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

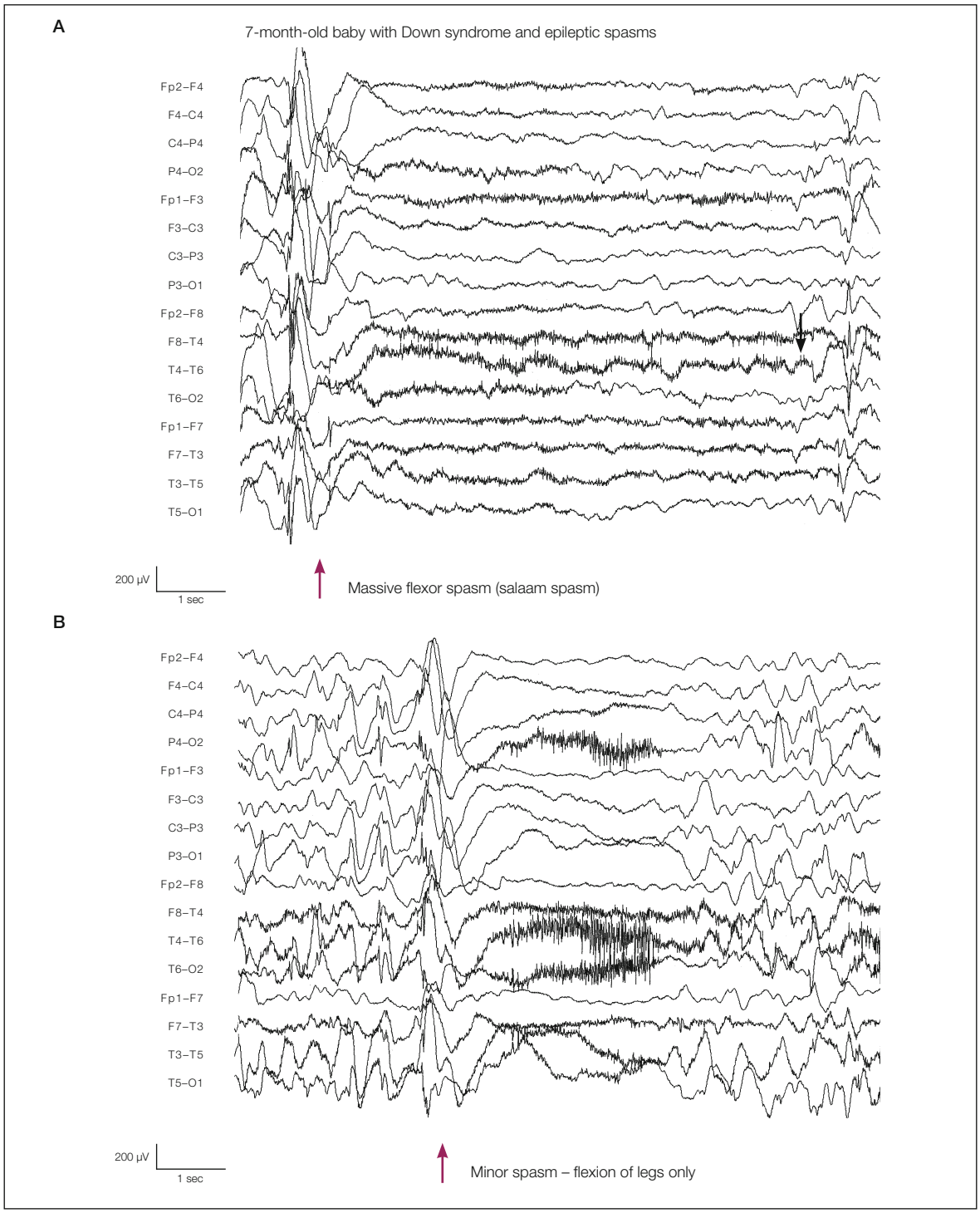

Figure 10.1 From a video-EEG recording of a 7-month-old baby with Down syndrome who developed West syndrome. There were numerous major (**A**) or minor (**B**) epileptic spasms.

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.

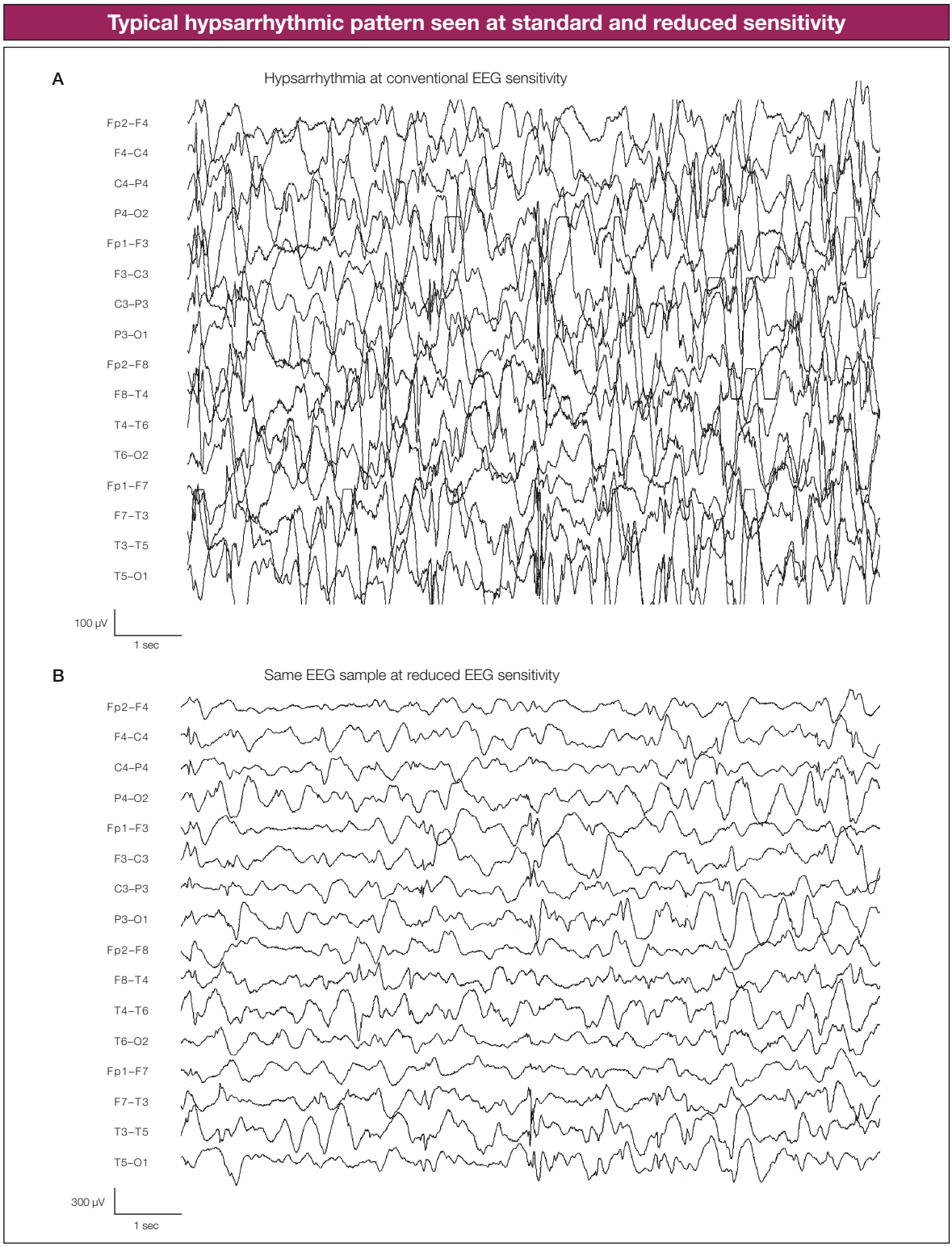

Figure 10.2 Same typical hypsarrhythmic pattern seen at standard (**A**) and reduced (**B**) sensitivity.

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

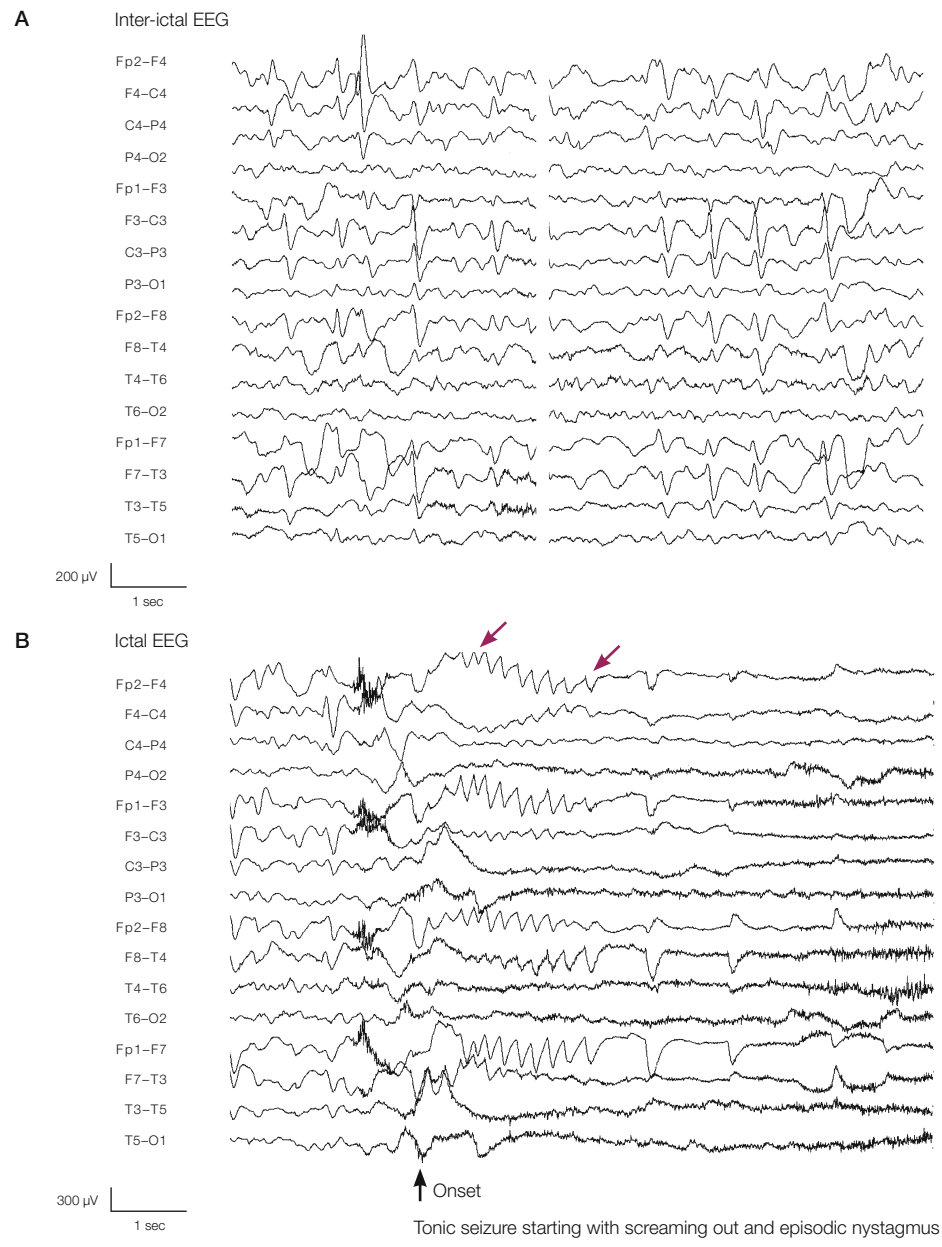

Figure 10.3 This girl had a marked neuronal migration deficit in the right hemisphere and her seizures were multiform and intractable to any medication. (**A**) A grossly abnormal inter-ictal EEG with continuous, high-amplitude, sharp–slow-waves or spike–slow-waves. These were multi-focal right or left, 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]

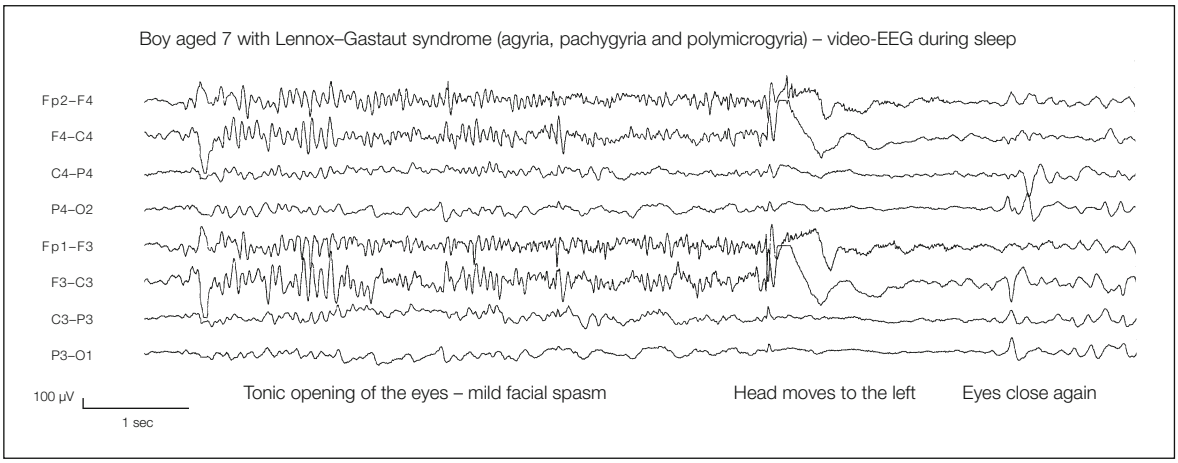

Figure 10.4 A tonic seizure presenting with mild clinical symptoms occurs during marked paroxysmal fast activity. Turning of the head and symmetrical flattening of the EEG follow. His older brother also had the same disease (Figure 6.6).

From a video-EEG of a young man aged 17 years with Lennox–Gastaut syndrome

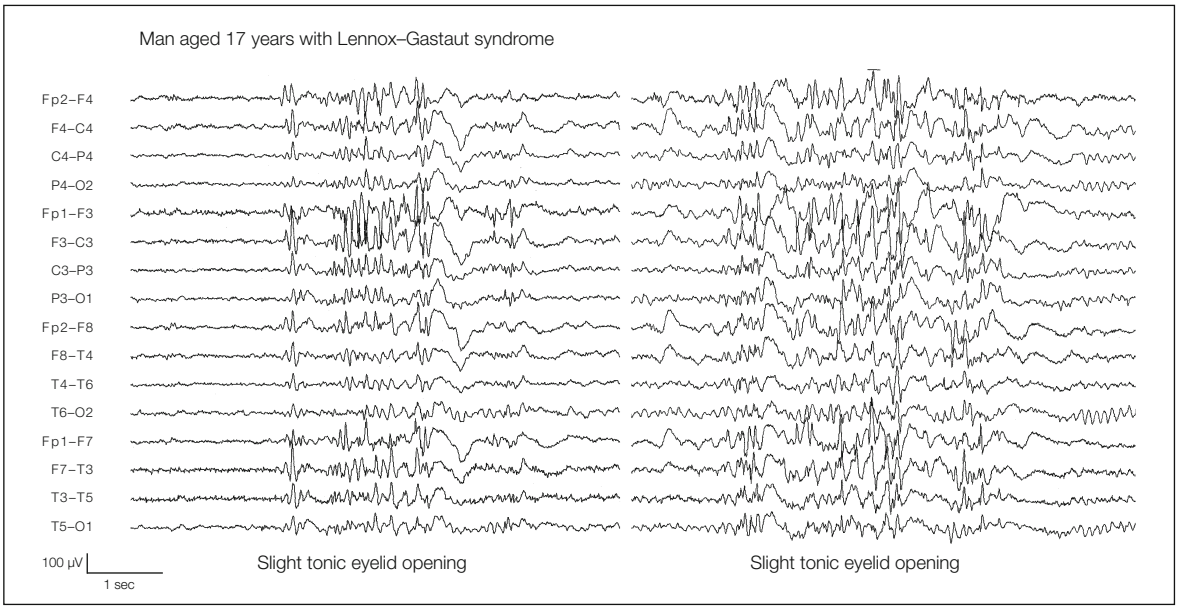

Figure 10.5 EEG fast paroxysms are associated with inconspicuous manifestations of tonic seizures (slight tonic eyelid opening) that would be impossible to detect without video-EEG recording.

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

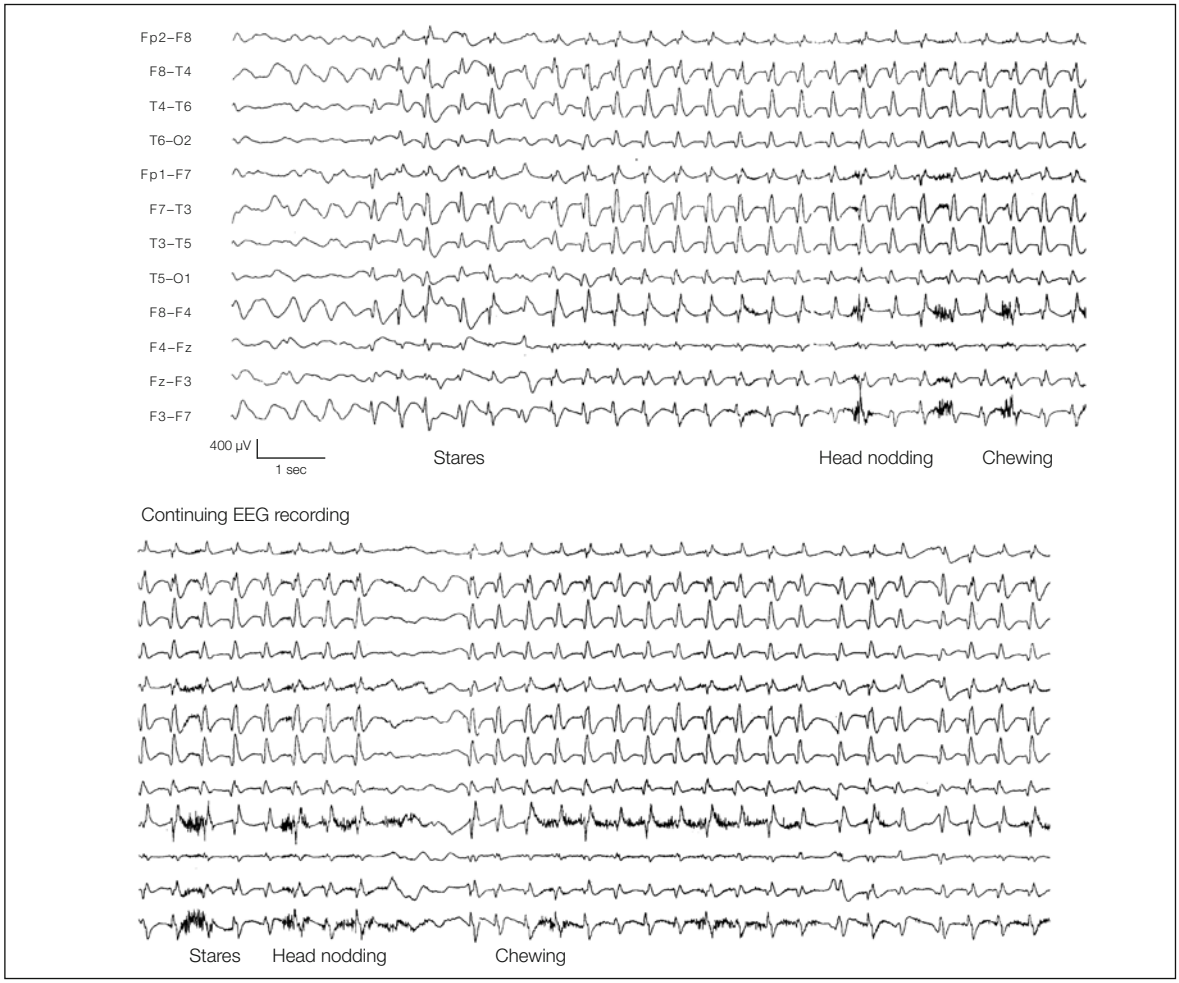

Figure 10.6 Boy, aged 11 years, with severe learning difficulties and frequent multiform seizures of Lennox–Gastaut. The ictal symptoms fluctuated and consisted of staring, head nodding and automatisms. The ictal discharge consisted of slow GSWD at 2–2.5 Hz.

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

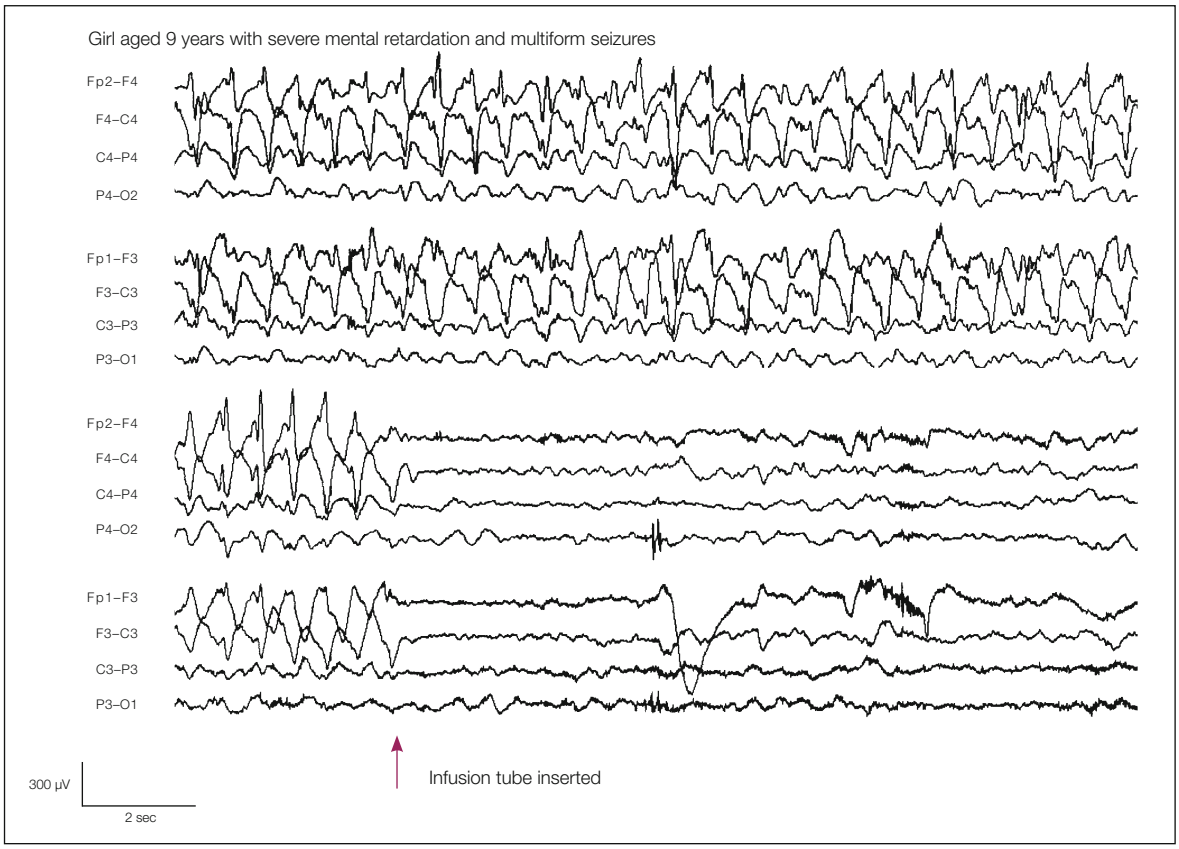

Figure 10.7 The EEG consisted of very-long slow GSWD at approximately 2 Hz. As a result of very severe learning disabilities, it was impossible to find any convincing differences in her behaviour and reactivity during or without EEG discharges. The discharge stopped simultaneously when the infusion tube 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

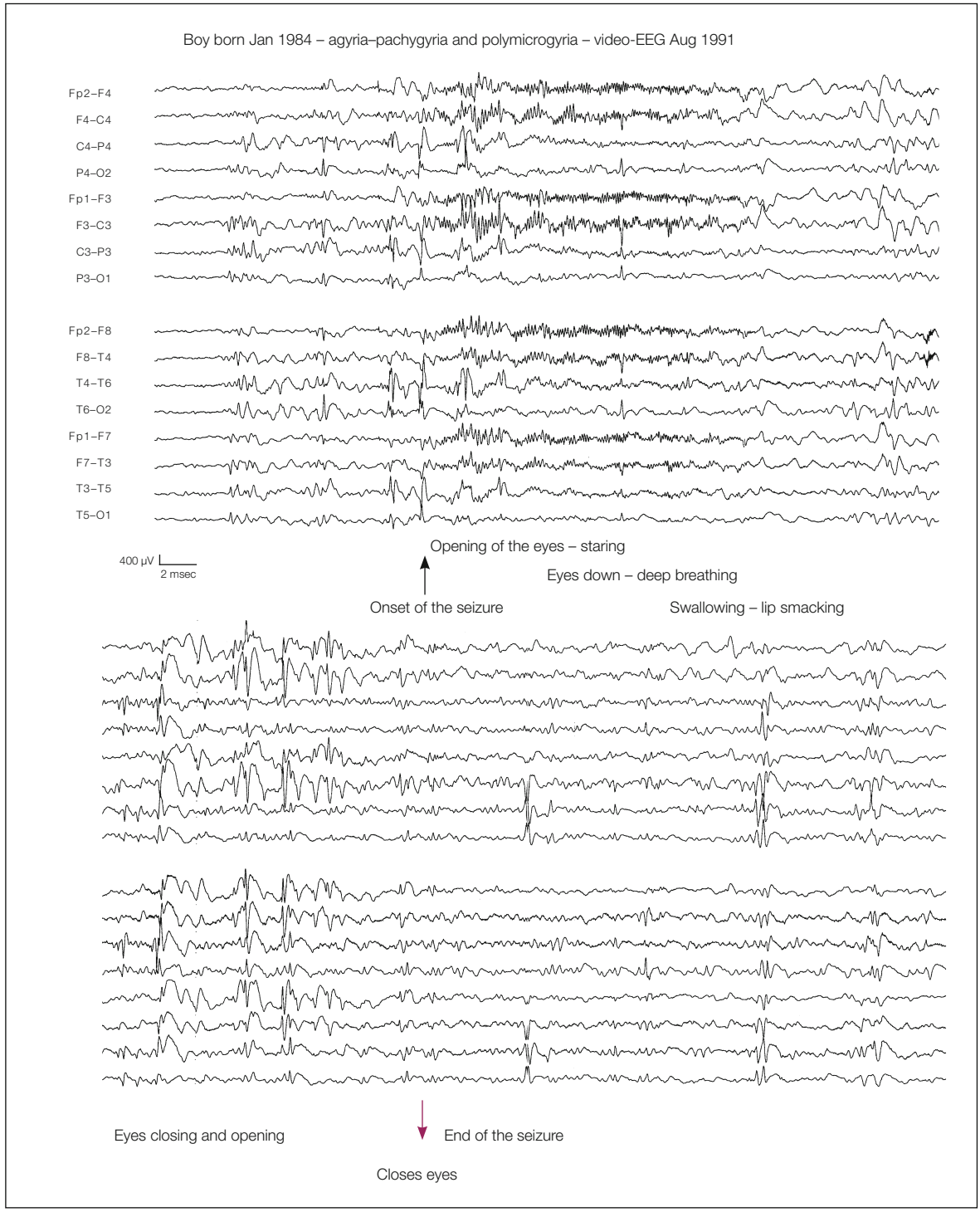

Figure 10.8 Note that the ictal discharge contains features of tonic (episodic fast activity) and absence (slow spike–waves) seizures. The annotated clinical manifestations were mild.

Ictal fast paroxysms of various frequencies in Lennox–Gastaut syndrome

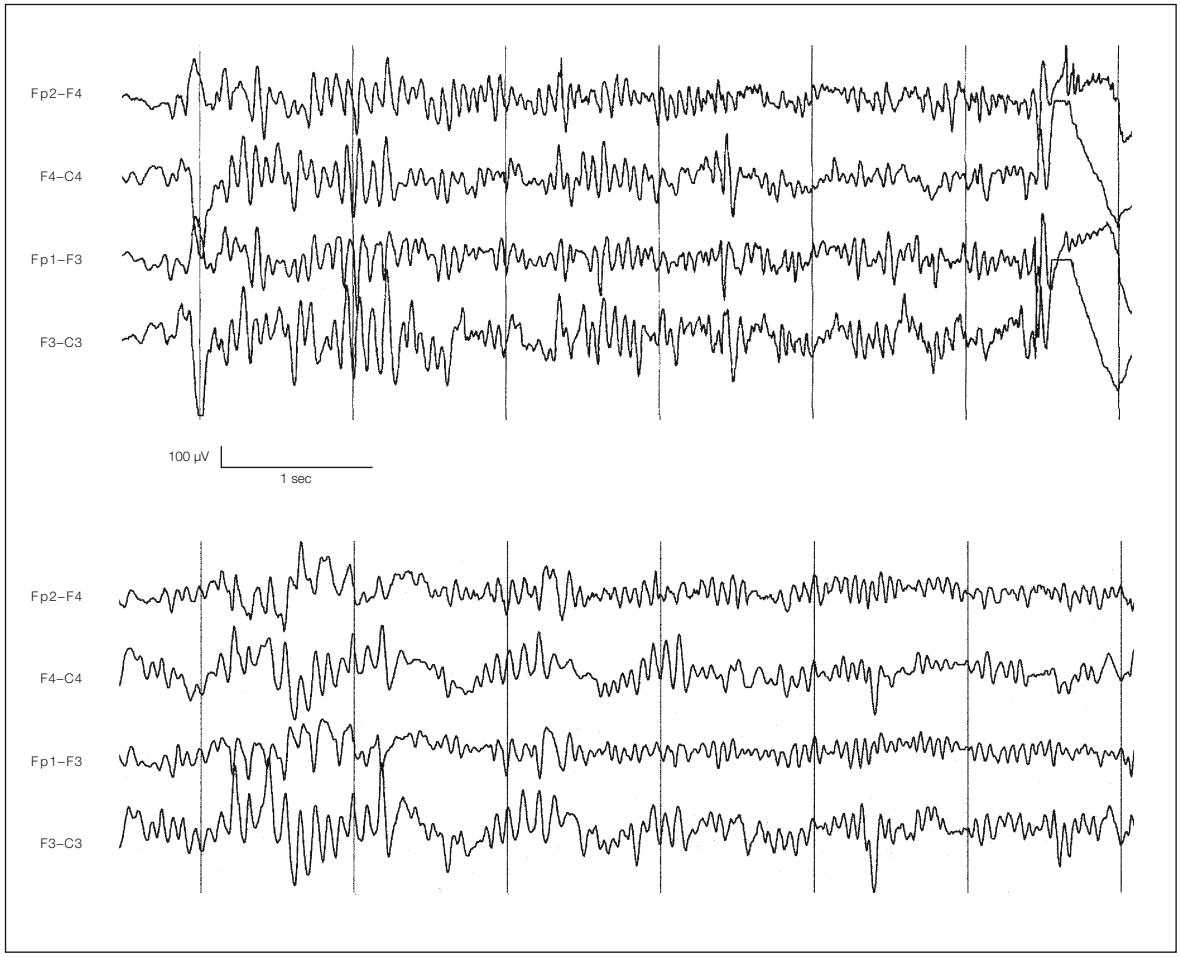

Figure 10.9

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

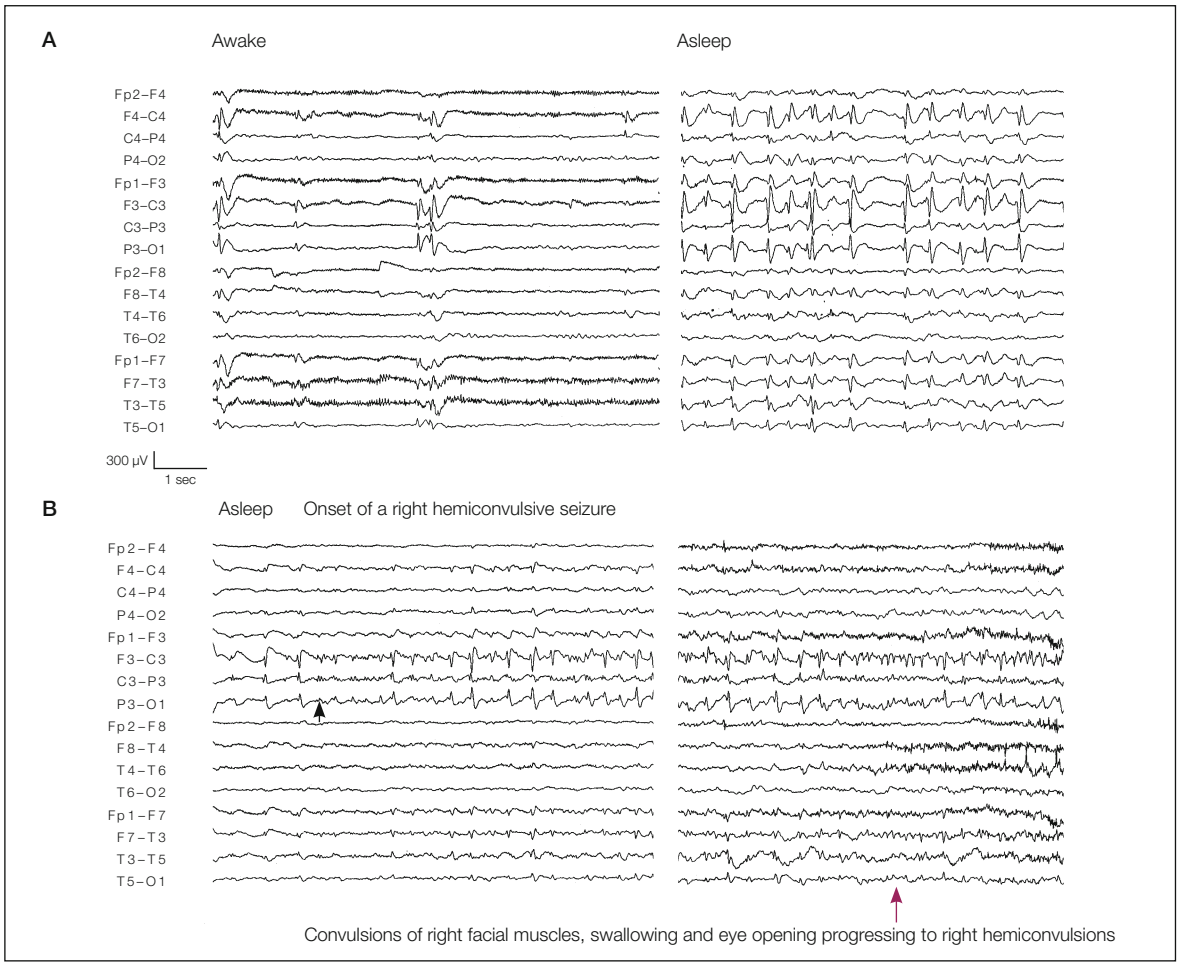

Figure 10.10 This boy had infrequent seizures, one of which was incidentally captured on a video-EEG recording before a PET scan. (**A**) Inter-ictally, there were clusters of sharp–slow-wave focal discharges, maximal around the left rolandic regions (left). They became continuous during natural sleep (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'

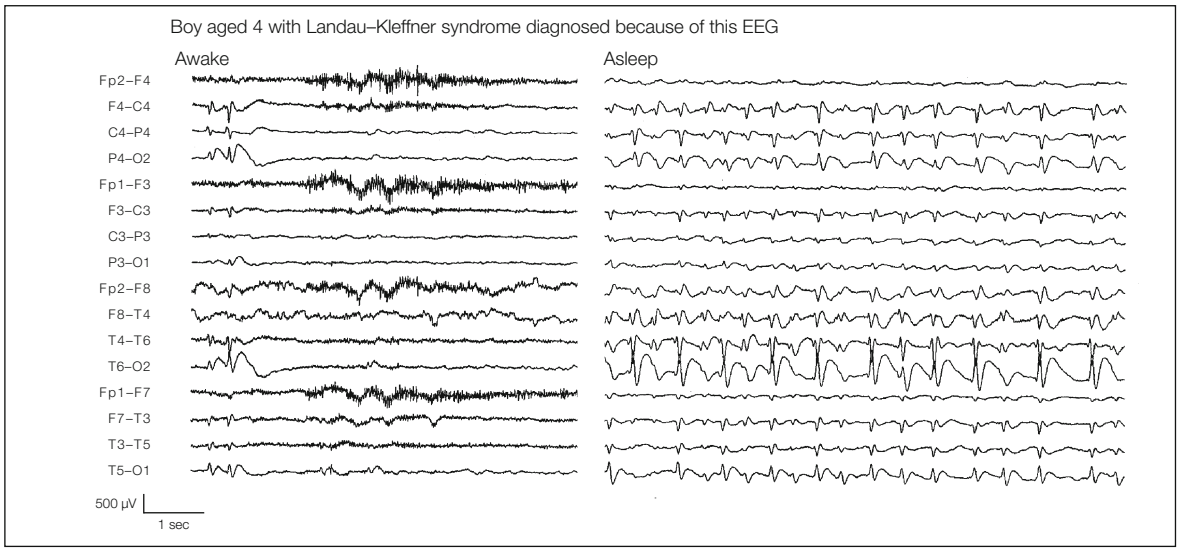

Figure 10.11 The EEG showed clusters of sharp–slow-wave focal discharges maximum around the right posterior temporal regions (left). Although this was a request for a routine EEG, the technologist allowed time to proceed with a sleep EEG during which the paroxysms became continuous (right). The possibility 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

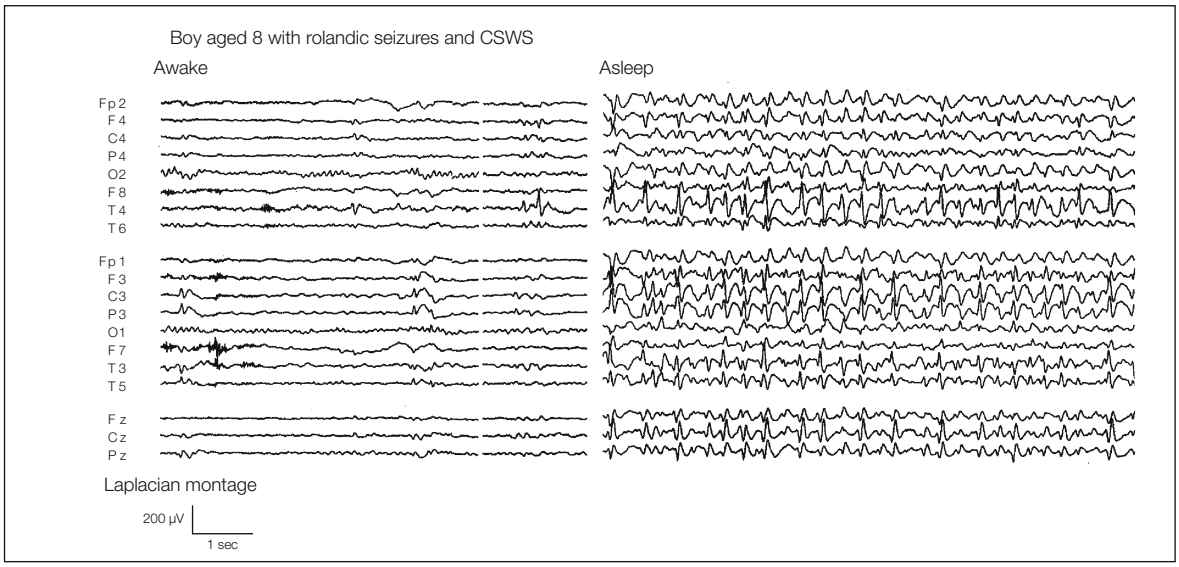

Figure 10.12 From a video-EEG recording of an 8-year-old boy who, at age 8 weeks, had three focal seizures of right-sided convulsions involving the face and upper limbs (Figure 9.1). Subsequent development was excellent, but at age 7 he started having rolandic seizures and later developed epilepsy with 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

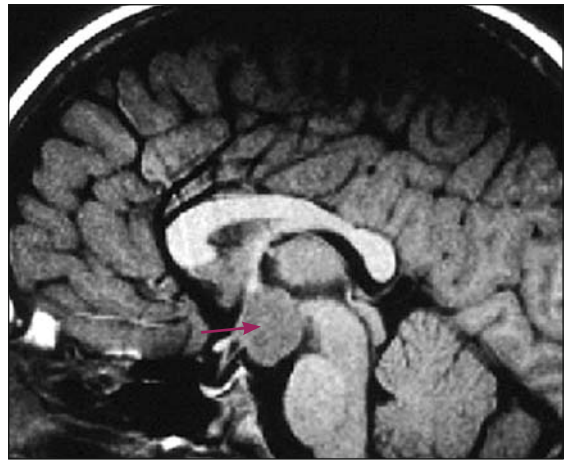

Figure 10.13 *Courtesy of Dr. Rod C. Scott, Institute of Child Health, London, UK.*

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]

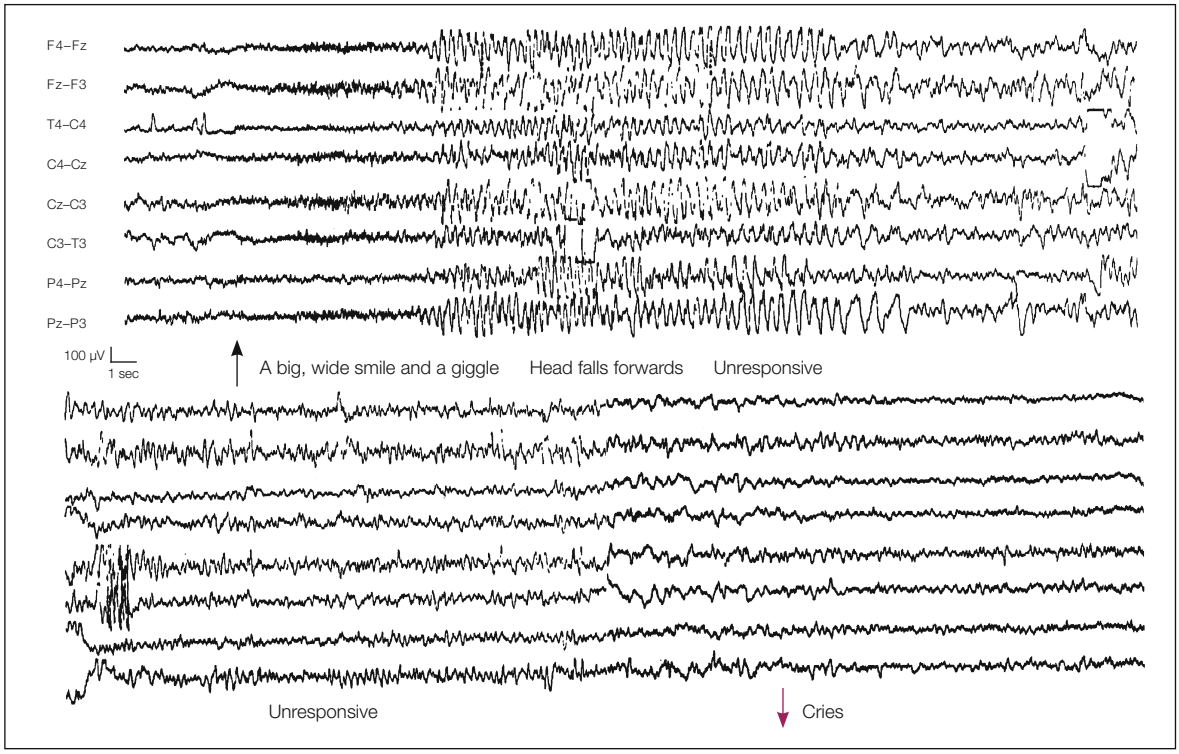

Figure 10.14 First noticed at age 2 years when her parents observed that, when told 'how beautiful' she is or 'come and get these candies', she reacted with a 'facial grimace', something like a 'frozen smile', 'a smile that freezes' and 'right-sided deviated lips with a smile'. This initially lasted 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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