME, myoclonus and photosensitivity (see management sections in relevant chapters). [163–167]

Levetiracetam is the only one of the newer AEDs to have been successfully submitted to a prospective RCT in JME and other IGEs with myoclonic jerks. The study concluded that 'levetiracetam proved to be highly efficacious in the treatment of refractory patients with IGE experiencing myoclonic seizures. Levetiracetam's outstanding tolerability profile was also confirmed.'[163]

Its efficacy on primarily GTCSs has also been documented with RCTs.[164] That levetiracetam is a first-class AED in syndromes of IGEs has also been more recently confirmed.[165–167]

Levetiracetam also appears effective in benign childhood focal epilepsies,[168–170] as well as epileptic encephalopathies such as Lennox–Gastaut,[171,172] Landau–Kleffner[173] syndrome and myoclonic syndromes.[174]

As expected by its favourable pharmacokinetic profile, levetiracetam was found to be effective, well tolerated and safe in patients with epilepsy and other concomitant medical conditions, including brain tumours.[175,176] Considering also its relatively safe profile, levetiracetam may be a first-choice AED in the elderly.[177,178]

Levetiracetam is available in oral and intravenous formulations. Parenteral formulations are needed when oral administration is temporarily not feasible.[179]

Dosage and titration

Adults: start treatment with 1000 mg/day (twice-daily dosing), which may be sufficient for seizure control. If needed, levetiracetam can be titrated in steps of 500 mg/week to a maximum of 3000 mg/day. Personally, I recommend starting with 250 mg twice daily and titrating upwards according to the response.

Children: start with 5–10 mg/kg/day, which may be sufficient for seizure control. If needed, levetiracetam can be titrated in steps of 5–10 mg/kg/week to a usual maintenance dose of 20–40 mg/kg/day (a maximum of 60 mg/kg/day has been used) given in two equally divided doses.[137,180–183]

Based on weight, the maintenance dose for children should be 30–40% higher than that for adults. The reason for this is that levetiracetam clearance in children is 30–40% higher than in adults.[184,185] The increase, compared with adults, is even higher in infants.[186,187]

Levetiracetam administered by intravenous infusion at dosages and/or infusion rates higher than those proposed are well tolerated in healthy subjects, and the pharmacokinetic profile is consistent with that for oral levetiracetam.[188,189]

Dosing: twice daily. Dose adjustment is required for patients with renal dysfunction, but not for patients with liver disease.

TDM: usually not needed (see useful note on page XXX) and can be efficacious from the starting dose. However, pregnancy appears to enhance the elimination of levetiracetam, resulting in a marked decline in plasma concentration, which suggests that TDM may be of value.[190]

Reference range: 6–20 mg/l (35–120 μmol/l).

Main ADRs

Levetiracetam is probably the AED that is most free from ADRs. Few major ADRs were reported in the clinical trials and, overall, their incidence in the levetiracetam-treated groups was little higher than that in the placebo groups.[191]

Frequent and/or important: the most common ADRs are somnolence, asthenia and dizziness, which are dose-dependent and reversible. Others include headache, infection (common cold or upper respiratory infections, which were not preceded by low neutrophil counts that might suggest impaired immunological status), anorexia, behavioural disturbances, pharyngitis and pain. No withdrawal-related behavioural ADRs were reported during the cross-titration period.[136,137] Levetiracetam interferes with rapid motor learning in humans due to suppression of excitatory activity in the motor cortex.[192]

Caution should be exercised when administering levetiracetam to individuals who may be prone to psychotic or psychiatric reactions (see disadvantages on page 530).

In an uncontrolled study, add-on levetiracetam was associated with a paradoxical increase in seizure frequency, particularly in mentally retarded patients and those with difficult-to-treat focal-onset seizures treated with high doses of levetiracetam.[193] This may be avoided by using a lower initial dose and a slower dose escalation than recommended.

FDA warning: All patients who are currently taking or starting on levetiracetam for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category C. Recently, in the UK Epilepsy and Pregnancy Register of 117 pregnancies exposed to levetiracetam (39 in monotherapy and 78 in combination with at least one other AED), only three infants (all in the polytherapy group) had a MCM (2.7%; 95% confidence interval [CI], 0.9–7.7%) (see also Table 7.15).[194]

Breastfeeding: there is an extensive transfer of levetiracetam from mother to foetus and into breast milk. However, breast-fed infants have very-low levetiracetam plasma concentrations, suggesting a rapid elimination of levetiracetam[190,195] (see also Table XX in Chapter 7).

Interaction with hormonal contraception: none.

Main mechanisms of action

It has a novel mechanism of action that is distinct from that of other AEDs by targeting a synaptic vesicle protein in presynaptic terminals.[196–198] Its anti-epileptic activity does not involve a direct interaction with any of the three main mechanisms of the other AEDs. Thus, levetiracetam does not modulate Na^+ and low voltage-gated (T-type) Ca^{2+} currents, and does not induce any conventional facilitation of the GABAergic system. In contrast, levetiracetam has been observed to exert several atypical electrophysiological actions, including a moderate inhibition of high voltage-gated N-type Ca^{2+} currents, reduction of intracellular Ca^{2+} release from the endoplasmic reticulum, as well as suppression of the inhibitory effect of zinc and other negative allosteric modulators of both GABA- and glycine-gated currents.

The apparent absence of any direct interaction with conventional mechanisms involved in the action of other AEDs parallels the discovery of a specific binding site for levetiracetam. Recent experiments have shown that the synaptic vesicle protein 2A (SV2A) is the binding site of levetiracetam.[199,200]

Studies in mice lacking SV2A indicate that this protein has a crucial role in the regulation of vesicle function, probably involving a modulation of vesicle fusion. These mice seem normal at birth, but develop unusually severe seizures by 1 or 2 weeks of age and die within 3 weeks after birth.[199] Brain membranes and purified synaptic vesicles from mice lacking SV2A did not bind a tritiated derivative of levetiracetam, indicating that SV2A is necessary for levetiracetam binding. Levetiracetam and related derivatives bind to SV2A, but not to the related isoforms SV2B and SV2C expressed in fibroblasts, indicating that SV2A is sufficient for levetiracetam binding. In contrast, none of the other AEDs tested revealed any binding to SV2A.[199]

The severe seizures observed in mice lacking SV2A support the interpretation that this protein influences mechanisms of seizure generation or propagation. Furthermore, there is a strong correlation between the binding affinity of a series of levetiracetam derivatives such as brivaracetam and their anticonvulsant potency in the audiogenic seizure mice model. These results suggest that levetiracetam's interaction with SV2A provides a significant contribution to its anti-epileptic activity.

Pharmacokinetics

The pharmacokinetic profile of levetiracetam closely approximates the ideal characteristics expected of an AED, with good bioavailability, rapid achievement of steady-state concentrations, linear and time-invariant kinetics, minimal protein binding, and minimal metabolism.[201]

Levetiracetam, comes especially close to fulfilling the desirable pharmacokinetic characteristics for an AED: (1) it has a high oral bioavailability, which is unaffected by food; (2) it is not significantly bound to plasma proteins; (3) it is eliminated partly in unchanged form by the kidneys and partly by hydrolysis to an inactive

metabolite, without involvement of oxidative and conjugative enzymes; (4) it has linear kinetics; and (5) it is not vulnerable to important drug interactions, nor does it cause clinically significant alterations in the kinetics of concomitantly administered drugs. Although its half-life is relatively short (6–8 hours), its duration of action is longer than anticipated from its pharmacokinetics in plasma, and a twice-daily dosing regimen is adequate to produce the desired response.[151]

Oral bioavailability: 100% and it is unaffected by food. Levetiracetam is rapidly and almost completely absorbed after oral administration with peak plasma concentrations occurring in about 1 hour. The pharmacokinetics are linear and time-invariant, with low intra- and inter-subject variability.

Protein binding: <10%. Levetiracetam is not appreciably protein-bound nor does it affect the protein binding of other drugs. Its volume of distribution is close to the volume of intracellular and extracellular water.

Metabolism/elimination: the major metabolic pathway of levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. This is not dependent on the hepatic CYP system. Further, levetiracetam does not inhibit or induce hepatic enzymes to produce clinically relevant interactions. Levetiracetam is eliminated from the systemic circulation by renal excretion as an unchanged drug, which represents 66% of the administered dose. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolites have no known pharmacological activity and are also renally excreted.

Elimination half-life: 6–8 hours. It is shorter in children and longer in the elderly and subjects with renal impairment.

Drug interactions

Unlike the majority of other AEDs, levetiracetam has no clinically meaningful drug–drug interactions.

Other AEDs: levetiracetam does not influence the plasma concentration of existing AEDs. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproate. Enzyme inducers may decrease levetiracetam plasma levels by 20–30%.[202]

Other non-AEDs: levetiracetam has no known interactions with other drugs such as oral contraceptives, warfarin and digoxin. It does not reduce the effectiveness of oral contraceptives.

Main disadvantages

There are some reports of increased behavioural and psychiatric abnormalities, particularly in children or patients that may be prone to such problems.[203–206] An explanation for this may be the fast titration recommended by the manufacturers. A recent short-term study found that add-on levetiracetam in patients with intractable focal epilepsies has a favourable neuropsychological and psychiatric impact.[207]

Oxcarbazepine

Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz-[b,f]azepine-5-carboxamide) is a 0-keto derivative of carbamazepine, but these two AEDs have some significant differences.[208] The anti-epileptic activity is mainly exerted via its major metabolite, hydroxy-10,11-dihydro-5H-dibenzazepine-5-carboxamide (MHD). It was first licensed as an AED in 1990 in Denmark.

Authorised indications

UK-SmPC: monotherapy or adjunctive therapy for focal seizures with or without secondarily GTCSs in patients ⩾6 years of age.

FDA-PI: (1) monotherapy or adjunctive therapy in the treatment of focal seizures in adults and as monotherapy in the treatment of focal seizures in children aged 4 years and above with epilepsy, and (2) as adjunctive therapy in children aged 2 years and above with epilepsy.

Note

Oxcarbazepine versus carbamazepine

Oxcarbazepine is similar to carbamazepine in its anti-epileptic efficacy and main mechanisms of action. However, it is better tolerated and has fewer interactions with other drugs because it does not undergo metabolism to 10,11–epoxide. In contrast to carbamazepine, involvement of the hepatic CYP-dependent enzymes in the metabolism of oxcarbazepine is minimal. Oxcarbazepine has a lower incidence of idiosyncratic reactions than carbamazepine; but hyponatraemia is more common with oxcarbazepine than carbamazepine.

The profile of oxcarbazepine is more similar to that of the slow-release carbamazepine preparations.

Clinical applications

Oxcarbazepine is a first class AED for monotherapy, conversion to monotherapy or adjunctive therapy for all types of focal seizures with or without secondarily GTCSs.[209–211] This has been documented in a series of clinical trials and by extensive clinical use. In 2003, it became the first AED to be approved by the FDA in 25 years for use as monotherapy in children with focal epilepsy.

Dosage and titration

Adults: start treatment with 150 mg/day and increase by 150 mg/day every second day until a target dose of 900–1200 mg/day is reached. Others start with 600 mg/day and increase weekly in 600 mg increments until a maintenance dose of between 1200 and 2400 mg/day is reached. I would recommend the principle of 'start low and go slow' to avoid ADRs and particularly rash.

In patients with impaired renal function (creatinine clearance <30 ml/min), oxcarbazepine should be initiated at one-half of the usual starting dose and increased slowly until the desired clinical response is achieved or ADRs appear.

Children: start with 10 mg/kg/day in two or three divided doses. The dosage can be increased by 10 mg/kg/day at approximately weekly intervals to a maximum of 30–46 mg/kg/day.

Dosing: twice or three-times daily.

TDM: because of striking pharmacokinetic changes, and clinical response, oxycarbazepine levels should be monitored throughout pregnancy and the puerperium.[212,213]

Reference range: MHD, 4–12 mg/l (50–140 µmol/l).

Main ADRs

Frequent and/or important: the most common CNS adverse events are headache, dizziness, fatigue, nausea, somnolence, ataxia and diplopia. Most of these are dose related, they usually occur at the start of therapy and subside during the course of therapy.

Serious: the reported rate of skin rash with oxcarbazepine is around 2% (adults) and 5% (children), as opposed to 5–10% with carbamazepine. Multi-organ hypersensitivity disorder and Stevens–Johnson syndrome have been reported.

Cross-reactivity with carbamazepine is approximately 25% (i.e. of the patients who have skin rash with carbamazepine, 25% will also have skin rash with oxcarbazepine). Therefore, given the availability of other AEDs, oxcarbazepine may not be a good option for patients who developed idiosyncratic reactions with carbamazepine or other AEDs e.g. lamotrigine and phenytoin.

Hyponatraemia (serum sodium level <125 mmol/l) occurs in 3% of patients on oxcarbazepine. This develops gradually during the first few months of treatment. It is usually benign and can be reversed by fluid restriction or a reduction in the dose of oxcarbazepine. Acute water intoxication is rare. Measurement of serum sodium levels are needed for patients with renal disease, those taking medication that may lower serum sodium levels (e.g. diuretics, oral contraceptives or non-steroidal anti-inflammatory drugs) or if clinical symptoms of hyponatraemia develop.

Consumption of large volumes of any fluid should be discouraged.

Oxcarbazepine is contraindicated in patients with a history of atrioventricular block.

FDA warning: All patients who are currently taking or starting on oxcarbazepine for any indication should be monitored for notable changes in behaviour that

could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category C. Seizure control may be lost during pregnancy in women on oxcarbazepine.[129] The concentration of oxcarbazepine and its metabolite decrease markedly during pregnancy and may increase several fold after delivery.[212,213]
Breastfeeding: oxcarbazepine and its active metabolite are secreted in significant amounts in breast milk.
Interaction with hormonal contraception: yes.

Main mechanisms of action

Oxcarbazepine exerts its anti-epileptic activity primarily through its major metabolite MHD. Like carbamazepine, blockade of voltage-sensitive sodium channels is its main mechanism of action. Others include reduction of the release of excitatory amino acids, probably by inhibiting high voltage-activated calcium currents. An effect on potassium channels might be clinically important.

Pharmacokinetics

Oral bioavailability: >95% and peak concentrations are reached within 4–6 hours. Absorption is unaffected by food.
Protein binding: only 38% of the MHD is bound to serum proteins, as compared with 67% for the parent compound.
Metabolism: oxcarbazepine is rapidly metabolised in the liver to form the pharmacologically active MHD. This is then conjugated to a glucuronide compound and excreted in the urine as a monohydroxy derivative.
Elimination half-life: 8–10 hours. This is shorter in children and longer in the elderly.

As a neutral lipophilic substance, the active metabolite MHD of oxcarbazepine is able to diffuse rapidly through the various membranes and the blood–brain barrier.

Drug interactions

The oxcarbazepine–MHD complex lowers plasma concentrations of some drugs, such as hormonal contraceptives and lamotrigine, and increases the plasma concentration of others, such as phenytoin. Conversely, strong inducers of the CYP enzyme system, such as carbamazepine and phenytoin, lower plasma levels of MHD by 29–40%.

Combination therapy with monoamine oxidase inhibitors should be avoided, because oxcarbazepine has structural similarities with tricyclic antidepressants.

Main disadvantages

- Oxcarbazepine is contraindicated in generalised seizures, such as absences or myoclonic jerks in syndromes of IGE.[214] It may not be effective in neonates and children <2 years of age.
- One out of four patients have cross sensitivity to idiosyncratic reactions with carbamazepine or other AEDs.
- Although it is among the first-choice AEDs for monotherapy in focal epilepsies, its use as polytherapy is less satisfactory because of drug–drug interactions.
- Unless levels of oxcarbazepine are adjusted, seizures may increase during pregnancy and toxicity may appear postpartum.

Useful clinical notes

- Conversion to oxcarbazepine from carbamazepine or phenytoin is complicated by the initial need for higher doses of oxcarbazepine than needed later as monotherapy.
- A carbamazepine dose of 200 mg appears to be equivalent to 300 mg of oxcarbazepine.
- It is possible to change from carbamazepine to oxcarbazepine abruptly, using a dose ratio of 200 mg carbamazepine to 300 mg oxcarbazepine, without the need for titration.[215] A lower ratio 1:1 or 1:1.25 is usually better tolerated, especially if the conversion is from slow-release preparations of carbamazepine. Levels of concomitant medication may be affected by the removal of the enzyme-inducing effects of carbamazepine.

Phenobarbital

Phenobarbital was introduced into clinical practice in 1912[49] and is still a widely used AED, particularly when cost is a problem.[216–219] It is highly effective in all seizure types except absences.[216–219]

Authorised indications:

UK-BNF for Children: all forms of epilepsy except absence seizures in patients of any age, including neonates.

USA: focal seizures and GTCSs in patients of any age, including neonates.

Current main applications

Phenobarbital is still a main AED for neonatal and febrile seizures (if treatment is needed) and established convulsive status epilepticus. It is the main monotherapy AED in resource-poor countries.

In small doses at night, phenobarbital is useful as adjunctive therapy in many forms of epilepsies other than absences. It is still used in some European countries in the treatment of JME.

Dosage and titration

'Start very low and go very slow' is particularly important.

Maintenance dose: adults 50–200 mg at night (initial 30 mg/day) and children 3–5 mg/kg/day.

Dosing: once daily prior to going to sleep.

TDM: necessary.

Reference range: 10–40 mg/l (43–172 µmol/l).

Main ADRs

Frequent and/or important: the most common CNS adverse events are drowsiness, sedation or aggression, depression, behavioural disturbances and impairment of cognition and concentration. Hyperkinesia (hyperactivity) is a major problem in children.

Serious: hepatitis, cholestasis, thrombocytopenia, agranulocytosis; skin rash and multi-organ hypersensitivity disorder and Stevens–Johnson syndrome.

Considerations in women

Pregnancy: category D.

Breastfeeding: phenobarbital is secreted in significant amounts in breast milk (40% of the plasma concentration) and may cause sedation to the baby. However, avoiding breastfeeding may cause withdrawal symptoms to the neonate.

Interaction with hormonal contraception: yes.

Main mechanisms of action

Phenobarbital exerts its anti-epileptic activity through multiple modes of action. Its primary effect is probably through its post-synaptic binding to $GABA_A$ receptors. It also blocks voltage-sensitive sodium and potassium channels, reduces presynaptic calcium influx and possibly inhibits glutamate-mediated currents.

Pharmacokinetics

Oral bioavailability: >90% and peak concentrations are reached within 8–12 hours.

Protein binding: 20–50%.

Metabolism: phenobarbital is metabolised in the liver, mainly through hydroxylation and glucuronidation, and induces most isozymes of the CYP system.

Elimination half-life: 2–7 days. It is a very long-acting barbiturate.

Drug interactions

Phenobarbital, a potent enzyme inducer (CYP2C, CYP3A, microsomal epoxide hydrolases and UGTs), has marked and clinically significant interactions with other drugs including AEDs and hormonal contraception. It lowers the plasma concentration of carbamazepine, clonazepam, lamotrigine, phenytoin (but may also raise phenytoin concentration), tiagabine, valproate and zonisamide. Plasma levels of phenobarbital decrease in co-medication with enzyme inducers; they increase with valproate, felbamate and dextropropoxyphene.

Main disadvantages

ADRs are the main disadvantage of phenobarbital. It is primarily unsuitable for children and elderly patients.

Useful clinical notes

- It is erroneous to attempt substitution of phenobarbital in well-controlled patients unless it is associated with unacceptable ADRs.
- Withdrawal should be in very small dosages and at long intervals because of the risk of withdrawal seizures.
- Always start and titrate slowly with small doses at night (20–30 mg). Avoid high doses (maximum in adults 200 mg).

Other available main barbiturate agents

Primidone probably has similar ADRs to phenobarbital and is of no better efficacy.

UK-SmPC: management of grand mal and psychomotor (temporal lobe) epilepsy. It is also of value in the management of focal and jacksonian seizures, myoclonic jerks and akinetic attacks.

FDA-PI: sole or adjunctive therapy in the control of grand mal, psychomotor and focal epileptic seizures in adults and children. It may control grand mal seizures refractory to other anticonvulsant therapy.

Barbexaclone is of similar effectiveness as phenobarbital, but less sedative.[221]

Phenytoin

Phenytoin was introduced into clinical practice in 1938[49] and is probably the most widely used AED.[222] It is highly effective in focal seizures and GTCSs.[216–218,220] It is contraindicated in absences and myoclonic jerks, progressive myoclonic epilepsies such as Unverricht syndrome, and probably in Lennox–Gastaut syndrome and other childhood epileptic encephalopathies (but may be effective in tonic seizures).

Authorised indications

UK-SmPC: control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

FDA-PI: control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Clinical applications

Phenytoin is still very useful in neonatal seizures (if phenobarbital fails), focal seizures and GTCSs (no other AED had superior efficacy than phenytoin in RCTs, but ADRs are hindering its use), and established convulsive or focal status epilepticus (often considered as the first choice).

Dosage and titration

Maintenance dose: adults 200–400 mg nocte (initially 50–100 mg/day) and children 5–10 mg/kg/day.

Dosing: once daily.

TDM: necessary, mainly because of its narrow therapeutic range and saturable kinetics (see metabolism).

Reference range: 10–20 mg/l (40–80 µmol/l).

Main ADRs

Serious early non-dose related: anticonvulsant hypersensitivity syndrome that may be fatal (Stevens–Johnson and Lyll's syndrome).

Dose-related: ataxia, drowsiness, lethargy, sedation and encephalopathy.
Chronic use: gingival hyperplasia, hirsutism and dysmorphism.
Other reactions: haematological, neurological (e.g. peripheral neuropathy and cerebellar atrophy) and others, such as systemic lupus erythematosus. Its effect on cognition is probably similar to that of carbamazepine, but much better than that of phenobarbital.

Considerations in women

Pregnancy: category D.
Breastfeeding: small amounts are excreted in breast milk.
Interaction with hormonal contraception: yes.

Main mechanisms of action

Blockade of voltage-sensitive sodium channels is the main mechanism of action of phenytoin.

Pharmacokinetics

Oral bioavailability: 95% and peak concentrations are reached within 4–12 hours. Absorption may be erratic; food and small bowel disease significantly alter its absorption.
Protein binding: >85%.
Metabolism: phenytoin is metabolised in the liver, mainly through para-hydroxylation by the hepatic P450 system. Its metabolism is dose-dependent because of hepatic enzyme saturation kinetics. At higher drug concentrations, phenytoin kinetics are non-linear and thus a small increase in dose may lead to a large increase in drug concentration as elimination becomes saturated.
Elimination half-life: 7–40 hours. This is plasma level and co-medication. It is shorter in children and longer in the elderly.

Drug interactions

These are multiple. Phenytoin, an enzyme inducer, significantly affects plasma levels of other drugs, including AEDs and hormonal contraception, and *vice versa*. It lowers the plasma concentration of clonazepam, carbamazepine, lamotrigine, tiagabine, topiramate, valproate, zonisamide and the active metabolite of oxcarbazepine. It often raises the plasma concentration of phenobarbital and sometimes lowers the plasma concentration of ethosuximide and primidone (by increasing conversion to phenobarbital).

Disadvantages

- Acute and long-term ADRs hamper its use.
- Long-term use of phenytoin is unsuitable for women because of aesthetic reasons and teratogenic properties.
- Therapeutic range is narrow and close to the toxic range requiring frequent monitoring of plasma levels. After a certain dose (100–200 mg/day), further increases should be small (25 mg/day) and over longer intervals (every 2–4 weeks).

Useful clinical notes

Phenytoin is a very effective drug in focal seizures and secondarily GTCSs, but it is often contraindicated in generalised epilepsies.

Other available phenytoin-related agents

Phosphenytoin for intramuscular and intravenous use; it is preferred to phenytoin because it does not produce adverse tissue effects (see Chapter 3, page XXX).[223–228]
Ethotoin and mephenytoin probably offer no advantage over phenytoin.

Pregabalin

Pregabalin [(*S*)-3-(aminomethyl)-5-methylhexanoic acid, also known as (*S*)-3-isobutyl GABA] is structurally related to gabapentin. It was introduced into clinical practice in 2004 for the treatment of certain types of peripheral neuropathic pain, generalised anxiety disorders and as an adjunctive therapy for focal seizures with or without secondarily generalisation.

Authorised indications

EMEA-SmPC: adjunctive therapy in adults with focal seizures with or without secondary generalisation.
FDA-PI: adjunctive therapy in adults with focal-onset seizures.

Clinical applications[229–232]

Post-marketing experience is still very limited and it appears that pregabalin is a narrow-spectrum AED that exaggerates myoclonus. Therefore, pregabalin should be only used in rational polytherapy in adults with intractable focal seizures who have failed to respond to other preferred AED combinations as detailed in Chapter 15 (page XXX).

Treatment-emergent myoclonic jerks, even in patients with focal seizures,[233,234] may be a warning sign against the use of pregabalin in generalised and other myoclonic epilepsies, where myoclonus is often a prominent symptom to treat.

Dosage and titration

Adults: start treatment with 150 mg/day and, based on individual patient response and tolerability, increase to 300 mg/day after an interval of 7 days, and to a maximum dose of 600 mg/day after an additional 7-day interval. The maintenance dose is 150–600 mg/day in either two or three divided doses taken orally.

Dosage adjustments are necessary in patients with renal impairment and the elderly.
TDM: probably not needed (see useful note on page XXX).
Reference range: not determined.

Main ADRs

Significant weight gain was noted in 5.6% of pregabalin-treated patients in all trials (see also page XXX).

The most commonly reported (>10%) ADRs in placebo-controlled, double-blind studies were somnolence and dizziness. Other commonly reported (>1% and <10%) ADRs were increased appetite, euphoric mood, confusion, decreased libido, irritability, ataxia, attention disturbance, abnormal coordination, memory impairment, tremor, dysarthria, paraesthesiae, blurred vision, diplopia, vertigo, dry mouth, constipation, vomiting, flatulence, erectile dysfunction, fatigue peripheral oedema, feeling drunk and abnormal gait.

There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema and Stevens Johnson syndrome.

Hypoglycaemic medication may need to be adjusted in diabetic patients who gain weight.

FDA warning: All patients who are currently taking or starting on pregabalin for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category C.
Others: weight gain, which is often significant, may be associated with polycystic ovary syndrome.

Main mechanisms of action

The precise mechanism of action of pregabalin is still unclear.[235] Despite being an analogue of GABA, pregabalin is inactive at $GABA_A$ and $GABA_B$ receptors and it has no effect on GABA uptake or degradation. Pregabalin probably decreases central neuronal excitability by binding to an auxiliary subunit ($\alpha_2\delta$ protein) of a high-voltage-gated calcium channel on neurones in the CNS. It reduces the release of certain neurotransmitters including glutamate, noradrenaline and substance P.

Pharmacokinetics

Oral bioavailability: >90%.
Protein binding: does not bind to plasma proteins.
Metabolism: pregabalin is not metabolised in the liver and does not induce hepatic enzymes. It is excreted renally.
Elimination half-life: 6 or 7 hours.

Drug interactions

Pregabalin does not affect the plasma concentration of other AEDs.[236] In addition, it does not interact with a number of other drug types, including hormonal contraception.

However, pregabalin appears to have an additive effect on the impairment of cognitive and gross motor function when co-administered with oxycodone (an opioid), and it potentiates the effect of lorazepam and ethanol.

Patients with galactose intolerance, glucose–galactose malabsorption or Lapp lactase deficiency should not take pregabalin.

Main disadvantages

It is still early to make any predictions for the role of pregabalin in the treatment of focal epilepsies. However, the high incidence of weight gain (consider the decline in the use of valproate because of this side effect and its causative relation with polycystic ovary syndrome in women), treatment-emergent myoclonic jerks and similarities with gabapentin[237] are not promising signs.

Rufinamide

Rufinamide[238–242] is a triazole derivative structurally unrelated to any currently marketed AED.

Authorised indications

EMEA-SmPC/FDA-PI: adjunctive treatment of seizures associated with Lennox–Gastaut syndrome in patients 4 years and older.

Clinical applications

Rufinamide is one of the latest AEDs marketed for the treatment of epileptic seizures. Its licenced indications are for Lennox–Gastaut syndrome, but the next step will probably be for adjunctive treatment of intractable focal epilepsies.

Dosage and titration

A lower maximum dose of rufinamide is recommended for patients being co-administered valproate, which significantly decreases clearance of rufinamide, particularly in patients with a low body weight of <30 kg.
Adults and children >30 kg: start treatment with a daily dose of 400 mg, which may be increased by increments of 400 mg/day as frequently as every 2 days, to up to a maximum recommended dose of 1800 mg/day (in the 30–50 kg weight range), 2400 mg/day (50.1–70 kg) or 3200 (>70 kg).
Children <30 kg not receiving valproate: start with a daily dose of 200 mg, which may be increased by increments of 200 mg/day as frequently as every 2 days, up to a maximum recommended dose of 1000 mg/day.
Children <30 kg also receiving valproate: start with a daily dose of 200 mg, which after a minimum of 2 days may be increased by 200 mg/day, to the maximum recommended dose of 400 mg/day.
Dosing: twice daily. Tablets can be crushed and administered in half a glass of water.
TDM: unknown.
Reference range: unknown.

Main ADRs

Frequent and/or important: headache, dizziness, fatigue, somnolence, ataxia and gait disturbances.
Serious: status epilepticus has been observed during clinical development studies, which led to the discontinuation of rufinamide in 20% of cases and none in the placebo group.

Idiosyncratic reactions and hypersensitivity syndrome (rash and fever with other organ system involvement; e.g. lymphadenopathy, liver function test abnormalities and haematuria may rarely occur with rufinamide).

Rufinamide is contraindicated in patients with familial short QT syndrome (see discussion of cardiac ARDs in Chapter 7). Formal cardiac ECG studies demonstrated shortening of the QT interval (by up to 20 msec) with rufinamide treatment. Reductions of the QT interval below 300 msec were not observed in the formal QT studies with doses up to 7200 mg/day. Moreover, there was no signal for drug-induced sudden death or ventricular arrhythmias.

Considerations in women

Pregnancy: category C.
Breastfeeding: unknown but it is likely to be excreted in the breast milk.
Interactions with hormonal contraception: yes.

Mechanism of action

Rufinamide reduces the recovery capacity of neuronal sodium channels after inactivation, prolonging their inactive state by limiting neuronal sodium-dependent action potential firing.

Pharmacokinetics

Oral bioavailability: is dose dependent; as the dose increases, the bioavailability decreases. Food increases the bioavailability of rufinamide by approximately 34% and the peak plasma concentration by 56%.
Protein binding: 34%.
Metabolism: rufinamide is extensively metabolized but has no active metabolites. The primary biotransformation pathway is carboxylesterase(s)-mediated hydrolysis of the carboxylamide group to the acid derivative CGP 47292. There is no involvement of oxidizing cytochrome P450 enzymes or glutathione in the biotransformation process.

Rufinamide is a weak inhibitor of CYP 2E1. It did not show significant inhibition of other CYP enzymes. Rufinamide is a weak inducer of CYP 3A4 enzymes.

Excretion: predominantly renal (85% of the dose).
Elimination half-life: 6–10 hours.

Drug interactions

Rufinamide does not have clinically relevant effects on other AEDs but may decrease phenytoin clearance and increase average steady-state plasma concentrations of co-administered phenytoin.

However, other AEDs significantly affect rufinamide plasma concentrations, which are decreased by co-administration with carbamazepine, phenobarbital, primidone, phenytoin or vigabatrin.

Conversely, rufinamide plasma concentrations significantly increase with valproate co-administration and these are pronounced in patients of low body weight (<30 kg).

No significant changes in the concentration of rufinamide are observed following co-administration with lamotrigine, topiramate or benzodiazepines.

Patients treated with drugs that are metabolised by the CYP3A enzyme system should be carefully monitored for 2 weeks at the start of, or after the end of, treatment with rufinamide or after any marked change in the dose. A dose adjustment of the concomitantly administered drug may need to be considered. These recommendations should also be considered when rufinamide is used concomitantly with drugs with a narrow therapeutic window, such as warfarin and digoxin. No data on the interaction of rufinamide with alcohol are available.

Rufinamide interferes with hormonal contraception. Women on hormonal contraceptives are advised to use an additional safe and effective contraceptive method.

Main disadvantages

Development of status epilepticus, idiosyncratic reactions that may be serious and significant interactions with enzyme inducers (they reduce its plasma concentration) and valproate (it increases its plasma concentration).

Stiripentol[243–248]

4,4-Dimethyl-1-[3,4-(methylenedioxy)-phenyl]-1-penten-3-ol was selected for possible antiepileptic effects from a series of alpha-ethylene alcohols. Stiripentol has been known for over 30 years but because of significant problems, it was only licensed in 2009 in Europe as an adjunct-AED for Dravet syndrome, under the brand name Diacomit.

Authorised indications

SmPC: use in conjunction with clobazam and valproate as adjunctive therapy for refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate.
FDA :Not yet approved.

Clinical applications

Limited to GTCS of Dravet syndrome. There are no clinical study data to support it as monotherapy in Dravet syndrome or other epilepsies. Studies in adult patients are disappointing.

Dosage and titration

Patients aged 3–18 years: Start with 10–20 mg/Kg/day in 2–3 divided doses and increase over 3 days using upwards dose escalation to reach the recommended dose of 50 mg/kg/day administered in 2 or 3 divided doses in conjunction with clobazam and valproate.

There are no clinical study data to support its safety at doses greater than 50mg/kg/day.
Dosing: two or three times daily.
TDM: unknown.
Reference range : unknown.

Main ADR

Frequent and/or important: anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia, dystonia and vomiting.
Serious: rash, potentiation of serious ADRs of valproate in young age groups. Transient aplastic anaemia and leukopenia have also been reported.

Considerations in women

Probably not relevant for this drug as it is licensed for Dravet syndrome only.
Pregnancy: category C.
Breastfeeding: unknown but possibly excreted in breast milk (animal data).
Interactions with hormonal contraception: yes.

Main mechanisms of action

Not fully elucidated. Direct antiepileptic effect is attributed to increase GABA levels in the brain through inhibition of synaptosomal uptake of GABA and/or inhibition of GABA transaminase. Its indirect efficacy in polytherapy is through increasing levels of other AEDs.

Pharmacokinetics

Oral bioavailability: easily and quickly absorbed but absolute bioavailability is unknown.
Protein binding: 99%
Metabolism: extensively metabolized mainly through demethylenation and glucuronidation (see below for drug interactions). Most is excreted in the urine.
Elimination half-life: 4.5 hours to 13 hours, increasing with dose.

Drug interactions

Multiple, complex and of high clinical significance. Stiripentol inhibits several cytochrome P450 isoenzymes such as CYP2C19, CYP2D6 and CYP3A4 and thus interacts with many AEDs (phenobarbital, phenytoin, carbamazepine, diazepines, tiagabine, valproate) and other medicines (theophyline, antihistamines such as astemizole, chlorpheniramine and many others), increasing their plasma levels with potential risk of overdose. It inhibits the metabolism of clobazam and its N-desmethylclobazam biotransformation, thus increasing their plasma concentrations.

Main disadvantage

Extremely difficult to use because of numerous drug interactions and of doubtful efficacy other than for its limited licensed indication.

Sulthiame

The story of sulthiame's transition from a disgraced to a useful drug is interesting.[249–253]

Sulthiame is a sulfonamide derivative with carbonic anhydrase-inhibiting properties (it is only one-sixteenth as potent as acetazolamide). It was first introduced as an AED in the 1960s, but its use was largely abandoned in the 1970s on the assumption that it had little, if any, anti-epileptic activity when used alone. Its anti-epileptic action was attributed to raised levels of concomitant medication (phenytoin, phenobarbital and primidone).[254,255] The significant improvement in the disturbed behaviour of mentally handicapped patients was debated and attributed to the sedative effect of sulthiame.[254] Reports that sulthiame, even in monotherapy, was a very effective drug in intractable epilepsies of infancy and childhood[256] were ignored.

Recently, sulthiame appears to have experienced a revitalisation with reports (including class 1 evidence) that it is probably the most effective drug in benign childhood focal epilepsies with regard to its effect in suppressing seizures and EEG abnormalities.[250–253] Sulthiame has also re-emerged as an AED in adults.[249]

Authorised indications

It is licensed in Australia, Germany, Ireland, Israel, and some other countries, but not by the EMEA or FDA or in the UK.

Clinical applications

Mainly in benign childhood focal epilepsies,[250–252] and epileptic encephalopathies, particularly those with EEG continuous spike–wave during sleep.[253] It may also be useful in some myoclonic epilepsies.[256]

Dosage and titration

Adults: start treatment with 250 mg and increase to 750–1000 mg. The recommended doses are much lower today than they were in the 1970s (200–600 mg/day compared to 600–3600 mg/day).

Children: 10–20 mg/day (this may also be high; a daily dose of 5 mg/kg is usually very efficacious and safe in children).

Dosing: two or three times daily.

TDM: not needed.

Reference range: it has not been precisely determined but may be around 4.1 mg/l (2.2–6.1 mg/l).

Clearance of sulthiame in children is higher than in adults and thus a higher dose/kg of sulthiame is needed to obtain an effective plasma concentration.

Main ADRs

Frequent and/or important: unsteadiness and giddiness, numbness, nausea, paraesthesiae of the face and limbs, hyperventilation (rapid or deep breathing), loss of appetite and weight loss, and rash.

Serious: idiosyncratic reactions as with other sulfonamides; metabolic acidosis and nephrolithiasis as with other carbonic anhydrase inhibitors (see topiramate, page XXX).

Considerations in women

Pregnancy: category D.

Mechanism of action

The main mechanism of the anti-epileptic effect of sulthiame is unclear and may be multiple. Sulthiame inhibits the enzyme carbonic anhydrase in glial cells, increases the carbon dioxide concentration and leads to an acidification of the extracellular fluid. This results in a reduction of the inward currents operated by NMDA receptors and calcium currents, causing a depression of intrinsic neuronal excitability. Sulthiame has also been found to inhibit voltage-gated sodium channels, reduce the concentration of the excitatory neurotransmitter glutamate in the hippocampus of rats and guinea pigs, as well as the concentration of GABA in cerebral hemispheres of mice.

Pharmacokinetics

Oral bioavailability: 100%.

Protein binding: 29%.

Metabolism: hepatic.

Excretion: renal.

Elimination half-life: 5–10 hours (in children younger than 12 years) and 9–15 hours (in patients older than 12 years).

Drug interactions

These are significant. Sulthiame inhibits the metabolism of phenytoin, phenobarbital and primidone, so these drugs are elevated to 'therapeutic' or 'toxic' levels, or rise steeply when sulthiame is introduced.[255]

Main disadvantages

Serious drug–drug interactions and lack of licensed indications by the FDA and EMEA.

Tiagabine

Tiagabine [(R)-*N*-(4,4-di-(3-methyl-thien-2-yl)-but-3-enyl)nipecotic acid hydrochloride] was first licensed as an AED in 1998.[257]

Authorised indications

EMEA-SmPC/FDA-PI: adjunctive therapy for focal seizures in patients ⩾12 years of age.

Clinical applications

The anti-epileptic efficacy of tiagabine is limited to focal seizures. Its role in clinical epileptology is probably limited to adjunctive medication in severe forms of focal epilepsies that failed to respond to other AED combinations.[258,259] It may also be effective in epileptic spasms of epileptic encephalopathies.

Dosage and titration

Dosage and titration depend on co-medication.

Adults: start treatment with 4–5 mg/day for the first week. Titrate in increments of 4–5 mg/day every week in two divided doses up to a total of 30–45 mg/day (in co-medication with enzyme-inducing drugs) or 15–30 mg/day (with non-enzyme-inducing drugs).

Children: start treatment with 0.1 mg/kg/day and titrate in increments of 0.1 mg/kg/day every 1 or 2 weeks up to a total of 0.5–2 mg/kg/day.

Children eliminate tiagabine more rapidly than adults.

Dosing: twice or preferably three and sometimes four times daily.

TDM: not useful.

Reference range: 80–450 µg/l (50–250 nmol/l).

Main ADRs

Frequent and/or important: fatigue, headache, dizziness, tremor, cognitive impairment, disturbed concentration, depression and word-finding difficulties.

Serious: none. Concerns that tiagabine, like vigabatrin (another GABAergic AED), may cause visual field defects have not been substantiated.[260,261]

Seizure exacerbation: treatment-emergent absence status epilepticus has been reported in a significant number of patients (see page XXX). An opinion by a panel of experts that 'treatment with tiagabine in recommended doses does not increase the risk of status epilepticus in patients with partial seizures'[262] probably refers to focal status epilepticus and not to generalised absence status epilepticus, where the main risk lies.[263,264]

All patients who are currently taking or starting on tiagabine for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category C.

Interaction with hormonal contraception: no.

Main mechanisms of action

Tiagabine is an AED specifically designed to increase GABA longevity in the synaptic cleft. It is a potent

and selective inhibitor of GABA uptake into neurones and glial cells. This brain GABAergic-mediated inhibition of tiagabine explains its anti-epileptic effect on focal seizures and also explains its pro-absence effect (see useful note on page XXX).[263,264]

Pharmacokinetics

Oral bioavailability: <96%. High fat meals slow the rate of absorption.

Protein binding: 96%. Salicylic acid and naprofen displace tiagabine.

Metabolism: tiagabine is metabolised by hepatic CYP before conjugation to inactive metabolites excreted in the urine and faeces. It is neither an hepatic enzyme inducer nor an inhibitor.

Elimination half-life: 7–9 hours, which decreases to 2 or 3 hours in the presence of hepatic enzyme inducers. The metabolism of tiagabine is reduced in patients with hepatic dysfunction, thus prolonging its half-life to 12–16 hours.

Drug interactions

Enzyme-inducing AEDs (phenytoin, carbamazepine and phenobarbital) significantly lower the plasma concentrations of tiagabine by a factor of 1.5–3 and shorten its half-life.

Valproate displaces tiagabine from its protein-binding sites.

Tiagabine does not affect other AEDs or hormonal contraception.

Main disadvantages

- Narrow-spectrum anti-epileptic efficacy against focal seizures only. Its use is prohibiited in IGE with absences because tiagabine is a pro-absence drug.
- Multiple drug interactions and complicated dosage and titration schemes.

Topiramate

Topiramate is a sulfamate-substituted monosaccharide designated chemically as 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate. It was first introduced into clinical practice in 1995.

Authorised indications

UK-SmPC: (1) monotherapy in patients ⩾6 years of age with newly diagnosed epilepsy who have GTCSs or focal seizures with or without secondarily generalised seizures; (2) adjunctive therapy in patients ⩾2 years of age who are inadequately controlled on conventional first-line AEDs for focal seizures with or without secondarily generalised seizures, seizures associated with Lennox–Gastaut syndrome and primary GTCSs. The efficacy and safety of conversion from adjunctive therapy to topiramate monotherapy has not been demonstrated.

FDA-PI: (1) initial monotherapy for focal onset or primary GTCSs in patients ⩾10 of age; effectiveness was demonstrated in a controlled trial in patients with epilepsy who had no more than 2 seizures in the 3 months prior to enrollment. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials; (2) adjunctive therapy for adults and pediatric patients ages 2–16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Clinical applications

Topiramate is a highly efficacious new, broad-spectrum AED, but significant ADRs hinder its clinical use.[265–273] It is probably the most effective of all the newer AEDs in focal seizures. In clinical use, topiramate has been recommended for all types of seizures – focal or generalised, and idiopathic

or symptomatic – in adults and children including difficult-to-treat epileptic encephalopathies, such as West and Lennox–Gastaut syndromes.

Dosage and titration

'Start very low and go very slow' is particularly important. Treatment with topiramate should be initiated at a very low dosage and be titrated at a very slow pace. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used. Maintenance doses are usually reached in 2 months.

Adults and children over 16 years: start with 25 mg nocte for the first week and then titrate in increments of 25 or 50 mg/day in two equally divided doses at 1 or 2 week intervals. The recommended maintenance dose is 200–400 mg/day. Some authors recommend a maximum dose of 800 mg/day, but this is rarely tolerated.

Children 6–16 years: start treatment with 25 mg or 1–3 mg/kg/day nocte for the first week. Titrate with increments of 1–3 mg/kg/day in two divided doses at 1- or 2-week intervals to a recommended maintenance dose of 5–9 mg/kg/day in two divided doses.

Children 2–6 years: start with 0.5–1 mg/kg/day nocte for the first week and then titrate as for older children.

Renally impaired patients: half of the usual dose is recommended. Patients with moderate or severe renal impairment may take 10–15 days to reach steady-state plasma concentrations compared with 4–8 days in patients with normal renal function.

Tablets should not be broken.

Therapy should not be withdrawn suddenly because of the risk of aggravating seizures.

Dosing: twice daily.

TDM: probably not needed (see useful note on page XXX).

Reference range: 9–12 mg/l (15–60 µmol/l).

Main ADRs

Topiramate is an inferior newer AED with respect to ADRs, which are common, multiple and sometimes severe or potentially fatal.[274,275] Withdrawal rates were low in controlled trials (4.8%),[266,276] but appear to be much more frequent in non-comparative and post-marketing studies.[265,277] On the positive side, topiramate lacks significant idiosyncratic reactions.

Frequent and/or important: somnolence, anorexia, fatigue and nervousness are common as in other AEDs, but most of the other frequent ADRs are of concern.

Serious: ADRs are numerous and diverse.

Abnormal thinking, consisting of mental slowing and word-finding difficulties, has been reported in 31% of patients with titration rates of 100 mg per week.[278,279]

Difficulty with concentration/attention, memory impairment, psychomotor slowing and speech disorders are often very severe, even when treatment starts with small doses and titration is slow.

Behavioural and cognitive problems are a limiting factor in some children. Topiramate was reported to have a negative impact on cognition with impairment of performance on tests requiring verbal processing, which was consistent with subjective complaints of patients.[280–281]

Weight loss (10% of patients) may be considered as beneficial by some women, but is sometimes relentless and extremely problematic.[265] A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while receiving topiramate.

Treatment-emergent paraesthesiae and abdominal pains may be confused with other systemic disorders.

Metabolic acidosis: hyperchloraemic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with use of topiramate. The incidence of persistent treatment-emergent decreases in serum bicarbonate is high and rises significantly with increasing topiramate dosages. Generally, the decrease in bicarbonate occurs early in treatment, although it can occur at any time during treatment.

Markedly abnormal low serum bicarbonate levels (i.e. an absolute value of <17 mEq/l and >5 mEq/l decrease from pretreatment levels) occurred in 11% of children receiving topiramate 6 mg/kg/day and 3% of adults receiving 400 mg/day. In placebo-controlled trials of migraine prophylaxis in adults, markedly abnormally low serum bicarbonate levels

occurred in 11% of those receiving 200 mg/day, 9% on 100 mg/day, 2% on 50 mg/day and <1% with placebo.

Diseases or therapies that predispose to acidosis, such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet or certain drugs (e.g. zonisamide) may be additive to the bicarbonate-lowering effects of topiramate.

Manifestations of acute or chronic metabolic acidosis may include hyperventilation, non-specific symptoms, such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor.

Depending on the underlying conditions, appropriate evaluation, including serum bicarbonate levels is recommended with topiramate therapy.

Chronic, untreated metabolic acidosis may increase the risk of nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (rickets in paediatric patients) and/or osteoporosis with an increased risk of fractures. Chronic metabolic acidosis in paediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae is unknown and has not been systematically investigated.

Nephrolithiasis: around 1.5% of adults and 0.6% children in clinical trials of topiramate developed renal stones. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis, such as zonisamide, may be at increased risk.

Topiramate, like other carbonic anhydrase inhibitors, reduces urinary citrate excretion and increases urinary pH.

Patients receiving topiramate should increase their fluid intake because this may reduce the risk of: (1) developing renal stones; and (2) heat-related adverse events during exercise and exposure to particularly warm environments.

Acute myopia with secondary angle-closure glaucoma is a syndrome reported in adults and children treated with topiramate.[282] Symptoms typically occur within 1 month of the start of treatment and include acute onset of decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, ocular hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Discontinuation of topiramate should be as rapid as is clinically feasible. Immediate specialist advice should be sought. If left untreated, elevated intra-ocular pressure can lead to serious sequelae, including permanent visual loss.

Oligohidrosis and hyperthermia: hypohidrosis or, more seriously, anhidrosis associated with hyperthermia, which infrequently results in hospitalisation, has been reported in association with topiramate. Symptoms include decreased or absence of sweating, elevation of body temperature, red face and tiredness, which worsen with exertion.

The majority of the reports have been in children and have occurred after exposure to hot environmental conditions. Patients, especially children, treated with topiramate should be monitored closely for evidence of such symptoms especially in hot weather.

Caution should be used when topiramate is prescribed with other drugs that predispose patients to heat-related disorders, such as zonisamide (such a combination should probably be avoided), other carbonic anhydrase inhibitors and anticholinergic drugs.

FDA warning: All patients who are currently taking or starting on topiramate for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Pregnancy: category C. There is no reliable information on human teratogenicity (see Table 7.15, chapter 7), but in animals even subtoxic doses of topiramate are teratogenic.[283]

Breastfeeding: breastfeeding is not recommended because of extensive secretion of topiramate into breast milk.

Interactions with hormonal contraception: there is a dose-dependent decrease in ethinyl estradiol exposure with topiramate doses between 200 and 800 mg/day, which may result in decreased efficacy of hormonal contraception or increased breakthrough bleeding.

Main mechanisms of action

The anti-epileptic effect of topiramate is probably due to multimodal mechanisms of action. These include blockage of voltage-dependent sodium channels, augmentation of the inhibitory activity of GABA at some subtypes of the $GABA_A$ receptor, antagonism with the AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV.

Pharmacokinetics

Oral bioavailability: >80%.

Protein binding: 15–41% over the blood concentration range of 0.5–250 µg/ml. The fraction bound decreases as blood concentration increases.

Metabolism: topiramate is not extensively metabolised and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis and glucuronidation. There is evidence of renal tubular reabsorption of topiramate.

Elimination half-life: 21 hours.

Drug interactions

The following anti-epileptic drug–drug interactions are of clinical significance with topiramate co-medication:

- In co-medication, phenytoin plasma levels may increase by 25% and topiramate decrease by 48%. Carbamazepine may decrease topiramate plasma by nearly a half.
- There is probably no interaction with lamotrigine and levetiracetam, and interactions with valproate are minimal.
- Concomitant use with other carbonic anhydrase inhibitors, such as zonisamide, should probably be avoided.

See also interactions with hormonal contraception.

Main disadvantages

Despite high efficacy, the current and future role of topiramate as a major AED is questionable, because of its very-poor profile in terms of multiple and severe ADRs. The most important of these reactions are those that occur in children, some of which (metabolic acidosis) may have predictable detrimental growth and bone-related sequelae in long-term use.

Its use may be limited to severe epilepsies intractable to other, better tolerated, AEDs.

Valproate

The introduction of valproate as an AED in the early 1960s revolutionised the treatment of generalised epilepsies.[284–285] Valproic acid (2-propyl pentanoic acid, 2-propyl valeric acid) is a short-chain branched fatty acid. Prior to the serendipitous discovery of its anti-epileptic activity in 1963, valproic acid was used as an organic solvent.

Valproate is a general term used to include all available forms of valproic acid, such as sodium valproate, magnesium valproate and sodium divalproex.

Authorised indications

UK-SmPC: In the treatment of generalized, partial or other epilepsy.

FDA-PI: (1) monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures and (2) use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

Valproate sodium injection is indicated as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible.

Clinical applications

Valproate is one of the most effective broad-spectrum AEDs for all types of seizures and epilepsies. It has superior efficacy in all types of generalised seizures (idiopathic and symptomatic), all syndromes of IGE and photosensitive epilepsy compared with any other drug so far, with the probable exception of levetiracetam. The efficacy of valproate has been well documented in long-term and worldwide clinical practice and controlled studies.

However, valproate is (1) far inferior to carbamazepine and some newer AEDs in the treatment of focal epilepsies and (2) has serious ADRs in women of child-bearing age and in patients of early childhood.

Unlike many other AEDs, valproate appears to have a very low potential to aggravate seizures.[287] When seizure aggravation occurs with valproate, it is in a specific clinical context, such as overdose, encephalopathy, or hepatic or metabolic disorders.[287]

Dosage and titration

Adults: start treatment with 200 mg/day in two equally divided doses for 3 days. Titrate in increments of 200 mg/day every 3 days to a maintenance dose of usually 1000–1500 mg/day (maximum 3000 mg/day) given in two equally divided doses. Higher initial dosage and faster titration rates are usually well tolerated.

Children: start with 10 mg/kg/day. Titrate in increments of 10 mg/kg/day every 3 days. The typical maintenance dose in childhood is 20–30 mg/kg/day in two equally divided doses.

Combined therapy: it may be necessary to increase the dose by 30–50% when used in combination with enzyme-inducing AEDs, such as phenytoin, phenobarbital and carbamazepine. On withdrawal of these AEDs, it may be possible to reduce the dose of valproate.

Dosing: twice or three-times daily, and once daily for slow-release formulations.

TDM: often not useful, because of poor correlation between valproate dose and plasma levels. However, because of significant drug interactions, monitoring of valproate and AEDs given concomitantly may be helpful when enzyme-inducing drugs are added or withdrawn.

Reference range (measures valproic acid): 50–100 mg/l (300–700 µmol/l).

Main ADRs

Valproate is associated with serious ADRs, particularly in children and women. Acute liver necrosis and acute pancreatitis, which may be fatal, are rare and more likely to occur in children receiving polypharmacy. An estimated 1–2% risk of neural tube defects, predominantly spina bifida aperta, in babies of women on valproate is well established,[288,289] and the overall risk of major teratogenic effects with valproate is two- to three-times higher than the background prevalence of major non-syndromic congenital anomalies (Table 7.15).[16] This together with polycystic ovary syndrome[290] and other endocrine ADRs,[291] makes the use of valproate in some women undesirable.

CNS-related ADRs: in contrast with other older AEDs, valproate is not usually associated with drowsiness and fatigability or significant dose-related effects on cognition or behaviour. Valproate encephalopathy is exceptional.

Tremor is the more troublesome CNS adverse effect of valproate. There is great individual susceptibility to the development of tremor, which is usually mild, but may become very intense, socially embarrassing and disabling. It is reversible and declines when the dose is lowered.

Systemic: the most serious are fatal hepatotoxicity and acute haemorrhagic pancreatitis.

Hepatic failure resulting in fatalities is primarily age-dependent and occurs mainly in children receiving polypharmacy and with organic brain disease. The risk is 1/600 before the age of 3 years. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups (range 1/8000–1/10,000 between 3 and 20 years

of age) and in monotherapy with valproate. Hepatic failure has usually occurred during the first 6 months of treatment. The diagnosis is based on clinical criteria with non-specific symptoms, such as malaise, weakness, lethargy, facial oedema, anorexia, vomiting and loss of seizure control. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months. However, this may not be helpful because:

- benign elevation of liver enzymes is common during valproate treatment
- severe hepatotoxicity is not preceded by progressive elevation of liver enzymes.

Raised liver enzymes are common during treatment with valproate, particularly if used in conjunction with other AEDs. These are usually transient or respond to dose reduction. Patients with such biochemical abnormalities should be reassessed clinically and liver function tests should be performed more frequently. An abnormally low prothrombin level, particularly in association with other relevant abnormalities, requires withdrawal of valproate. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Acute haemorrhagic pancreatitis with markedly increased amylase and lipase levels is another rare, but serious, adverse effect of valproate treatment. It develops within the first 3 months of treatment, is more prevalent in children and with polytherapy.

Hyperammonaemic encephalopathy, which is sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders. When urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment with valproate.

Thrombocytopenia and other haematological abnormalities:[292] it is recommended that platelet counts and coagulation tests are performed before initiating therapy and at periodic intervals, because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation and abnormal coagulation parameters. Evidence of haemorrhage, bruising or a disorder of haemostasis/coagulation is an indication for reduction or withdrawal of valproate.

Weight gain occurs in 20% of patients and is sometimes marked; women are more vulnerable. This is usually reversible if valproate is withdrawn early.

Hair loss and changes in hair texture or colour are relatively rare; they usually occur in the early months of valproate treatment and may resolve spontaneously despite continuation of the drug.

Other ADRs concern the gastrointestinal system (e.g. anorexia, constipation, dry mouth, stomatitis) and urogenital system (e.g. urinary incontinence, vaginitis, dysmenorrhoea, amenorrhoea and urinary frequency).

FDA warning: All patients who are currently taking or starting on valproate for any indication should be monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression (see page xxx).

Considerations in women

Valproate treatment in women raises many issues, as has been detailed on many occassion in this book.

Pregnancy: category D.[288,289,293] Valproate is teratogenic. It crosses the placenta and causes a spectrum of congenital anomalies, such as neural tube defects, craniofacial malformations and skeletal defects. The incidence of these anomalies is much higher when valproate is given as co-medication with other AEDs (Table 7.15).

Breastfeeding: There appears to be no contraindication to breast feeding; excretion in breast milk is low and with no clinical effects.

Interaction with hormonal contraception: none.

Other issues: see endocrine abnormalities.

Main mechanisms of action

The main mechanism of action is unknown and a combination of several mechanisms may be responsible:

- reduction of sustained, repetitive, high-frequency firing by inhibiting voltage-sensitive sodium channels, activating calcium-dependent potassium conductance and possibly by direct action on other ion channels
- valproate has a GABAergic effect through elevation of brain GABA by various mechanisms, such as inhibiting GABA-transaminase (GABA-T),

enhancing GABA-synthesising enzymes, increasing GABA release and inhibiting GABA uptake. However, this GABAergic action is observed only at high valproate levels and may explain its efficacy in other, but not absence, seizures. GABAergic drugs that affect $GABA_B$ receptors have a pro-absence action because they potentiate absences (see useful note on page XXX). Another explanation for the effect of valproate on absence seizures is that this drug, like ethosuximide, reduces a low threshold (T-type) calcium-channel current,[294] but this effect has not been supported by other studies.[295]

Pharmacokinetics

Oral bioavailability: almost complete. Absorption of valproate varies according to the formulation used. Absorption is rapid and peak levels are reached within 2 hours after oral administration of syrup or uncoated tablets. This is longer (3–8 hours) with enteric-coated tablets.

Protein binding: valproate is highly protein bound (about 90%). However, if the plasma level of valproic acid rises above 120 mg/l or if the serum albumin concentration is lowered, the binding sites may become saturated, causing the amount of free drug to rise rapidly, out of proportion to any increase in dosage. Valproate may displace phenobarbital or phenytoin from plasma protein-binding sites.

Metabolism: hepatic. Valproate has a complex metabolism. It is rapidly and nearly totally eliminated by hepatic metabolism with numerous metabolites that contribute to its efficacy and toxicity. Two metabolites of valproate, 2-ene-valproic acid and 4-ene-valproic, are among the most pharmacologically active and have a similar potency to the parent drug. They are both produced by the action of CYP enzymes induced by other AEDs. They are eliminated primarily in the urine.

The major elimination pathway is via glucuronidation (40–60%). The remainder is largely metabolised via oxidation pathways, β-oxidation accounting for 30–40% and ω-oxidation, which is CYP dependent. Only 1–3% of the ingested dose is excreted unchanged in the urine.

Elimination half-life: this is variable, but generally appears to be 8–12 hours (range 4–16 hours). It is shorter in patients receiving enzyme-modifying AEDs or in long-term valproate treatment of children and adults. Many antipsychotic and antidepressant drugs result in competitive metabolism or enzyme inhibition when given as a co-medication with valproate.

Drug interactions

There are numerous drug interactions with valproate because:

- its metabolism is sensitive to enzymatic induction
- it inhibits the metabolism of other drugs
- it has a high affinity for serum proteins; it may be displaced or displace other drugs.

Effect of other AEDs on valproate: enzyme inducers, particularly those that elevate levels of UGTs, such as phenobarbital, phenytoin and carbamazepine, may increase the clearance of valproate, thus reducing plasma valproate levels by 30–50%.

The addition of ethosuximide may reduce the plasma concentration of valproate.

Effects of valproate on other AEDs: valproate does not interact with most of the newer AEDs. A notable exception is lamotrigine.[296] Valproate is a potent inhibitor of UGT-dependent metabolism of lamotrigine, and doubles[251] or triples[76] its plasma half-life.

The addition of valproate to ethosuximide or phenobarbital may double the plasma concentration of these AEDs with concomitant toxicity.

There is evidence of severe CNS depression, with or without significant elevations of barbiturate or valproate plasma concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Plasma barbiturate concentrations should be measured, if possible, and the barbiturate dosage decreased, if appropriate.

Plasma levels of carbamazepine decrease to around 17%, while those of carbamazepine-10,11-epoxide increase by 45% on co-administration with valproate.

Valproate displaces phenytoin from its plasma albumin-binding sites and inhibits its hepatic metabolism. Valproate significantly increases the free fraction of phenytoin and reduces its total plasma concentration.

Valproate does not interact with hormonal contraception.

Main disadvantages

The superior efficacy of valproate in generalised seizures is hindered by serious acute and chronic ADRs. It is particularly unsuitable for:

- women, because of hormonal changes, weight gain and teratogenicity; it is virtually impossible to prescribe valproate to young women today. There are increasing numbers of litigations against physicians and health authorities by parents of children with foetal valproate syndrome (even if the risks were appropriately explained to them) on a scale characterised by the media as 'bigger than thalidomide'.
- young children, particularly those <2 years, who are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants or with congenital metabolic disorders, mental retardation or organic brain disease.

Valproate is the superior AED for generalised epilepsies, but its use in focal epilepsies is of very limited value, because:

- the doses of valproate required to be effective are much higher in focal than generalised epilepsies
- ADRs , particularly in some women, make its use undesirable
- there are other, more effective and safer drugs for focal seizures (see Chapter 15).

Vigabatrin

Vigabatrin (γ-vilyl-GABA; 4-amino-hex-5-enoic acid) was a result of a rational approach to design compounds that enhance the effect of the inhibitory neurotransmitter GABA.[297–314]

Authorised indications

UK-SmPC: (1) monotherapy in the treatment of infantile spasms and (2) treatment in combination with other anti-epileptic drugs for patients with resistant partial epilepsy with or without secondary generalisation, where all other appropriate drug combinations have proved inadequate or have not been tolerated.

FDA-PI: not yet licensed, but expected soon.

Clinical applications

The use of vigabatrin as an AED is, in clinical practice, limited to infantile (epileptic) spasms for which it is the initial treatment of choice.[297]

Exceptionally vigabatrin may be used cautiously in the treatment of patients with intractable focal seizures that have failed to respond to all other appropriate AED combinations and surgical procedures.[297,298]

Dosage and titration

Adults: start treatment with 500 mg/day and titrate in increments of 500 mg/day every week. Typical adult maintenance dose is 1000–3000 mg/day given in two equally divided doses.

Because the excretion is mainly renal, the dose should be reduced in patients with renal insufficiency and creatinine clearance <60 ml/l.

Children with infantile spasms: start treatment with 50 mg/kg/day and adjust according to the response over 7 days, up to a total of 150–200 mg/kg/day.

Dosing: despite its short half-life (5–7 hours), vigabatrin may be given once or twice daily, because inhibition of GABA-T results in a relatively long duration of action, and GABA levels in the CSF can remain elevated for up to 120 hours after a single oral dose.

TDM: unnecessary; useful only to check compliance.[71,72]

Reference range: 6–278 µmol/l, which is irrelevant in clinical practice.

Main ADRs

Visual field defects are the main concern.[305,312] Other ADRs include sedation, dizziness, headache, ataxia, paraesthesiae, memory, cognitive and behavioural disturbances, weight gain and tremor. There is no evidence of idiosyncratic ADRs.

Visual field defects: there is a high prevalence of visual field defects occurring in around one-third of patients (adults and children)[312] treated with vigabatrin. Vigabatrin also produces retinal electrophysiological changes in nearly all patients.[260,311,312]

Visual field loss resulting from vigabatrin is not usually reversible. However, visual acuity, colour vision and the loss of amplitude on the electroretinogram may be reversible in patients with minimal or no visual field loss. There is some evidence that visual field defects remain stable with continuous treatment. It is, therefore, feasible to continue treatment with vigabatrin in these cases, provided visual field monitoring is performed regularly.[311]

In one study involving 24 children treated with vigabatrin, visual field constriction or abnormal ocular electrophysiological studies were seen in over 50% of cases.[312]

The mechanism of vigabatrin-induced visual field defects are probably due to reversible oedema of the myelin in the optic nerves, retinal cone system dysfunction or both.

Main mechanisms of action

The anti-epileptic activity of vigabatrin is by selective and irreversible inhibition of GABA-T, thus preventing the breakdown of GABA. Vigabatrin produces dose-dependent increases in GABA concentrations in the CSF and decreases in GABA-T activity. Raised brain GABA levels inhibit the propagation of abnormal hypersynchronous seizure discharges.

Vigabatrin may also cause a decrease in excitation-related amino acids.

Pharmacokinetics

Oral bioavailability: 80–100%.

Protein binding: none.

Metabolism: it is not metabolised and 70% is excreted unchanged in the urine. It is eliminated by the kidneys by glomerular filtration.

Elimination half-life: 5–8 hours (not clinically important).

Drug interactions

There are no drug interactions of any clinical significance, except for lowering the concentration of phenytoin.

Considerations in women

Pregnancy: category C.

Breastfeeding: only small amounts of the drug are excreted in breast milk.

Interactions with hormonal contraception: none.

Main disadvantages

Visual field defects have virtually eliminated vigabatrin from common clinical practice except for infantile spasms.

Aggravation of seizures: vigabatrin is a pro-absence agent which aggravates absence seizures and provokes absence status epilepticus.[310] This alone would prohibit use of vigabatrin in IGEs with absences.

Vigabatrin, in addition to its aggravation effect on typical absence seizures, may also exaggerate atypical absences (such as those occurring in Lennox–Gastaut syndrome) and myoclonic seizures (such as those occurring in progressive or non-progressive myoclonic epilepsies).

Useful clinical note

Visual field defects may not be clinically detectable. Therefore, patients should be monitored with perimetry prior to and every 6 months during vigabatrin treatment. Electrophysiological testing is considered to be more accurate than perimetry for the direct vigabatrin effect on the outer retina.[314] The manufacturers provide a procedure for testing children <9 years of age for visual field defects.

Two lessons to be learned from vigabatrin

First lesson: Numerous RCTs failed to detect common and serious visual field defects

Vigabatrin was used as an adjunctive medication in the treatment of focal epilepsies from 1989, when it was first licensed in Europe. Concern over neuropathological findings of microvacuolisation of white matter in animals caused trials of vigabatrin to be halted in 1983, but trials were resumed when a lack of evidence (including visual-evoked responses) for toxicity in humans was found.

Numerous RCTs (mostly of class I and II in the ratings of 'therapeutic articles')[299–306] were all consistent in their conclusion that vigabatrin was a 'relatively safe drug with a relatively benign adverse-effect profile'. They all failed to identify vigabatrin-associated irreversible visual field defects. It was astute clinicians who first reported these serious ADRs,[305] but even after this report had been published, a class I RCT found vigabatrin to be 'less effective but better tolerated than carbamazepine'.[306] Results of proper testing for visual field defects are not given; that the patients did not have abnormalities on visual confrontation testing is not reassuring. When such ADRs come to light, good clinical practice mandates that patients are informed and offered the appropriate testing. Visual field testing performed by a protocol amendment post hoc (after termination of another RCT) showed abnormalities in 10% of vigabatrin-treated patients.[307]

Second lesson: Authorities failed to warn of the pro-absence effects of vigabatrin

That vigabatrin is a pro-absence AED should be evident by its action on $GABA_B$ receptors. No such warning was given to practising physicians,[309] who only discovered this effect when patients with IGEs experienced significant deterioration and absence status epilepticus.[310]

Zonisamide

Zonisamide is a synthetic 1,2-benzisoxazole derivative (1,2-benzisoxazole-3-methanesulfonamide). It is chemically classified as a sulfonamide with a structural similarity to serotonin. It was first introduced as an AED in Japan in 1989.[315,316]

Efficacy, dose and mean plasma levels were similar in multi-centre studies with Japanese and Caucasian subjects.[315,317]

Authorised indications

EMEA-SmPC: Adjunctive therapy in adult patients with focal seizures with or without secondary generalisation.
FDA-PI: Adjunctive therapy in the treatment of focal seizures in adults with epilepsy.

Clinical applications[318–332]

Zonisamide appears to be an effective broad-spectrum AED with extensive clinical use in Japan. It is efficacious in focal seizures with or without GTCSs, primarily and secondarily generalised seizures including epileptic spasms of West syndrome, other epileptic encephalopathies such as Ohtahara syndrome, and probably progressive myoclonic epilepsies such as Unverricht syndrome.

Dosage and titration

'Start low and go slow' is an important part of treatment with zonisamide.[316] Significant adjustments are needed in co-medication with hepatic-enzyme inducers.

Adults: Start with 100 mg/day in one or two equally divided doses. After two weeks, the dose may be increased to 200 mg/day for at least two weeks. It can be increased to 300 mg/day and 400 mg/day, with the dose stable for at least two weeks to achieve steady state at each level. Evidence from controlled trials suggests that zonisamide doses of 100–600

mg/day are effective, but there is no suggestion of increasing response above 400 mg/day.

Because of the long half-life of zonisamide, up to two weeks may be required to achieve steady state levels upon reaching a stable dose or following dosage adjustment. Some experts prolong the duration of treatment at the lower doses in order to fully assess the effects of zonisamide at steady state, noting that many of the side effects of zonisamide are more frequent at doses of 300 mg per day and above. Although there is some evidence of greater response at doses above 100–200 mg/day, the increase appears small and formal dose-response studies have not been conducted.

Marked renal impairment (creatinine clearance <20 ml/min) requires slower dose escalation and lower maintenance doses.

Dosing: once or twice daily.

Children: start with 1–2 mg/kg/day for the first week and titrate in increments of 1–2 mg/kg/day every 2 weeks. Usual childhood maintenance dose is 4–8 mg/kg/day (maximum 12 mg/kg/day) in two equally divided doses.

TDM: useful, although there is insufficient evidence to support a clear relation between the plasma concentration of zonisamide and clinical response.[317] Zonisamide monitoring may be needed in order to adjust the dosage in co-medication with phenytoin, phenobarbital or carbamazepine.

Reference range: 15–40 mg/l (45–180 µmol/l).

Main ADRs

Zonisamide causes many ADRs.

Frequent and/or important: sedation, somnolence, fatigue, dizziness, agitation, irritability, anorexia, weight loss, nausea, diarrhoea, dyspepsia, dry mouth, slowing of mental activity, depression, ataxia, visual hallucinations, photosensitivity, resting and postural hand tremors.

Potentially serious: some of the ADRs are similar to those of topiramate. These are:

- cognitive impairment, including word-finding difficulty; this is worse in children with plasma concentrations >140 µmol/l
- weight loss and anorexia that may become very severe
- nephrolithiasis in 4% of patients on prolonged zonisamide therapy
- oligohidrosis and anhidrosis often accompanied by hyperthermia, especially in children and hot environments.

Additional severe ADRs are those seen with the sulfonamides, such as rash, Stevens–Johnson syndrome, toxic epidermal necrolysis and major haematological disturbances including aplastic anaemia, which very rarely can be fatal. The incidence of rash requiring discontinuation of therapy has been approximately 2% in clinical trials.

Depression and psychosis may be common, particularly in children. In one study, 14 of 74 patients experienced psychotic episodes within a few years of commencement of zonisamide.[323]

Seizure exacerbation: treatment-emergent status epilepticus has been reported in 1.1% of treated patients, compared to no reported cases in placebo-treated individuals.[298,301]

Considerations in women

Pregnancy: category C.

Breastfeeding: the transfer rate of zonisamide through breast milk is high at about 50%.

Interaction with oral hormonal contraception: none.

Main mechanisms of action

The anti-epileptic mechanism of zonisamide is probably multimodal. Zonisamide blocks the sustained repetitive firing of voltage-sensitive sodium channels and reduces voltage-dependent T-type calcium current without affecting the L-type calcium current. It has mild carbonic anhydrase activity and inhibits excitatory glutamatergic transmission. It exhibits free radical-scavenging properties.

Pharmacokinetics

Bioavailability: 100%.

Protein binding: 40–60%.

Metabolism and route of elimination: zonisamide is metabolised in the liver and eliminated by the kidneys. It is metabolised partly by CYP3A4 (reductive cleavage), and also by N-acetyl-transferases and conjugation with glucuronic acid; therefore, substances that can induce or inhibit these enzymes

may affect the pharmacokinetics of zonisamide. It does not induce hepatic enzymes. Nearly half of zonisamide is excreted unchanged in the urine.

Elimination half-life: 60 hours, which decreases to 27–38 hours in the presence of hepatic enzyme inducers.

Interaction with other drugs

Plasma concentrations of zonisamide are altered by drugs that either induce or inhibit CYP3A4. Phenytoin, phenobarbital and carbamazepine increase zonisamide plasma clearance and reduce its half-life to 27–38 hours.[324] Valproate also reduces its half-life to 46 hours.

Zonisamide does not appear to affect phenytoin, but significantly increases the plasma concentration of carbamazepine epoxide when added to carbamazepine.

Concomitant administration of carbonic anhydrase inhibitors, such as acetazolamide or topiramate, is probably ill advised because of the increased potential for renal stone and metabolic acidosis.

Main disadvantages

Zonisamide has significant ADRs, some of which may be severe such as cognitive, psychotic episodes, anhidrosis and hyperthermia, nephrolithiasis and Stevens–Johnson syndrome. It also has many interactions with other AEDs in polytherapy.[324]

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