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# Epileptic Encephalopathies in Infants and Children

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## Abstract

Epileptic encephalopathies represent a group of devastating epileptic disorders that appear early in life. They are characterized by pharmacoresistant generalized or focal seizures, persistent severe EEG abnormalities, and cognitive dysfunction or decline. The ictal and interictal epileptic discharges are age-specific and either are the main cause or contribute to cognitive deterioration in the idiopathic or symptomatic group, respectively. Despite choosing the most appropriate antiepileptic drugs for the seizure type and syndrome, the results are often disappointing, and polytherapy and/or alternative therapy becomes unavoidable; in those cases, consideration should be given to the quality of life of the child and carers. In this chapter, we will discuss the clinical and electroencephalographic characteristics and evolution and management of age-related epileptic encephalopathies, recognized by the International League Against Epilepsy, as follows: early infantile epileptic encephalopathy (Ohtahara syndrome), early myoclonic encephalopathy, epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), severe myoclonic epilepsy in infancy (Dravet syndrome), myoclonic-atonic epilepsy (Doose syndrome), Lennox-Gastaut syndrome, epileptic encephalopathy with continuous spike-and-wave during sleep, and Landau-Kleffner syndrome. Their clinical features, prognosis, etiologies, and treatment are presented and updated.

**Keywords:** electroclinical seizures, epileptic encephalopathy, pharmacoresistant epilepsy, epilepsy, electroencephalography

## 1. Introduction

The concept of epileptic encephalopathy (EE) is based on the clinical descriptions of some epileptic syndromes during the last century, such as West syndrome (WS) and Lennox-Gastaut syndrome (LGS). Delay in development in one, and intellectual disability in the other, was considered partly due to interictal epileptic discharges [1]. The idea that not only seizures but also apparently subclinical epileptic activity could affect cognitive functions was gaining strength in the scientific community related to epilepsy. According to this, the control of this epileptic activity could improve these deficits [1]. This notion was better profiled in the description of neuropsychological deficits related to continuous or sub-continuous paroxysmal activity during sleep, with the first description of the Landau-Kleffner syndrome (LKS) [2].

The definition of EE was better defined by Dulac in the 1990s and was incorporated into the proposed classification of the International League Against Epilepsy (ILAE) in 2001 [3]. In this proposal, the term EE was used for disorders in which “the epileptiform anomalies themselves are believed to contribute to the progressive disturbance of

brain function.” In 2006, Engel defined EE as disorders in which the evidence suggests the idea that neurological impairment depends on epilepsy and not on an underlying metabolic, degenerative, or encephalitic process, so that it excludes these progressive etiologies from the possible etiologies of EE [4]. Engel also emphasizes the importance of distinguishing between the deficits that are due to the cause of epilepsy, those that are due to pharmacotherapy, and those that are due to epilepsy itself.

The ILAE Working Group of 2010 pointed out the recognition achieved by the scientific community in relation to the EE [5]. The notion that epileptic activity itself may contribute to cognitive and behavioral deficiencies that exceed beyond what might be expected from causal pathology alone underlies the concept of EE. Deficits caused by epileptic discharges can be global or focal and can occur in a broad spectrum of severity.

In 2012, Capovilla proposed the term epileptogenic encephalopathy. They refer to progressive disorders of various etiologies that can cause deterioration and epilepsy, such as brain tumors, neurodegenerative or metabolic diseases, and presumed inflammatory or autoimmune conditions [1]. In epileptogenic encephalopathies, deterioration is independent of epilepsy, even if epilepsy could worsen the clinical picture; in some cases, the same etiology can produce encephalopathy without epilepsy. This distinction is important for the treatment; in the EE the treatment must be aggressive. On the other hand, if the deterioration is due to the etiology, there is a risk of unjustified excessive treatment. It is known that drugs, especially in polytherapy, can aggravate the neuropsychological deficits in these patients.

## **2. Neonatal epileptic encephalopathies: early infantile epileptic encephalopathy with suppression-burst pattern (Ohtahara syndrome) and early myoclonic encephalopathy (EME)**

### **2.1 Overview**

Early myoclonic epilepsy and early infantile epileptic encephalopathy (or Ohtahara syndrome) are age-dependent EEs that occur in the earliest stages of life. Although they share some clinical, electroencephalographic and prognostic characteristics, they are distinguished by their clinical presentations and different etiologies [6].

In 1976, Ohtahara et al. report an epileptic syndrome that affected very young babies with a typical electroencephalographic pattern, and they called it “early infant epileptic encephalopathy with suppression-burst” [7]. Ohtahara observed that this disorder progressed frequently to West syndrome (WS) and then to a Lennox-Gastaut syndrome (LGS) [8]. Ohtahara syndrome (OS), as it has been called since the 1980s, has also been known for other terms, such as myoclonic epilepsy with neonatal onset, neonatal epileptic encephalopathy with periodic electroencephalographic bursts, and early myoclonic epileptic encephalopathy.

In 2001, the ILAE Classification and Terminology Working Group included both OS and EME within EEs [3]. Both syndromes are similar in terms of age of onset, a characteristic of suppression-burst EEG, and the presence of several types of superimposed seizures; due to this, their differentiation is difficult and often impossible at the beginning of the disease [9]. On the other hand, motor manifestations at this age are difficult to classify.

### **2.2 Seizures: symptoms and semiology**

In both syndromes, seizures begin almost after birth, usually during the first month of life [9]. In OS, the most typical seizures are epileptic spasms and tonic

seizures, in groups or isolated [10]. In patients with hemispheric structural lesions, seizures can be unilateral or at least asymmetric. On the other hand, in the EME, myoclonic (axial, segmental, or erratic) seizures are more characteristic. The frequency of seizures is flexible and can be almost continuous. Erratic and segmental myoclonus usually occurs in the first days [11]. In erratic myoclonus, the jerking seems to change arbitrarily from one area of the body to another, mainly in the face and extremities, although axial myoclonus could also appear. Subtle focal or clonic seizures may continue to myoclonus. Additionally, the complex motor manifestations that are associated with bursts of paroxysmal activity on the EEG are difficult to classify as spasms or myoclonus. Both conditions can present focal seizures commonly; these can be with deviation of the eyes, tonic posture, or hemiconvulsions; subtle attacks can also occur with autonomic phenomena, such as flushing or apnea [9].

## 2.3 Electroencephalography features

### 2.3.1 Background

The EEG may be normal at the beginning of the EME, which is why successive EEGs must be repeated to define the diagnosis. When the clinical presentation is complete, there is no temporal or spatial organization or physiological characteristics in wakefulness or sleep [11].

### 2.3.2 Interictal abnormalities

The typical pattern is the suppression-burst (S-B); it consists of bursts of high-voltage asynchronous delta or theta waves, interspersed with spikes and polyspikes from 150 to 350  $\mu$ V that last from 1 to 6 seconds and alternate with low voltage ( $<10$   $\mu$ V) or complete suppression activity intervals of 2–5 seconds in duration [8]. In the EME, the bursts are shorter, and the suppression periods are much longer [11]; the S-B pattern in OS occurs in both wakefulness and sleep, while the S-B pattern in EME, which usually is present only during sleep [9].

The S-B pattern may vary in configuration and the interhemispheric synchronization of the bursts; they may predominate in one hemisphere, especially when associated with lateralized structural anomalies, such as focal cortical dysplasia or hemimegalencephaly [11]. During the suppression periods, focal epileptiform discharges can be observed [12].

The S-B pattern may persist beyond the first year of life, or it may progress to hypsarrhythmia between 3 and 6 months of age; it's coinciding with the development of epileptic spasms in the WS context [11]. The early transition to hypsarrhythmia is more common in the OS, while in the EME the S-B can continue in the infancy until a transient evolution to hypsarrhythmia in the middle and late infancy [10]. There are reports of evolution to the slow spike-wave pattern characteristic of LGS.

### 2.3.3 Ictal EEG

During tonic spasms, EEG shows desynchronization with or without rapid activity [8]. By means of video-electroencephalography (video-EEG) with electromyographic recordings from deltoid muscles, we observe that each burst is to be associated with tonic contraction of variable duration [13]. The erratic myoclonus of EME habitually has no EEG correlate, whereas limb/axial myoclonus are usually associated with bursts of spikes and polyspikes.

Complex stereotyped movements that are difficult to classify as either spasms or myoclonias are also associated with bursts of activity. There is no correlation between

the duration of the burst and the type of seizure [11]. Focal seizures and subclinical phenomena are associated with focal discharges of spikes or sharp wave [8].

2.3.4 EEG differential diagnosis

A discontinuous EEG pattern with resemblances to S-B can be seen in neonatal hypoxic ischemic encephalopathy, but in this condition, the pattern is generally transient and can be reactive. Treatment for neonatal status epilepticus, such as midazolam, sufentanil, and fentanyl infusion, may exhibit a pattern evocative of S-B.

2.4 Etiology

The etiologies of OS are diverse, including specific genetic mutations, cortical brain malformations, mitochondrial disorders, nonketotic hyperglycinemia, and severe perinatal hypoxic-ischemic injury. On the other hand, EE vitamin-responsive disorders need to be ruled out as a potential underlying etiology; in certain cases the cause is unknown.

The most frequent genetic abnormalities linked with OS are aristaless-related homeobox (ARX) gene mutations at Xp22.13, cyclin-dependent kinase-like 5 (CLDK5) (STK9) gene at Xp22, solute carrier family 25 [mt carrier, glutamate carrier-1/GC-1] member 22 (SLC25A22) gene at 11p15.5, STXBP1 (MUNC18-1) gene microdeletion at 9 q33.3-q34.11, KCNQ2 gene mutations, SCN2A gene mutations, and GABRA1 gene mutations [14].

EME is usually associated with inherited metabolic disorders, such as nonketotic hyperglycinemia, organic acidemias, Zellweger syndrome, and molybdenum cofactor deficiency [15]. Until the report of Cohen in 2014, in two siblings with early myoclonic encephalopathy, born to consanguineous parents of Arab Muslim origin, a potential mutation of SLC25A22 should be considered in infants presenting as EME, severe microcephaly, and autosomal recessive inheritance with negative metabolic workup [16].

Several of the genes may manifest as phenotypes that overlap not only with OS and EME but also with other EEs such as West syndrome [14].

**Box 1** shows differences between early epileptic encephalopathies [17].

| EME  | OS  |
|--|---|
| <i>Clinical</i><br>Early myoclonus progressively becoming erratic, fragmented, and massive, followed by focal seizures and rarely tonic spasms | <i>Clinical</i><br>Characterized by tonic spasms, focal seizures, and rarely massive myoclonus; this is never erratic |
| <i>EEG</i><br>The S-B pattern is continuous in both awake and sleep states   | <i>EEG</i><br>The S-B pattern is limited or more distinct during sleep  |
| <i>Etiology</i><br>Structural brain abnormalities, a few metabolic, non-familial. Genes found: ARX, STXBP1, KCNQ2, and PNKP                    | <i>Etiology</i><br>Cryptogenic, familial, and metabolic. Genes found: ErbB4 and SEC25A22                              |
| OS, Ohtahara syndrome; EME, early myoclonic encephalopathy; S-B, suppression-burst; ARX, aristaless-related homeobox                           |   |

**Box 1.**  
*Differences between early infantile epileptic encephalopathy (EME) and Ohtahara syndrome (OS).*



## 2.5 Treatment and prognosis.

There is no specific treatment efficacious for these epileptic syndromes. For OS, adrenocorticotrophic hormone (ACTH)/corticosteroids, vigabatrin, levetiracetam, zonisamide, phenobarbitone, rufinamide, and ketogenic diet should be tried. Resective surgery may be useful in cases of focal cortical dysplasia or hemimegalencephaly. Patients diagnosed as EME should receive a trial of pyridoxine. In cases with nonketotic hyperglycinemia, oral administration of ketamine, tryptophan, and dextromethorphan, in combination with benzoate, may improve the neurological symptoms [18]. Vigabatrin and sodium channel blocker AEDs should be avoided in the myoclonic phase of EME.

Prognosis in both syndromes is very poor, and the response to treatment is very disappointing. About half of patients die within weeks or months from onset, and the others progress with severe neurological impairments. Two-thirds of the survived OS patients develop infantile spasms, around 3–7 months, and numerous advances to LGS after 1 year of age [18]. In EME, the erratic myoclonus will improve spontaneously with time, and then they will carry on having focal seizures, despite its treatment.

## 3. Infantile spasms (IS) and West syndrome (WS)

### 3.1 Overview

West syndrome (WS) was first described by Dr. WJ West of Tunbridge, United Kingdom, in 1841, in a letter addressed to the editor of *The Lancet*. West reports the characteristic clinical features in his own son. In 1952, Gibbs and Gibbs describe hypsarrhythmia, the characteristic electroencephalographic feature of WS [1]. WS is an age-dependent epilepsy that usually starts in the first year of life, most frequently between the first 3 and 9 months of life; however spasms can also affect older children but rarely beyond the age of 2 years. Even though the triad of epileptic spasms in cluster, developmental regression, and hypsarrhythmia on the EEG defines WS, it is not always associated with the classical hypsarrhythmic EEG pattern, and patients do not always have developmental regression at the beginning of the disease [19]. The recent ILAE classification included the term “epileptic spasms” (ES), rather than “infantile spasms,” when this seizure type is observed at other ages. Hypsarrhythmia can also be incidentally recorded in the absence of spasms.

### 3.2 Seizures: symptoms and semiology

ES are a seizure type, characterized by short-term muscle contractions that affect predominate proximal and truncal muscles which lead to abrupt flexion, extension, or mixed movements. According to EEG-EMG polygraphy records, an epileptic spasm reaches the full contraction more slowly than myoclonia but faster than a tonic seizure [20]. Usually, ES occurs in clusters but may be isolated. Clusters of ES increase progressively in frequency and intensity, reach a peak, and then gradually decline before they stop.

Some ES are limited to making only grimaces, deviation of the eye, and nodding; they can also be subclinical; it's called “subtle” ES. On the other hand, ES may be asymmetric, or asynchronous, concomitant with various focal manifestations that may implicate the limbs, head, or eyes; sometimes ES may express with compartmental and vegetative features. If ES is preceded or followed by, or interspersed with, focal seizures, it suggests a focal lesion [21].

### **3.3 Electroencephalography**

#### *3.3.1 Background*

Continuously abnormal during the wakefulness and sleep.

#### *3.3.2 Interictal abnormalities*

A typical interictal presentation in WS, hypsarrhythmia, refers to a high-voltage (hypsos = height), disorganized, and chaotic (without any discernible normal background rhythm = arrhythmia) EEG pattern. At onset, hypsarrhythmia may be present only during the drowsiness and light sleep, but it soon grows into profuse during the wakefulness.

Sometimes epileptic discharges appear to be focal or multifocal, however, without a rhythmic or organized pattern. This electrical manifestation is almost continuous, although in initial stages, background activity can be observed intermittently. Hypsarrhythmia predominates in the posterior regions; rarely, posterior predominance is observed, especially after the first year of life [11]. This pattern of hypsarrhythmia reaches its peak in stage 1 of sleep, is less persistent in stages II and III of sleep (as multifocal spikes and sharp discharges), and disappears completely in REM sleep.

Different variants of hypsarrhythmia have been reported further than its typical presentation; these include (1) hypsarrhythmia with increased interhemispheric synchronization, (2) asymmetric hypsarrhythmia, (3) hypsarrhythmia with episodes of voltage attenuation, (4) hypsarrhythmia with a consistent focus of epileptic discharges or focal slowing, and others [22].

When the EEG shows atypical hypsarrhythmia, an underlying structural origin can be suspected; for example, predominating focal discharges or slow complexes could indicate a focal lesion, diffuse high-voltage theta-alpha activity may indicate lissencephaly or pachygyria, and persistent asymmetry or asynchrony may suggest a focal lesion or agenesis of the corpus callosum.

#### *3.3.3 Ictal EEG*

Ictal activity associated with ES includes a diffuse high-amplitude triphasic slow wave, a low-amplitude brief fast discharge, or a short-lasting diffuse flattening of ongoing activity [13, 20]. A transient disappearing or reduction of the hypsarrhythmic pattern could be seen during a cluster of ES. Patients with brain lesions may show an asymmetry of the ictal high-amplitude slow wave because of the more involved hemisphere. Focal or unilateral fast discharges directly preceding the high-voltage slow wave are greatly suggestive of focal cortical lesion [11].

### **3.4 Etiology**

WS etiology can be genetic, structural or metabolic, or unknown. Prenatal and perinatal etiologies explain more than 40% of the cases; they include central nervous system malformations, neurocutaneous syndromes (especially tuberous sclerosis), metabolic disorders, hypoxic-ischemic encephalopathy, central nervous system infections, and other acquired conditions [23].

Underlying etiology may be genetic, either chromosomal abnormalities or single-gene defects. The mutations in specific genes are ARX, GAMT, ALG13, CDKL5, SCN2A, STXBP1, SCN1A, ALG13, GABRB3, DNM1, SCN8A, MAGI2, ACADS, WDR45, and GABRA1 [23, 24].

### 3.5 Treatment and prognosis

The key short-term aims of therapy are the rapid abolition of ES and the elimination of hypsarrhythmia. Effective treatment is associated with better outcome, at least in patients where the underlying pathology is not responsible for significant neurological deterioration. Therefore, children with WS, who are developmentally normal prior to spasms, continue to be normal after successful early treatment; on the other hand, children with WS, who have some cognitive problems prior to spasms, remain to have cognitive deficits, even after successful treatment related to the underlying pathology [25].

Other factors that contribute to unfavorable outcome are onset at age < 3 months, psychomotor retardation, existence of other seizure types, persistence of abnormal EEG features, mild to gross neurologic deficits, significant computed tomography/MRI findings, and long duration of therapy. All unfavorable prognostic factors seem to relate to the underlying pathology; some symptomatic cases may develop autism or LGS [26].

With the exception of IS in the setting of tuberous sclerosis complex (TSC), there is relatively broad consensus that hormonal therapy is the most effective class of initial treatment for IS [27]; but the best agent, dose, and length of treatment are not clear. The most studied medications are natural adrenocorticotrophic hormone (ACTH, a 39 amino acid peptide), synthetic ACTH (sACTH, a truncated peptide spanning the first 24 N-terminal residues), prednisolone, and prednisone (the prodrug of prednisolone).

The highest short-term response rates (freedom from ES and hypsarrhythmia on treatment day 14) have been observed with ACTH administered at high dose ( $150 \text{ U/m}^2$  body surface areas per day, divided into two daily doses) [28]. Although some authors reported that short-term response was far superior with this regimen of ACTH in comparison to prednisolone at dose of  $2 \text{ mg/kg/day}$  [29], a sequence of studies has suggested that higher dose regimens of prednisolone are as effective as ACTH. In the UKISS study, no difference in response rate between prednisolone ( $40\text{--}60 \text{ mg/day}$ ) and a “moderate” dose of sACTH ( $0.50\text{--}0.75 \text{ mg}$  on alternate days) was observed, although treatment allocation was not randomized [30]. Likewise, in a debatably underpowered retrospective analysis, Kossoff and colleagues reported that efficacy of high-dose prednisolone ( $40\text{--}60 \text{ mg/day}$ ) was similar to historical experience with high-dose natural ACTH [31]. In other relatively small study evaluating short-term efficacy of very high-dose prednisolone ( $8 \text{ mg/kg/day}$ ; max  $60 \text{ mg/day}$ ) followed by high-dose natural ACTH in prednisolone nonresponders, the EEG-confirmed response to prednisolone (63%) was analogous to the reported ACTH response in most current studies [25].

More recently, in a large-scale prospective observational study led by the National Infantile Spasms Consortium (United States) without randomized treatment distribution, Knupp and colleagues reported that response rates to natural ACTH (most with high-dose protocol;  $150 \text{ U/m}^2/\text{day}$ ) and oral corticosteroids (most with high-dose prednisolone;  $40\text{--}60 \text{ mg/day}$ ) were statistically indistinct [32]. In the only modern randomized controlled trial comparing high-dose prednisolone ( $40\text{--}60 \text{ mg/day}$ ) with moderate-dose sACTH ( $0.5\text{--}0.75 \text{ mg}$  on alternate days), Wanigasinghe and colleagues found that response to prednisolone was superior, though the response rate to sACTH was inexplicably low [33].

Given the cost of a typical course of ACTH exceeds 100,000 USD, a typical course of prednisolone costs less than 100 USD; many of treatment protocols for WS begin with prednisolone/prednisone and leave ACTH as an alternative for patients without response to this drug.



All hormonal therapies exhibit similar—and important—adverse event profiles. The main risk is immunosuppression, which can be severe and potentially lethal, as well as hypertension, with the potential to yield congestive heart failure [34]. As such, avoidance of infectious contacts and screening for asymptomatic hypertension are key safety measures to be endorsed during any course of hormonal therapy. In addition, most clinicians prescribe antibiotic prophylaxis for pneumocystis pneumonia, screen for asymptomatic hyperglycemia, monitor serum potassium given modest risk of hypokalemia, and also screen for adrenal or pituitary insufficiency after a course of hormonal therapy.

Vigabatrin (VGB) is an irreversible inhibitor of  $\gamma$ -aminobutyric acid (GABA) transaminase, with proven efficacy in the treatment of IS in several randomized, controlled trials [35, 36]. Nevertheless, short-term response rates to VGB are considerably lower in comparison to the hormonal therapies. With respect to long-term outcomes, the superiority of hormonal therapy is not as clear [37, 38]. Although a large-scale trial of VGB versus high-dose hormonal therapy has not been undertaken in a TSC cohort, several studies indeed suggest that response to VGB is substantially higher among patients with WS associated with TSC in comparison to patients with other etiologies [39–41]. There is broad consensus that patients with IS in the setting of TSC should receive first-line treatment with VGB [27].

Overall, VGB is moderately effective (and highly effective in the setting of TSC) and confers moderate risk. The threat of visual field loss is relatively low and perhaps diminished by short courses of therapy; the risk of reversible and habitually asymptomatic MRI toxicity is moderately high and dose-dependent [41].

The hypothesis that combination therapy is superior to either therapy alone was proven in the International Collaborative Infantile Spasms Study (ICISS) [42], in which the investigators randomized new-onset patients with IS to receive either hormonal therapy (prednisolone or sACTH) alone or in combination with VGB. The combination therapy group exhibited superior response rates with respect to clinical outcome (parent-reported freedom from ES on days 14–42), electroclinical outcome, and time to cessation of ES.

A minority of children with IS are good candidates for surgical resection [43]. The etiologies best suitable to surgical resection include cortical dysplasia, cortical tubers in TSC, and various acquired structural lesions, for example, unifocal stroke or hemorrhage. The role of nonresective surgical approaches (e.g., corpus callosotomy) is not well established in these patients [43].

There are rare occasions in which a specific metabolic etiology of IS prompts a specific therapeutic intervention, either as an alternative or adjunct to first-line therapy [44]; the most notable examples include pyridoxine (vitamin B6) dependency (treated with pyridoxine or leucovorin), pyridoxal-5-phosphate deficiency (treated with pyridoxal-5-phosphate), glucose transporter type 1 (Glut1) deficiency (treated with the ketogenic diet), and nonketotic hyperglycinemia (ameliorated to some extent by sodium benzoate and other interventions to promote central glycine clearance) [45].

Other treatments are supported by very limited reports of efficacy. It includes traditional antiseizure drugs such as topiramate, zonisamide, valproic acid, felbamate, and benzodiazepines clonazepam and nitrazepam. Among nonpharmacologic therapies, numerous studies suggest substantial efficacy for treatment of IS with the ketogenic diet; most of these are retrospective, and none has utilized placebo controls or unbiased outcome assessment. Prognosis depends on etiology and is better in children without apparent structural cause. In nearly half of the patients, WS evolves into LGS or multifocal epilepsies.

## 4. Severe myoclonic epilepsy in infancy (Dravet syndrome)

### 4.1 Overview

Severe myoclonic epilepsy of childhood was described in 1978 by Charlotte Dravet and included among epileptic encephalopathies in the 2001 proposal [3]. However, the acceptance that DS is a channelopathy of the SCN1A gene, as well as the presence of neurological deterioration in the early stages of the disease, has questioned whether the deterioration is really due to epileptic seizures or due to channelopathy [46].

Estimated prevalence of Dravet syndrome (DS) is about 1% of epilepsy syndromes in infancy and childhood, being more frequently in male. According to different descriptions of the natural course during of DS childhood, two phases have been identified: early phase (first year of life) and a steady phase (from 2 to 5 years of life); the electroclinical features are different between these phases. Early phase is characterized by long hemi- or generalized convulsive seizures, typically related with fever, while in the steady phase, seizures that predominate are myoclonic seizures (MS), atypical absences, and complex partial seizures (CPS); also, events of nonconvulsive status may occur. Cognitive development slows down progressively causing moderate/severe intellectual disability generally after the age of 4–5 years. Most patients develop ataxia, pyramidal signs, and hypotony, which persist to adulthood.

Seizure behavior should vary in time; association between seizures and fever may be absent; also CPS and MS may begin in the early phase. Diagnosis of DS may be delayed because of the variability in evolution, the seizure polymorphism, and the non-specific EEG features. Long-term prognosis is always bad, pharmacoresistance is the rule, and most patients go on severely cognitively impaired.

### 4.2 Seizures: symptoms and semiology

The typical picture is previously healthy children who begin with seizures in the first year of life; its seizures should be unilateral or generalized convulsive (clonic or tonic-clonic), are commonly prolonged (more than 10 min), and could be progressed into status epilepticus (SE). Seizures are usually triggered by fever, or occur after immunization, but may also be afebrile. In the second or third year of life, other types of seizure, generally afebrile, can occur [47] in the absence of MS, which starts later [48].

The seizure pattern changes over time; SE is the most problematic through the first 2 years of life and decreases in frequency after 5 years of age. In early childhood, frequent nonconvulsive seizures may negatively impact neurodevelopment. In the adolescent and adult years, brief but frequent nocturnal generalized convulsive seizures are the most common and place the patient at risk of sudden unexpected death in epilepsy (SUDEP). The details of seizures observed in DS are described then:

#### A. Convulsive seizures

1. Unilateral with clear hemiclonic or tonic convulsions that may alternate sides in the same patient can offer a significant sign to early diagnosis.
2. Generalized tonic-clonic seizure (GTCS).
3. Falsely generalized (FG) and unstable seizures. FG are bilateral convulsive with asymmetric clonic or tonic movements and postures, at times predominating on one side or changing sides during the seizure.

- B. Focal seizures, commonly CPC, are accompanied with autonomic features like pallor, cyanosis, respiratory changes, and drooling and oral automatisms, with eyelid or distal jerks. These seizures are short (few minutes) but can progress into a unilateral or generalized motor seizure.
- C. Myoclonic seizures (MS) should manifest like massive axial movements with falls or as a few jerks; erratic myoclonias are not rare.
- D. Atypical absences (AA) could appear frequently linked with a myoclonic component.
- E. Nonconvulsive status epilepticus (NCSE) or obtundation status is prolonged episodes (hours or days) of diminishing of consciousness with loss of contact or variably reduced responsiveness and somnolence, with erratic or segmental myoclonus. This NCSE may be initiated, punctuated, or terminated by GTCS or be combined with axial myoclonic, myoclonic-atonic, or clonic seizures.
- F. Tonic seizures are rare and may be triggered by intermittent photic stimulation (IPS), visual patterns, hot water immersion, and physical effort.

Sensitivity to photic or pattern stimulation is noted in approximately 40% of patients, particularly in younger children.

Worsening of seizures or SS may be provoked by blocking sodium channels AEDs, such as carbamazepine, phenytoin, lamotrigine, and vigabatrin.

In adults, seizures are more frequent during sleeping, especially long-lasting clonic seizures or short tonic-clonic seizures, while MS, AA, and focal seizures have a tendency to remit.

### **4.3 Electroencephalography**

EEG abnormalities are non-specific, but interictal EEG is useful for differential diagnosis; however sequential EEG recordings may show the evolution of DS, whereas ictal recordings with EMG polygraphy document seizure polymorphism [11].

#### *4.3.1 Background*

In wakefulness state background activity is normal at onset, despite the frequent seizures; diffuse or asymmetric slowing may be seen if EEG is performed immediately after a seizure or may remain on for a few days. During sleeping normal patterns, initially after the first year, there is usually a gradual slowing of the background activity, more obvious if seizures are frequent. Physiological sleep phenomena and organization mostly remain conserved, except numerous nocturnal seizures occur.

#### *4.3.2 Interictal abnormalities (IA)*

It may be present at the beginning (22% of patients) and grow during the evolution (77%) [48]. Generalized focal and multifocal abnormalities, spikes, and spike-wave or polyspike-wave discharges, symmetric or not, predominate over the frontal and central areas, but occur over the temporal and occipital areas, too. IA is typically greater during sleeping [48, 49]. The evolution of the EEG aspects with age is not always similar and being dependent on the number and duration of seizures.

### 4.3.3 Ictal EEG

- Unilateral seizures. The ictal discharge is characterized by rhythmic (2–3/second) bilateral slow waves of higher amplitude over the hemisphere contralateral to the clinical manifestations and intermixed with 10/second recruiting rhythms. In others, the EEG pattern can onset over the frontal or frontal-central regions of one hemisphere, or with bilateral asymmetric onset, but always predominant over the frontal areas.
- Falsely generalized and unstable seizures. In this type of seizures, the EEG discharge is of bilateral symmetric or asymmetric onset with a slow spike, occasionally followed by a brief attenuation, and fast activities intermixed with slow waves. Whereas, the ictal discharge change topographically in a same seizures, in unstable seizures [47].
- In CPS ictal EEG consists of a rhythmic sequence of fast polyspikes intermixed with theta activity during the last part of the seizure, involving the temporal-parietal-occipital region of one hemisphere for the duration of the seizure [47].
- MS are accompanied by generalized spike or polyspike-wave discharges at 3 Hz or more, lasting 1–3 seconds and of higher voltage over the central-parietal areas.
- AA are linked with generalized regular or irregular spike-wave discharges at 2–3.5 Hz, lasting 3–10 seconds.
- In obtundation status EEG background activity is substituted by diffuse delta slow waves, superimposed with multifocal spikes and spike-waves, sharp waves, and generalized spike-and-wave discharges preponderating over frontal-central areas.
- Tonic seizures are associated with diffuse discharges of polyspikes at 8–9 Hz [15].

### 4.4 Etiology

DS is a channelopathy due to mutation in the SCN1A gene which encodes the alpha 1 subunit of the voltage-gated sodium (Nav1.1) channel reported in 80% of patients [50]. Almost half of SCN1A mutations are truncations, and most DS SCN1A mutations are de novo [51]. SCN1A mutations are not pathognomonic of DS; it could be observed in a spectrum of febrile epilepsy syndromes, which ranges from genetic epilepsy with febrile seizures plus (GEFS+) to DS. The mutations in the SCN1A gene also constitute a risk factor for SUDEP by causing cardiac and respiratory dysfunctions [52]. Another gene implicated in DS is GABRA1 [53].

### 4.5 Treatment and prognosis

The aim of treatment in patients with DS is reducing seizure frequency, minimizing comorbidities, limiting antiepileptic drug toxicity, and avoiding seizure-related injury and SUDEP [54]. A greater degree of cognitive and behavioral impairment has been associated to higher frequencies of seizures [55, 56].

It is prominent that seizures are triggered by hyperthermia and less frequently by photosensitivity or pattern sensitivity; thus antipyretics for fever, minimizing



warm baths or exercising on warm days, and avoiding photosensitivity triggers are recommended [54].

Sodium channel-blocking drugs such as carbamazepine, oxcarbazepine, lamotrigine, and phenytoin should also be avoided because they can aggravate seizures.

Valproic acid, clobazam, topiramate, levetiracetam, and stiripentol are the drugs of choice. Stiripentol combined with valproic acid and clobazam, as well as topiramate, give promising results [54, 57, 58]. The ketogenic diet is an alternative with good results for several patients, achieving a reduction of the seizures by 50% or more [59, 60].

The prognosis for children with DS is poor; the complete cessation of epileptic seizures is not achievable in these patients. Since the onset of disease, the neurological status worsens, and about 10–20% of afflicted children will die prematurely [61, 62]. Early mortality, sometimes due SUDEP, occurs in about 10% of patients. However, the outcome, in at least some children, improves with early diagnosis and appropriate therapeutic intervention.

## **5. Epilepsy of infancy with migrating focal seizures (EIMFS)**

### **5.1 Overview**

EIMFS, previously called malignant migrating partial seizures of infancy, is a rare and severe condition described in 1995 [63]. EIMFS is characterized by focal “migrating” or “random” seizures beginning within the first 6 months of life, severe global developmental delay, and acquired microcephaly. Epilepsy is highly pharmacoresistant. At onset brain MRI is typically normal, but later it may show delayed myelination, thin corpus callosum, and cerebral atrophy [64]. Patients with intractable seizures have a progressive deterioration with major axial and limb hypotonia, loss of visual contact, and loss of other motor and social skills. Pyramidal and/or extrapyramidal features with athetotic movements may appear; about 18% of the patients died [65].

De novo KCNT1 mutations have been reported in about 50% of patients with sporadic EIMFS [64–66].

### **5.2 Seizures: symptoms and semiology**

It is accepted that the natural history of the EIMFS goes through three distinct phases [63]. The first phase starts in the first 6 months of life and lasts a few weeks or months; patients have sporadic seizures with frequency every few weeks or months. Seizures used to be focal motor with quick generalization or associated with autonomic features like apnea, flushing, or cyanosis [63, 67]. The second phase, called “stormy phase,” arises between 1 and 12 months; seizures become more frequent, occurring in clusters several times a day or being practically continuous for several days. Seizure consists of lateral deviation of the head and eyes, twitches of the eyelids, unilateral clonic or tonic jerks of one or both limbs, apnea, flushing and/or cyanosis of the face, chewing movements, and secondary tonic-clonic seizures [68]. Additionally, clinical manifestations may be “subtle” or absent even with the long duration of seizures.

The age at onset of the third phase is variable, from the end of the first year to the fifth year of age. This phase is typically seizure-free, even if interposing illnesses can trigger recurrent seizures or SS. Some patients can evolve to a WS [63, 65].

Migrating focal seizures (MFS) are seizures which occur usually in clusters that last for a few days and are then followed by a few weeks or months of recovery. Within a cluster, seizures are very frequent and may even extend to SS. Clusters increase in frequency within the first 2 years of life.

## 5.3 Electroencephalography

### 5.3.1 Background

EEG is usually normal during the first months apart from slowing for many hours after long-lasting seizures. As the disease progresses, background activities become gradually diffusely slower with decline of physiological features. Activity may show alternating asymmetries, with slow activity that change from one hemisphere to another [63]. In seizure-free periods, sleep and wakefulness are obviously differentiated; nevertheless sleep spindles are rare, asynchronous, and asymmetric.

### 5.3.2 Interictal abnormalities

Interictal abnormalities are usually absent at onset; spikes rapidly grow in frequency and develop multifocal within a few months; multifocal spike-and-wave activities do not show any specific pattern and are not activated in sleep.

### 5.3.3 Ictal EEG

Epileptic discharges (ED) sequentially involve different areas of the brain, such as describing a random migration, without a specific pattern. The ictal pattern is characterized by rhythmic monomorphic activity in the alpha-theta frequency range, although delta waves, spikes, and spike-waves can also be observed. It is common for epileptic activity to remain limited to one region for a period of time and then decrease in frequency until stop, with a tendency to progressively involve an adjacent area. ED is continued with slow postictal activity without prolonged voltage decrement [63, 68]. When epileptic seizures are frequent, ED changes from one region to another and from one hemisphere to another so that consecutive focal epileptic discharges overlap resulting in a continuous and changing multifocal ictal activity and a very complex epileptic status pattern [11].

## 5.4 Treatment

Migrating partial seizures are usually refractory to pharmacologic treatment though some cases have responded to bromide (60–80 mg/kg/day), with a termination of the seizures for several months after almost 3 weeks of therapy [69]. Even so, one should be aware of a potential bromoderma tuberosum, which could be appearing with high doses of potassium bromide therapy [70]. Intravenous levetiracetam (60 mg/kg) rapidly interrupted migrating partial status in two children with a good tolerability and safety [71]. Other successful treatments include a combination of sodium bromide, stiripentol, and levetiracetam [72], rufinamide and acetazolamide [73, 74], and stiripentol associated with clonazepam.

## 6. Epilepsy with myoclonic-atonic seizures (EMAS) or Doose syndrome

### 6.1 Overview

In 1970, Herman Doose reported seizures in 51 previously normal children between 1 and 5 years of age described as myoclonic and atonic, frequently combined with absences and GTCS and tonic seizures [75]. Doose suggested a genetic etiology [76] and later refined his criteria and emphasized that tonic seizures are rare [77].

In 1989, the ILAE recognized the syndrome of myoclonic-astatic epilepsy with a genetic predisposition, and in 2010 the term changed to “epilepsy with myoclonic-atic seizures” (EMAS). Features that define EMAS are (1) normal development previous to the start of seizures; (2) onset between 7 months and 6 years of age, of myoclonic, myoclonic-atic, or atonic seizures; and (3) EEG with generalized spike or polyspike-and-wave discharges.

EMAS represents 1–2% of cases with childhood epilepsy and shows a variable clinical course and age-dependent spectrum. Onset peaks at about 3 years and is more prevalent in boys, ratio about 2:1. A long-term follow-up study showed a common evolution which was classified, according to the definitive seizure outcome, into favorable, intermediate, and unfavorable forms [78]. Cumulative percentage remission reached 40% within 6 months, 63% within 1 year, and 89% within 3 years after seizure onset [78]. Even in children with a favorable clinical course, seizures can be initially pharmacoresistant, sometimes demanding additional ACTH or ketogenic diet; in unfavorable patients, epilepsy remains refractory to treatment with the occurrence of long-lasting episodes of NCSE. Cognition is habitually normal during the first months of the disease, although patients are often severely hyperkinetic; intellectual outcomes range from favorable to unfavorable [79, 80].

## **6.2 Seizures: symptoms and semiology**

The main seizure types range from myoclonic to atonic. MS, atonic seizures (before called astatic), and myoclonic-atic seizures typically occur a few days or weeks after the onset of GTCS or clonic seizures.

It is common for the first seizures to be clonic seizures or GTCS, which occur in normal children; sometimes they can be preceded by febrile seizures (FS). In a few months, the frequency of crises increases gradually and AA may appear. Nonconvulsive SS may be of myoclonic-atic, myoclonic, or AA type and may be resistant to treatment. Some patients with a poor outcome may have brief tonic seizures.

The types of seizures observed in EMAS are:

1. Epileptic drop attacks or seizures that cause falls, which can be of three different types taking account the postural change, the temporal sequence of falling, and EMG polygraphy.
  - Myoclonic flexor seizures with sudden flexion or extension of the head and trunk.
  - Myoclonic-atic seizures with initial change as the myoclonic flexor type, but following falling is produced by loss of muscle tone.
  - Atonic seizures with sudden slumping or collapsing to the floor as a result of transient loss of muscle tone.
2. Generalized clonic seizures occur during both wakefulness and sleep. The clonic component commonly appears as the repetition of massive MS. Clonic movements habitually increase in frequency and may become very rapid resulting in a “clonic vibratory” seizure that usually ends with gradually decreasing frequency of the clonic jerks.
3. GTCS, in which clonic component is preceded by a tonic phase lasting a few seconds.

4. Some patients may have prolonged recurrent AA with associated blurring of consciousness and often random segmental myoclonus or head nodding.
5. NCSE which consists of a cluster of myoclonic-astatic, MS, or AA. Clinically, we observe loss of contact or somnolence. Patients may have salivating and speech trouble ranging from dysarthria to mutism. Sometimes, erratic myoclonus in the face, the upper limbs, the eyelids, mouth, tongue, and fingers should be observed, associated with ataxic, hypotonia, tremor, and difficulty in walking.
6. Generalized tonic seizures with or without few clonic components occur during sleeping. When predominant, these seizures are associated with unfavorable outcome; they are resistant to treatment. When the tonic phase is preceded by a myoclonic jerk, seizures are termed “myotonic.”

### 6.3 Electroencephalography

#### 6.3.1 Interictal background

Background activity is normal at the onset of the disease. A characteristic 4–7-Hz diffuse theta rhythm, usually predominating over the central-parietal areas (central theta waves), is often present, intermixed with normal waking activities and increasing during the drowsiness. In some children, background may be diffusely slow. During sleeping, physiological features are usually seen at the onset, while diffuse slowing with loss of sleep architecture can occur during the evolution, mainly in the severe forms of the spectrum [11].

#### 6.3.2 Interictal abnormalities

In wakefulness there may be no epileptiform discharges. If this is present, generalized spike-waves discharges are at 2–3 Hz, predominant over the frontal-central areas. They may show not consistent asymmetries between the hemispheres. Focal or multifocal spikes may also be present; these are rarely abundant and may predominate on one side, but not consistently so, and are not associated with focal slowing [11]. During sleeping, focal and generalized spike-wave discharges may increase and acquire a typical polyspike component.

#### 6.3.3 Ictal EEG

Generalized bilaterally synchronous single or multiple spike-and-wave discharges with 2–4 Hz frequency are commonly associated with all three seizures types that produce drop attacks, although spike-wave discharges are briefer for myoclonus.

The EMG correlate of the jerk is a burst of muscle activity lasting 100 ms; this is followed by a post-myoclonic silent period of EMG inhibition that lasts for 60–500 ms, which is synchronous for the recorded muscles and time-locked to the onset of the slow wave [78]. Both the brisk jerk and the post-myoclonic silent period concur to produce the typical drop.

AA corresponds of generalized irregular spike-wave discharges at 1.5–3 Hz. During NCSE, EEG shows no normal background activity, is characterized by diffuse and irregular spikes and slow waves persisting continuously throughout the episode, and is in combination with erratic myoclonus recorded on the EMG. Generalized tonic seizures correspond to burst of generalized spikes during sleep and eventually wakefulness.



## **6.4 Etiology**

Patients with Doose syndrome have probably a multifactorial inheritance, some of the first to be diagnosed with SCN1A mutations, but others have also been found to have sodium channel subunit beta-1 (SCN1B) and gamma-aminobutyric acid receptor subunit gamma-2 (GABRG2) mutations. However, these genes have not been found consistently in sporadic cases [79].

## **6.5 Treatment**

Ethosuximide is reported to be one of the more effective antiepileptic drugs (AED), especially when absence seizures are the primary seizure type. Valproic acid and lamotrigine are also beneficial; however, lamotrigine probably cause paradoxical worsening in individuals for whom myoclonic seizures are prominent [79]. Levetiracetam and zonisamide have been anecdotally used and may be helpful [23]. The ketogenic diet is a widely reported therapy for Doose syndrome and may be the most efficacious treatment; expert consensus guideline for optimal use of the ketogenic diet listed Doose syndrome as one of the principal indications for this treatment [79]. Seizure remission has been reported even without changes to medication, which suggest that spontaneous remission of seizures does occur.

## **7. Lennox-Gastaut syndrome (LGS)**

### **7.1 Overview**

LGS is an electroclinical syndrome defined by the Marseille School between 1966 and 1972 but was first reported by Lennox and Davis as an epilepsy starts in childhood and characterized by diffuse slow spike-waves (SSW) at <2.5 Hz and several types of seizures including tonic seizures, atypical absences, and “drop attacks” [81]. The electroclinical description proposed by Beaumanoir and adopted by the ILAE Classification Commission in 1989 concerns 2–4% of childhood epilepsies and affects boys more frequently than girls [81]. In about 70–75% of patients, LGS is associated with a variety of inherited or acquired structural anomalies or chromosomal disorders, whereas in the other 25–30%, there is no identifiable etiology [82]. Electroclinical phenotype is similar in spite of the different etiologies because of a common underlying mechanism [83]; functional neuroimaging has indicated that epileptic activity in LGS recruits widespread areas of association cortex and that tonic seizures are expressed through the reticular formation of the pons [84]. Other epileptic syndromes like frontal epilepsies with secondary bilateral synchrony, EMAS, DS, late-onset ES, atypical benign partial epilepsy of childhood, and ring chromosome 20 epilepsy syndrome are the differential diagnoses; thus, an exhaustive evaluation of the medical history along with an EEG during the wakefulness and sleep is very important for the accurate diagnosis of the syndrome.

### **7.2 Seizures: symptoms and semiology**

Seizures start from 1 to 10 years but more frequently between 1 and 8 years; however, onset may occur in younger or older ages, even into adulthood. LGS may follow other types of epileptic syndromes, such as focal epilepsies, OS, and WS.

Diagnosis of LGS requires the following features: (1) many types of seizure, but inevitably include tonic seizures (TS) and atypical absences (AA), (2) cognitive impairment, and (3) typical interictal and ictal EEG patterns.

TS are mandatory for the diagnosis of LGS; they are diurnal and nocturnal, facilitated in NREM sleep, and typically occur in clusters. TS consist of sudden flexion of the neck and body, raising of the arms in flexion or extension, extension of the legs, and contraction of the face muscles. It continuing of the eyes and autonomic manifestations (apnea and facial flushing tachycardia), and can culminate as diffuse tremor (rapid, small-amplitude jerks affecting the whole body). They are axial and involve typically the proximal parts of the limbs, symmetrically or with unilateral predominance. TS can produce sudden falling, associated or not with brief loss of consciousness; the distal limb muscles are relatively spared.

AA is the second most common seizure, present in about 75% of patients. The main clinical manifestation is a brief lapse in consciousness, although some awareness may be preserved [82]; they are subtle and difficult to recognize without concurrent formal assessment of cognition and responsiveness. They are of long duration with the EEG discharge lasting >20 seconds, but their onset and termination are not always clinically discernible. Associated clinical features may include eyelid and mouth myoclonias and a decrease in muscle tone that may lead to a fall.

“Drop attacks” (sudden falls) are also frequent, affect 30–60% of patients, and are habitually related with a brief tonic seizure or an epileptic spasm [81]; the definition of seizure type that cause sudden falls must be requiring Video-EEG and polygraphic recording.

Drop attacks, and other types of seizures observed in LGS, are not specific to this syndrome; these are tonic-clonic, focal, myoclonic, and myoclonic-atonic. Episodes of SE may occur in about 60% of patients, consisting of alteration of consciousness with continuous SSW, and may be linked with serial tonic seizures [83].

## 7.3 Electroencephalography

### 7.3.1 Background

EEG is variable depending on etiology (structural, chromosomal, or idiopathic) and age, ranging from almost normal to, most often, poorly structured without physiological features and generally altered by continuous interictal abnormalities.

### 7.3.2 Interictal abnormalities

Generalized interictal features during the wakefulness and sleep are mandatory for diagnosis of LGS [11].

In wakefulness, high-amplitude, diffuse, and synchronous SSW at 1.5–2.5 Hz is typical. Slow SSW has maximal amplitude over frontal areas and ranges in duration from a few seconds to a few minutes or sub-continuous. The complexes typically consist of a spike (duration < 70 ms) or a sharp wave (70–200 ms), followed first by a positive deep and then by a negative wave (300–500 ms) [81]. Such stimuli, as eye opening, noise, calling the patient’s name, and pain, tend to decline the occurrence or terminate SSW [81]; on the other hand, relaxation and drowsiness favor their occurrence. Hyperventilation (HV) and intermittent photic stimulation (IPS) usually have little influence on the SSW activity.

Characteristic features during sleeping are:

- SSW discharges that are activated during slow sleep, with more marked tendency toward bilateral synchrony than in wakefulness.
- Bursts of high-amplitude generalized polyspikes and polyspike-waves.

- “Paroxysmal fast activity” (PFA), which consists of sequences of rhythmic activity at 10–25 Hz and lasts for a few seconds (2–10 seconds) during NREM sleep. PFA is an essential diagnostic criterion.

These may be subclinical or accompanied by subtle change of axial muscle tone, which is detectable only by EMG electrodes as the ictal expression of a tonic seizure [81]. Interictal abnormalities and seizures decrease in REM sleep.

Focal abnormalities are usually present in patients with structural lesions; they are non-specific and depend on the underlying pathology: focal or multifocal spikes, spike-waves, polyspikes, slow waves, and focal bursts of rapid rhythms.

### **7.3.3 Ictal EEG**

EEG pattern associated with typical seizures of LGS are:

- TS correspond to fast bilateral rhythmic spikes at 15–25 Hz. Amplitude is low at onset but increases as the discharge progresses, preponderating over the anterior areas and the vertex; occasionally diffuse slow waves follow after the end of the seizure [81].
- AA is concomitant with an irregular, diffuse, high-amplitude, more or less symmetric SSW that predominates over the frontal areas. AA may be difficult to differentiate from the interictal SSW pattern.

## **7.4 Etiology**

LGS is classified as genetic, structural or metabolic, or unknown. Approximately 70% of children with LGS have symptomatic. The underlying etiologies include a history of encephalitis, meningitis, tuberous sclerosis, brain malformations (e.g., cortical dysplasias), birth asphyxia, and trauma. LGS may also follow the diagnosis of West syndrome [23]. If unknown, then it can be either idiopathic or cryptogenic. Idiopathic refers to unknown etiology with the underlying cause being suspected as genetic; in contrast to cryptogenic, the underlying cause is also not known but is presumed to be structural or metabolic. The causative role of mutations in other genes (such as GABRB3, ALG13, SCN8A, STXBP1, DNM1, FOXG1, or CHD2) has been elucidated in recent exome studies or in case reports in patients with LGS without a history of infantile spasms [85].

## **7.5 Treatment and prognosis**

The long-term prognosis varies and has not improved using new AED as compared with earlier prescribed drugs [86].

Valproate is a first-choice drug, which has an effect in multiple seizure types including drop attacks; useful combinations are with clobazam, ethosuximide, lamotrigine, levetiracetam, topiramate, zonisamide, and rufinamide. We should avoid too many drugs as well as carbamazepine, oxcarbazepine, and vigabatrin, which may deteriorate some types of seizures. Felbamate carries the risk of aplastic anemia and hepatic failure and is used in exceptional cases [17].

Alternative treatment options for LGS include ketogenic diet, vagal nerve stimulation (VNS) or thalamic electrical stimulation, and corpus callosotomy (CC) [87]. VNS and CC showed more than 50% reduction in seizure frequency in patients with LGS. A study showed that CC may be more beneficial than VNS only in “drop

attack” seizures [87], while another study did not show any significant difference between the two procedures [88].

Prognosis is typically poor with children having seizures into adulthood and 75–95% with intellectual disability and behavioral and psychiatric disorders [82]. The risk of death is increased, compared with their peers of the same age, usually due to seizures and falls.

## **8. Encephalopathy with electrical status epilepticus during slow sleep (ESES)**

### **8.1 Overview**

The term “electrical status epilepticus during sleeping” which was first described by Tassinari [1] refers to the EEG pattern (continuous spike-wave complexes exclusively during non-rapid eye movement (NREM) sleep), with a spike-wave index accounting for at least 80–85% of slow sleep. Other concept, “continuous spikes and waves during sleeping” (CSWS) are considered synonymous of ESES, but indicates both, EEG features and clinical neuropsychological characteristics, of this EE [89, 90].

Encephalopathy with ESES is an EE characterized by seizures of various types and neurological deterioration in cognitive, motor, and behavioral areas. The encephalopathy is caused by a prominent activation of epileptic abnormalities during NREM sleep [11]. Anti-seizure drugs, immune modulatory agents, and surgery [91] have been used to treat conditions associated with ESES. In spite of the long-term favorable outcome of epilepsy and ESES, the prognosis is protected because of the persistence of severe cognitive and behavioral disturbances in about a half of the patients.

### **8.2 Seizures: symptoms and semiology**

ESES syndrome is manifest with epilepsy and encephalopathy:

1. Epilepsy onset can fluctuate from 2 to 12 years, with a peak at about 4–5 years, and can appear before the identification of ESES pattern. Mostly, seizures are present during ESES, but in others there is no history of clinical seizures at any time. Semiology and frequency of seizures can vary; the presence of TS during sleeping excludes this diagnosis. Three groups of seizures type have been proposed: [11].
  - Motor seizures, rare and nocturnal during the evolution of the syndrome
  - Unilateral partial motor seizures or secondary TCGS, principally occurring during sleeping
  - Rare nocturnal seizures in which AA develops during the course of ESES, often associated with negative myoclonus or atonic components leading to sudden falls
2. Encephalopathy manifests at the beginning or the worsening of neuropsychological troubles, which include global cognitive regression and various degrees of language impairment (acquired aphasia), behavioral disorders (hyperactivity, attention deficits, and disturbances of personality), and deterioration of motor skills (dystonia, dyspraxia, ataxia, and negative myoclonus) [11].



## **8.3 Electroencephalography**

### *8.3.1 Background*

During the wakefulness, it depends on the underlying etiology.

### *8.3.2 Interictal abnormalities*

During the wakefulness, the EEG is characterized by focal or multifocal slow spikes, frequently intermixed with diffuse slow spikes and waves. In some children, the interictal EEG pattern may be similar to those observed in idiopathic focal epilepsies; in other cases, a background asymmetry, the presence of polyspikes or repetitive fast spikes, or other features may indicate underlying structural pathologies (e.g., disorders of neuronal migration). These interictal EEG abnormalities may increase when ESES starts; in addition, diffuse bursts of 2–3-Hz spike-and-wave discharges may appear [11].

The typical EEG pattern consisted of continuous or sub-continuous slow spike-and-waves, at 1.5–2.5 Hz, persisting through all NREM sleep; it appears immediately after patients fall asleep. This EEG pattern is commonly observed between 4 and 14 years and develops 1 or 2 years after the onset of seizures.

The epileptic discharges can vary from mainly focal (frontal, centrottemporal, etc.) or multifocal to unilateral, or diffuse (occasionally with shifting from a unilateral to a diffuse pattern in the same patient). In the original description, a spike-wave index (SWIs), ranging from 85 to 100% and measured during overnight sleep EEG recording, was considered an essential feature for the diagnosis [92]; however, SWIs under 85% have been used for the diagnosis of ESES syndrome as well [11].

## **8.4 Etiology**

The good outcome is the rule, independent of the etiology and is observed besides cortical malformations such as multilobar polymicrogyria. ESES syndrome has been associated with a few genes including neuroserpin/SRPX2 and ataxin 1/ATX1 [23]; most recently, pathogenic de novo involves genes previously associated with autism (MDGA2 and SHANK3), seizures (GRIN2A), or language impairment (CDH13) [93]. Furthermore, SLC9A6 mutations have been found in patients with Christianson syndrome and CSWS [94]. The reason for manifestation of ESES in most patients is not known [23].

## **9. Landau-Kleffner syndrome (LKS)**

### **9.1 Overview**

The first description of the Landau and Kleffner syndrome (LKS) is due to William Landau and Frank Kleffner, who in 1957 reported six children with different types of seizures and acquired aphasia [2]. No other descriptions were made until the 1980s, when different authors described several new cases [95].

LKS is a type of ESES syndrome which manifests with an acquired epileptic aphasia (auditory agnosia) that occurs in the child with already developed age-appropriate speech. Like ESES, LKS is characterized by epileptic EEG pattern particularly prominent during sleeping, with or without manifest clinical seizures. Although in the first descriptions LKS is not related to brain organic lesions, patients with LKS may have congenital or acquired brain lesions [11].

## 9.2 Epileptic aphasia and seizure symptoms and semiology

LKS appear usually from 2 to 8 years of age; almost 60% of cases have epilepsy as the first symptom, while aphasia in the rest. Aphasia is a verbal auditory agnosia with a subacute onset, followed by rapid reduction of spontaneous speech, with perseverations, paraphasias, phonological errors, and verbal stereotypies; it can progress to mutism. Aphasia frequently has a course with remissions and exacerbations, usually related to quantitative variations of paroxysmal activity during sleeping [2, 96, 97]. The duration of the language disorder is very variable, though if it persists unchanged for more than a year, spontaneous recovery is rare. After a flexible time, aphasia stabilizes and regularly recovers before adulthood [98].

Although between 70 and 80% of patients present with epileptic seizures, these tend to be rare, sometimes a single seizure, which often occurs during sleeping. The seizures present clinical heterogeneity that includes subtle motor events such as ocular flicker, ocular deviation, simple motor focal seizures, AA, unilateral motor seizures, and, eventually, GTCS. CPSs are uncommon, while tonic seizures have never been reported. The course of the epilepsy is typically benign and seizures respond excellent to AED. Seizures eventually disappear over time, generally by about the age of 15 years [98].

## 9.3 Electroencephalography

### 9.3.1 Background

Normal.

### 9.3.2 Interictal paroxysmal abnormalities

#### 9.3.2.1 Wakefulness

High-amplitude repetitive spikes and spike-waves with variable topography over time. Unilateral discharges are more common early in the course of LKS, habitually located in the temporal regions (>50% of the children) or in the parietal-occipital regions (around 30% of the children). Generalized spike-wave discharges have also been reported.

#### 9.3.2.2 Sleep

At the beginning of sleep, epileptic discharges (ED) are also initiated. The ED can be partial, often on posterior temporal topography. Unilateral subclinical discharges can be detected alternating between both hemispheres. During the development of the disease, the EEG of the sleep will show a pattern of bilateral spike-wave activity, continuous or sub-continuous, during more than 85% of the NREM sleep time (ESES syndrome) [97]. LKS is a clinical subtype included in the wide spectrum of the clinical manifestations of ESES syndrome.

## 9.4 Etiology

In most patients the cause of LKS remains unknown. Autoimmune etiology has been suspected because of minor immunological irregularities reported in a number of patients and because of the response of LKS patients to immunotherapy [23]. Mutations in GRIN2A (16p13.2) have been reported as a major genetic cause of LKS and of the syndrome known as epileptic encephalopathy with continuous spikes and waves during slow-wave sleep (CSWS) [99]. Children with LKS have, most

of the time, a normal development until the start of language regression. Seizures of LKS often respond well to treatment with AED, but the speech and language impairments often persist, despite seizure control [100]. Occasional cases can be secondary to structural lesions such as benign temporal lobe tumors with improvement after focal resection [101].

### **9.5 Treatment of encephalopathies with CSWS, including LKS**

The aim of treatment is to stop seizures and eliminate epileptic discharges in the EEG; this will prevent and reverse cognitive decline in the idiopathic group and will prevent any further deterioration predetermined by the underlying pathology [18]. For it, early diagnosis and rapid appropriate and effective treatment are required.

Seizures in LKS are easier to control than seizures in CSWS. Many old and new AEDs are effective, depending on the seizure types. Valproate, sulthiame, benzodiazepines, ethosuximide, levetiracetam, lamotrigine, intravenous immunoglobulin (IVIG), corticosteroids, and ketogenic diet could be effective. The sodium channel-blocking AEDs are contraindicated [17]. In some cases, with severe linguistic impairment, subpial intracortical transections have been successful.

## **10. Conclusion**

Epileptic encephalopathy is defined as a condition where the epileptic activity itself may contribute to the severe neurological and cognitive impairment seen, over and above that would be expected from the underlying pathology alone. The epilepsy syndromes at high risk of this are a disparate group of conditions characterized by epileptic seizures that are difficult to treat and developmental delay. Knowledge of the various severe epilepsy syndromes is vital to understanding the rationale for treatment.

### **Conflict of interest**

The authors declare no conflicts of interest.

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