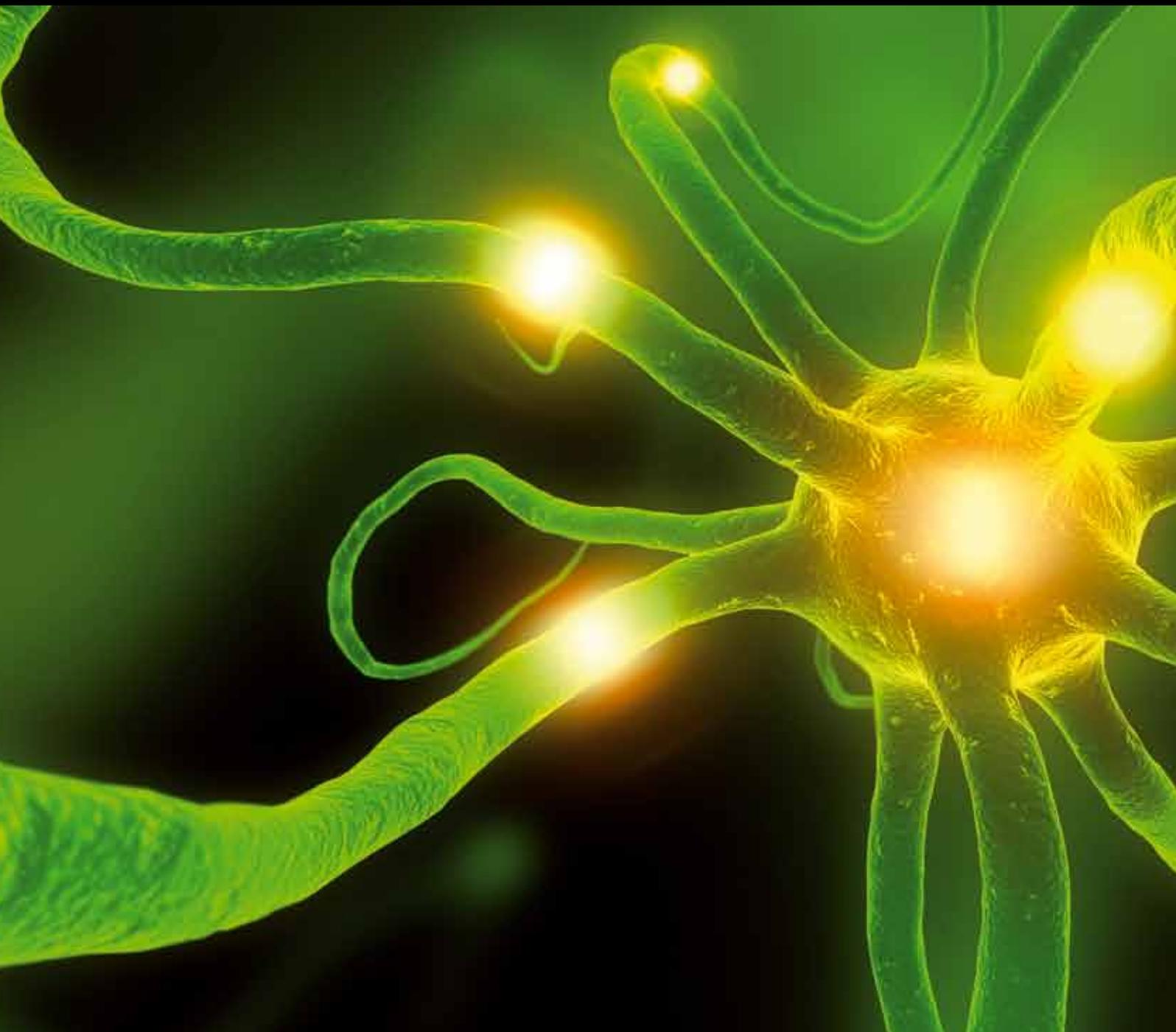


Epilepsy Research and Treatment

Epileptic Encephalopathies in Children

Guest Editors: Brahim Tabarki, Giangennaro Coppola, and Elaine Wirrell





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Editorial

Epileptic Encephalopathies in Children

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Received 25 July 2013; Accepted 25 July 2013

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Epileptic encephalopathies in children are severe disorders in which cognitive, sensory, and motor development is impaired by recurrent clinical seizures or prominent interictal epileptiform discharges. They include Ohtahara syndrome, early myoclonic epileptic encephalopathy, West syndrome, malignant migrating partial seizures in infancy, Dravet syndrome, Lennox-Gastaut syndrome, myoclonic atonic epilepsy, continuous spike wave in slow sleep, Rasmussen encephalitis, and other diseases. These epilepsies share several important characteristics: diverse causes; severe and frequent seizures; diffusely abnormal background activity on electroencephalograms that is often profound; medical intractability; and severe consequences for a normal development. Recently, several gene mutations have been found in several epileptic encephalopathies.

- (1) P. Jain and colleagues provide a summarizing article on the clinical evaluation and management of commonly encountered epileptic encephalopathies in children.
- (2) Wong-Kisiel and Nickels focus on electroencephalogram findings of childhood epileptic encephalopathy syndromes and provide sample illustrations.
- (3) J. Y. Yu and P. L. Pearl provide an overview of inborn metabolic errors associated with persistent brain disturbances due to highly active clinical or electrographic ictal activity. They also highlight the clues when to suspect a metabolic disease in a patient with epilepsy.

- (4) I. S. Fernández and colleagues review the chapter entitled Continuous Spikes and Waves during Sleep and provide detailed review about the electroclinical presentation and the management.
- (5) H. R. Kayyali et al. review the reported literature on the surgical approach to some of these epileptic encephalopathies in children.

These manuscripts represent an exciting and insightful snapshot of current knowledge of epileptic encephalopathies in children. State-of-the-art, existing challenges and emerging future topics are highlighted in this special issue.

Acknowledgment

The authors would like to thank all authors, reviewers, and guest editors for making this special issue in *Epileptic Encephalopathies in Children* possible.

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Review Article

Electroencephalogram of Age-Dependent Epileptic Encephalopathies in Infancy and Early Childhood

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Received 15 May 2013; Accepted 1 July 2013

Academic Editor: Elaine Wirrell

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Epileptic encephalopathy syndromes are disorders in which the epileptiform abnormalities are thought to contribute to a progressive cerebral dysfunction. Characteristic electroencephalogram findings have an important diagnostic value in classification of epileptic encephalopathy syndromes. In this paper, we focus on electroencephalogram findings of childhood epileptic encephalopathy syndromes and provide sample illustrations.

1. Introduction

Epilepsy electroclinical syndromes have characteristic seizure semiology, frequency, duration, inciting factors, and age of seizure onset and are often associated with specific electroencephalogram (EEG) findings. Epileptic encephalopathies are syndromes in which the epileptiform abnormalities are thought to contribute to a progressive cerebral dysfunction. The ictal and interictal EEG patterns can help define the electroclinical syndromes, identify potential etiologies, and guide treatment. A detailed description of each genetic etiology is beyond the scope of this review. This review focuses on the neurophysiological features, including variant patterns relevant to selected etiologies (Table 1).

2. Neonatal/Infantile Onset Epilepsy Syndromes

2.1. Early Infantile Epileptic Encephalopathy

2.1.1. Clinical Presentation. Ohtahara first recognized early infantile epileptic encephalopathy (EIEE) in neonates who suffered frequent tonic seizures and subsequently developed significant intellectual disability [1]. Later studies of infants with EIEE show average seizure onset within 2-3 months after birth. Brief tonic seizures occur hundreds of times per day,

often in clusters of 10 to 40 seizures. Focal seizures present as tonic eye deviation or unilateral clonic contractions. Myoclonic seizures are not a prominent feature [2].

2.1.2. Long-Term Prognosis. Mortality in EIEE is high during childhood, with 50% dying during the first 2 years of life [2]. Survivors into childhood have pharmacoresistant epilepsy with severe intellectual disability. EIEE evolves to West syndrome during infancy in 75%, Lennox-Gastaut syndrome in older children, or focal epilepsy [3].

2.1.3. Etiologies. Cerebral structural abnormality is the most common etiology of EIEE. However, in 13–38% of patients, STXBPI mutation results in synaptic vesicle protein with impaired neurotransmitter release [4–6]. Children with STXBPI mutation develop a paroxysmal movement disorder during infancy, which persists beyond the intractable phase of the epilepsy [6].

2.1.4. Interictal EEG. Suppression burst pattern is a distinct EEG feature during the early phase of EIEE. This EEG pattern is characterized by a suppression phase less than 10 μ V lasting from 3 to 5 seconds with paroxysms of high-voltage 150–350 μ V delta-theta bursts of spikes, polyspikes, and sharp waves that alternate at regular intervals [1]. The suppression

TABLE 1: Summary of clinical characteristics and EEG features at presentation in early and childhood onset epileptic encephalopathy.

Epilepsy syndrome	Clinical features				EEG features at presentation		
	Age of seizure onset	Seizure types	Underlying etiology	Prognosis	Background	Interictal	Ictal
Early infantile epileptic encephalopathy (ohtahara syndrome)	First 2 weeks of life	Tonic seizures	Cerebral structural abnormality, genetic abnormalities (i.e., <i>STXBPI</i>)	25% die by 2 years or evolves to West syndrome and profound disability	Suppression burst pattern in awake and sleep	High voltage (150–350 uV) paroxysm	Generalized paroxysms or focal discharges
Early myoclonic encephalopathy	First weeks of life	Myoclonic seizures (erratic/fragmentary/generalized); focal seizures	Metabolic genetic etiologies (nonketotic hyperglycinemia, pyridoxine/pyridoxal-5-phosphate dependency, molybdenum cofactor deficiency, organic aciduria, amino-acidopathies)	50% die within first year or profound disability	Suppression burst pattern, enhanced by sleep	High voltage (150–350 uV) paroxysm	Generalized paroxysms or focal discharges
Migrating focal seizures in infancy	3 months	Focal motor seizures with autonomic manifestations	Unknown; SCN1A, PLCB1, KCNT1 mutations; 2q24, 16p11.2 copy number variants	High mortality before 1 year or profound disability (cortical visual impairment; acquired microcephaly)	Hemispheric background slowing	Multifocal discharges, maximal in temporal and rolandic regions	Rhythmic, monomorphic alpha or theta discharges in noncontiguous brain regions
West syndrome	3–8 months	Epileptic spasms	Heterogenous (congenital cortical malformations, tuberous sclerosis, trisomy 21, trisomy 18, CDKL5, ARX, MECP2)	Depends on etiology; other seizure types evolve by about 5 years	Poorly organized, high amplitude (500–1000 mV), generalized slowing	Multifocal epileptiform discharges with generalized electrodecrement	Generalized sharp wave followed by electrodecrement
Dravet syndrome	6 months	Febrile status epilepticus, alternating hemic convulsions → absence, and myoclonic seizures	80% SCN1A mutation	Mortality in childhood 10%, intellectual disability, or crouched gait without spasticity in adults	Normal, generalized or focal slowing	Generalized, multifocal or focal discharges; photoparoxysmal response	Generalized paroxysms or focal discharges
ESES-related syndromes	5–8 years	Focal seizures	CSWS structural; LKS unknown	Relapsing-remitting course or age limiting by teenage years	Normal or focal slowing	Focal/multifocal/generalized discharges; marked sleep activation with increased interictal spatial distribution or bilateral synchrony; sleep spike wave index >85%; CSWS-frontal predominant LKS-temporal predominant	Focal discharges

TABLE 1: Continued.

Epilepsy syndrome	Clinical features			EEG features at presentation			
	Age of seizure onset	Seizure types	Underlying etiology	Prognosis	Background	Interictal	Ictal
Lennox-Gastaut syndrome	1–8 years	Multiple (tonic, atonic, absences, myoclonic, or focal)	Heterogenous	Intellectual disability	Normal or generalized slowing	Frequent slow spike waves 1.5–2.5 Hz or multifocal	Absence-low spike and waves; tonic-generalized attenuation with recruiting rhythm; atonic-generalized polyspike/spike waves, or attenuation; myoclonic-generalized polyspike/spike waves
Myoclonic-atonic epilepsy	7 months–6 years	Multiple (atonic, myoclonic, absences, or rarely tonic)	No consistent etiology	50% normal cognition at last followup	Normal or mild diffuse/focal slowing	Generalized polyspike-and-wave discharges; photoparoxysmal response	Generalized spike or polyspike-and-wave
Progressive myoclonic epilepsies	Varies by etiology	Prominent myoclonic seizures	Inborn errors of metabolism and mitochondrial disorders (Tay-Sachs, Alpers syndrome, Lafora disease, Unverricht-Lundborg disease, or neuronal ceroid lipofuscinosis)	Developmental regression/dementia; mortality depends on etiology	Generalized slowing	Generalized/multifocal discharges; photoparoxysmal response in Unverricht-Lundborg and neuronal ceroid lipofuscinosis	Generalized discharges

ES: electrical status epilepticus in slow wave sleep; CSWS: continuous spike wave in sleep; LKS: Landau-Kleffner syndrome.

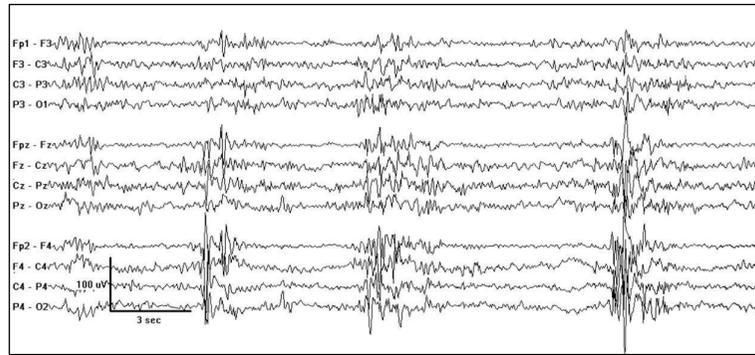


FIGURE 1: Increased burst amplitude over the right hemisphere in an one-month-old girl with right frontal cortical dysplasia.

burst pattern continues during both awake and sleep states. This pattern does not imply specific etiology and can also be seen due to hypoxic ischemic encephalopathy, metabolic derangement, medication effects, and hypothermia.

For those who survive, EEG wake-sleep differentiation occurs from 40 days to 5 months, with more apparent suppression burst in sleep [7]. During wakefulness, suppression burst pattern evolves into hypersarrhythmia pattern, diffuse slowing, multifocal abnormalities, or pseudoperiodic pattern with improved background organization [8]. Asynchronous attenuations present during wakefulness become more synchronized during sleep. Focal slowing, interictal focal spikes, and increased amplitude bursts may lateralize over the side of the structural abnormality (Figure 1). By one year of life, the EEG shows generalized background slowing and generalized or focal paroxysmal fast activity.

2.1.5. Ictal EEG. The burst activities of the suppression burst pattern coincide with tonic seizures [7]. Focal seizures may start as focal rhythmic spike and wave activity followed by tonic seizures. Ictal discharges for focal seizures show no particular localization and any focus can be involved.

2.1.6. EEG Variants. Compared to other etiologies, EEGs of affected patients with STXBPI mutation have longer periods of suppression and bursts [6].

2.2. Early Myoclonic Encephalopathy

2.2.1. Clinical Presentation. Neonates with early myoclonic encephalopathy (EME) have no apparent perinatal complications or insults and present shortly after birth with progressive decreased alertness and hypotonia. Myoclonic seizures are the initial semiology, followed by focal seizures or epileptic spasms. Myoclonic seizures may begin as fragmentary or focal erratic myoclonus involving regions of the face and limbs, at times nearly continuously, and then become more generalized with time. Focal seizures may manifest as gaze deviation or autonomic disturbances. Between 3 and 4 months of age, seizures evolve into epileptic spasms [9].

2.2.2. Long-Term Prognosis. The long-term prognosis of EME is poor. Approximately 50% of infants die in the first year [1]. Those who survive have profound intellectual disability.

2.2.3. Etiologies. Unlike EIEE, metabolic and genetic etiologies are more common than structural abnormalities. EME has classically been associated with nonketotic hyperglycemia. However, the etiology is unknown in up to 50% and investigations for pyridoxine or pyridoxal-5-phosphate dependency, molybdenum cofactor deficiency, organic aciduria, and amino acidopathies should also be completed [10, 11].

2.2.4. Interictal EEG. The interictal EEG shows the characteristic suppression burst background initially (Figure 2). In contrast with EIEE, the suppression burst pattern in EME is enhanced by sleep with shorter burst duration. The EEG evolves to atypical hypersarrhythmia or multifocal epileptiform discharges with profound slowing of the background EEG activity at age from 3 to 5 months. Hypersarrhythmia pattern may persist for months before a return to burst suppression pattern [12].

2.2.5. Ictal EEG. The ictal EEG often shows no correlation with the presenting erratic myoclonia [12] (Figure 3). When focal seizures or epileptic spasms occur, the EEG correlate is not different from focal neonatal seizures seen in nonsyndromic cases.

2.3. Migrating Focal Seizures in Infancy

2.3.1. Clinical Presentation. Migrating focal seizures in infancy is also known as malignant migrating partial epilepsy of infancy, first described by Coppola in 1995 [13]. The mean age of seizure onset is 3 months but can occur as early as the neonatal period [14]. Infants have normal development before seizure onset. At presentation, there are sporadic focal motor seizures with rapid evolution to bilateral convulsive seizures. Autonomic manifestations such as apnea, flushing, or cyanosis often occur. The seizures increase in frequency and become nearly continuous multifocal or bihemispheric seizures. Ictal semiology reflects the affected cortical regions. Epilepsy becomes intractable. Profound psychomotor developmental delay ensues. Seizures of multifocal onset may evolve into epileptic spasms, with or without interictal hypersarrhythmic pattern [13, 15–17].

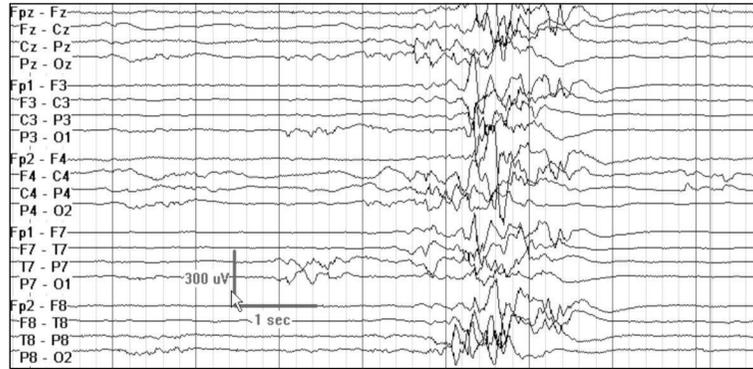


FIGURE 2: Generalized suppression burst pattern in a newborn with early myoclonic encephalopathy.

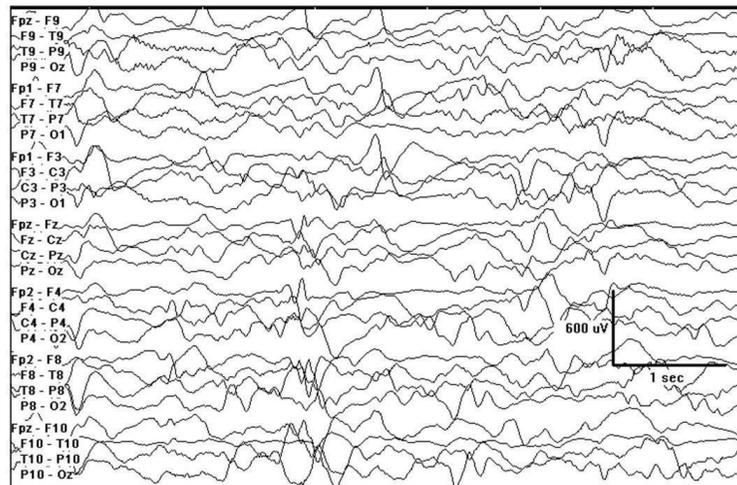


FIGURE 3: High amplitude poorly organized slow background with multifocal epileptiform discharges and intermittent generalized electrodecrement, consistent with hypsarrhythmia at age 4 months in a child with early myoclonic encephalopathy due to nonketotic hyperglycinemia.

2.3.2. Long-Term Prognosis. Although better seizure control may be accomplished between 12 and 14 months, neurologic regression and stagnation continue. Children develop cortical visual impairment. Acquired microcephaly or evidence of brain atrophy is seen during followup. There is high mortality before 1 year of age. Illnesses easily trigger clusters of seizures or occasional status epilepticus.

2.3.3. Etiologies. The etiology is heterogeneous and often is unknown. Genetic etiologies include SCN1A mutations, duplication of 16p11.2, homozygous deletion of the PLCB1 gene, and KCNT1 de novo gain-of-function mutation. Deletion in 2q24 was reported in a single patient [18–22].

2.3.4. Interictal EEG. The EEG at seizure onset shows increased background slowing for several months. The background slow waves shift from one hemisphere to the other. Shortly after initial seizures, multifocal discharges emerge and are present during wakefulness and sleep [23]. Epileptiform discharges are most prominent in the temporal and rolandic areas. As seizure frequency subsides after age one year, the EEG shows a low voltage “burnt out” slowing [24].

2.3.5. Ictal EEG. Ictal onset shifts in consecutive seizures from one lobe to another and from one hemisphere to another (Figure 4). Although the involved ictal regions vary, the ictal pattern is very similar. Ictal EEG shows rhythmic, monomorphic alpha or theta frequency discharges in a localized cortical area, then expand to contiguous regions, or may develop independently in different areas [13]. Tandem seizures in different noncontiguous brain regions may occur, with one seizure beginning before the waning of the other. Ictal and interictal EEGs almost overlap. The original ictal EEG discharges may persist or fade and be replaced by new patterns, thus producing a very complex multifocal status epilepticus.

2.4. West Syndrome

2.4.1. Clinical Presentation. West syndrome refers to the triad of epileptic spasms, intellectual disability, and EEG hypsarrhythmia. Spasm onset is between 3 and 8 months, characterized by brief truncal and neck flexion coinciding with bilateral arm abduction, typically occurring in clusters. Developmental regression occurs.

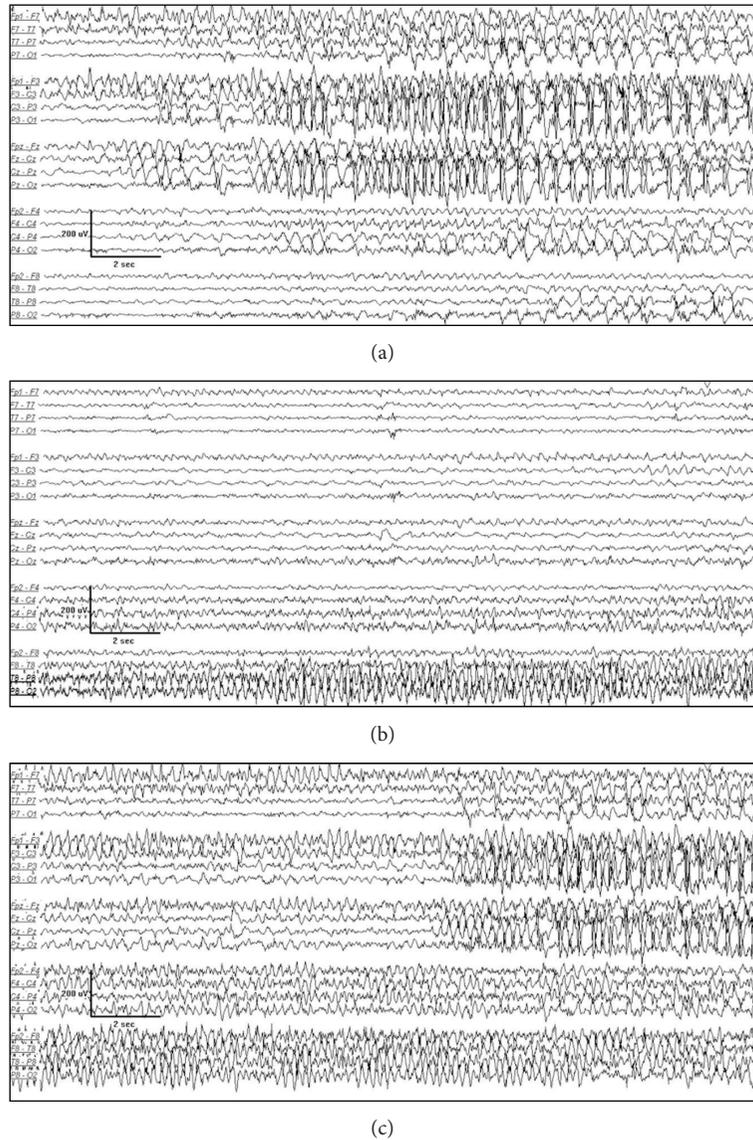


FIGURE 4: 3-month-old female with migrating focal seizures in infancy. (a) Left central onset seizure, (b) right temporal onset seizure 2 minutes later, and (c) independent left central onset seizure with ongoing right temporal lobe seizure 15 minutes later.

2.4.2. Long-Term Prognosis. The long-term prognosis of West syndrome is poor, especially if not treated early. Epileptic spasms typically resolve by age 5 years. Other seizure types often emerge and children may develop Lennox-Gastaut syndrome. Learning disorders, intellectual disability, and autistic features are common. Although an etiology is found in the majority of children with epileptic spasms, those of unknown etiology can have a more favorable prognosis if early effective treatment is provided [25].

2.4.3. Etiologies. Epileptic spasm etiologies are heterogeneous and include structural, metabolic, and genetic causes. Classically, tuberous sclerosis complex (TSC) has been associated with epileptic spasms and must be excluded at initial evaluation. Asymmetric spasms characterized by unilateral head turn, asymmetric upper extremity flexion or extension,

or automatisms suggest lateralized structural abnormality. Congenital central nervous system malformation or TSC accounts for more than half of the cases of epileptic spasms, followed by 15% due to chromosomal abnormalities including trisomy 21 and trisomy 18. Monogenic etiologies including X-linked CDKL5, ARX, and MECP2 are increasingly recognized, particularly in children with seizure onset less than 3 months of age and atypical Rett-like features [25]. Hypermotor-tonic-spasm sequence is not diagnostic for a specific etiology but should raise a suspicion for CDKL5 mutation [26].

2.4.4. Interictal EEG. The classic hypsarrhythmia is an interictal EEG pattern of a poorly organized, high amplitude (500–1000 μ V), slow background with accompanying multifocal epileptiform discharges, and generalized electrodecrement

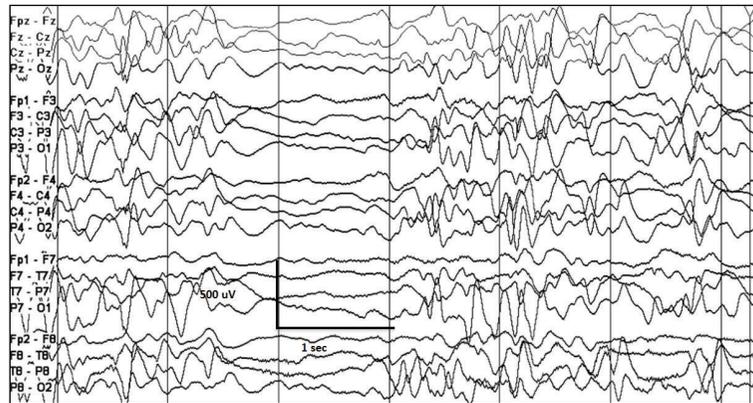


FIGURE 5: Interictal EEG recording of typical hypsarrhythmia in a two-year-old girl with West syndrome due to genetic mutation.

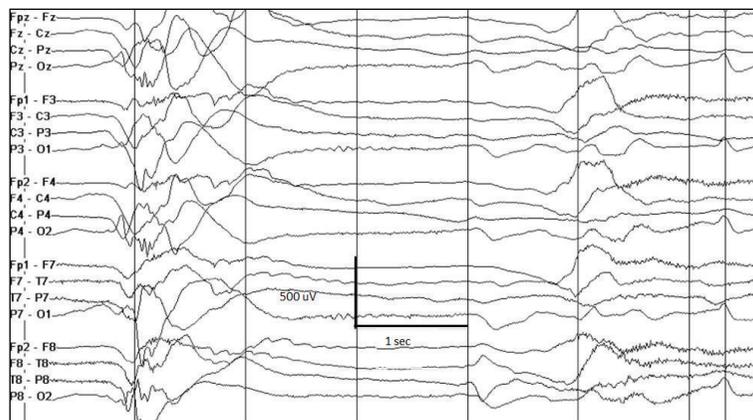


FIGURE 6: Ictal EEG recording of epileptic spasms in a two-year-old girl with West syndrome due to genetic mutation.

(Figure 5). There may be generalized discharges on the interictal recording, but repetitive trains of generalized discharges are uncommon. Lack of hypsarrhythmia in the routine outpatient EEG does not exclude the diagnosis of epileptic spasms. The characteristic EEG features may be present only during non-REM sleep, particularly early in the course of the epilepsy. Prolonged video EEG with recorded spasms and a sleep recording remains an essential diagnostic tool.

2.4.5. Ictal EEG. The EEG during the epileptic spasms typically demonstrates a high amplitude generalized sharp wave followed by generalized electrodecrement (Figure 6). The electrodecrement differentiates short spasms from myoclonic seizures.

2.4.6. EEG Variants. Variant patterns of classic hypsarrhythmia, including more organized or synchronous background, voltage lower than $500 \mu\text{V}$, and persistently focal features or asymmetries are often referred to as “modified hypsarrhythmia” but may occur in up to 1/3 of epileptic spasms [27, 28]. In partially treated spasms, especially in older children, the background may be more organized, synchronous, and of

lower voltage (Figures 7 and 8). Persistent asymmetry of the ictal or interictal EEG suggests a focal lesion (Figure 9). However, the EEG and semiology may lack lateralizing or localizing features, despite focal structural etiology. Therefore, all children with intractable epileptic spasms due to structural etiology should be evaluated for possible resective surgery, regardless of the presence or absence of localizing EEG features [29, 30].

The EEG in children with CDKL5 initially demonstrates multifocal epileptiform discharges with gradual evolution to hypsarrhythmia or modified hypsarrhythmia, which persists well into early childhood. The prolonged duration of hypsarrhythmia is not typically seen in other causes of West syndrome [6, 31, 32].

The presence of prehypersarrhythmia patterns remains controversial. Retrospective analysis of serial EEGs prior to onset of hypsarrhythmia has demonstrated gradual evolution of multifocal potentially epileptogenic discharges with nearly normal background to frequent bihemispheric discharges with abnormal background [33]. Children who demonstrate worsening EEG background and an increase in bihemispheric epileptiform discharges should be considered at risk for developing epileptic spasms.

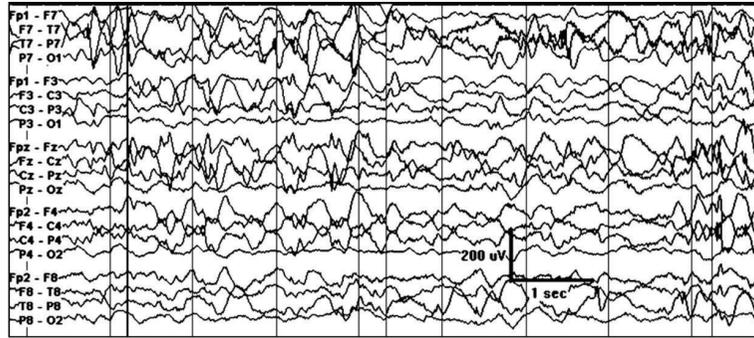


FIGURE 7: Interictal EEG recording of modified hypsarrhythmia in an 8-month-old child with partially treated epileptic spasms; note the lower amplitude of the background.

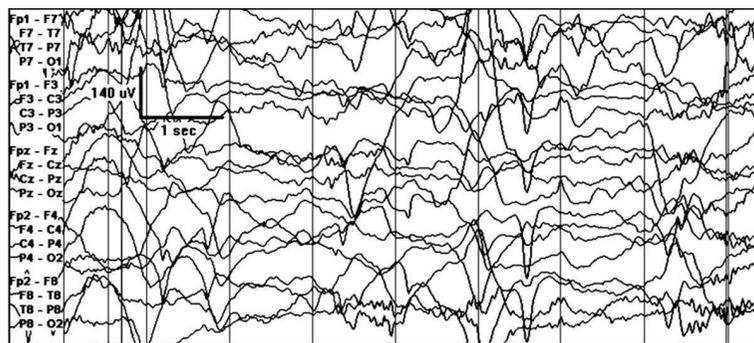
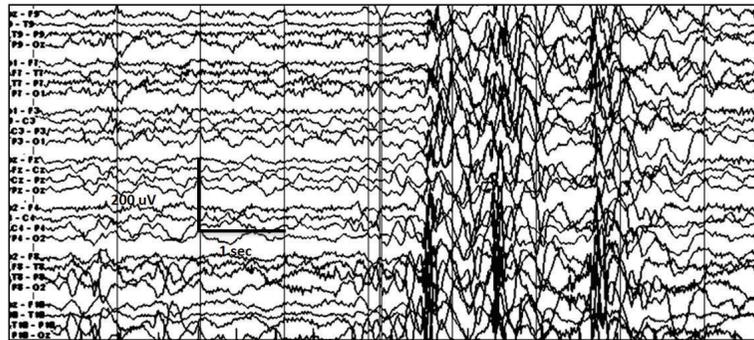
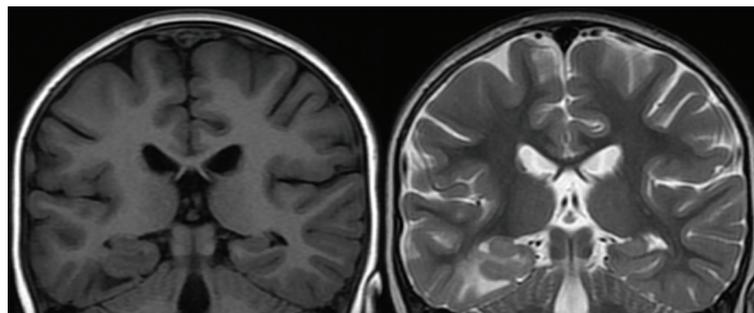


FIGURE 8: Ictal EEG recording of epileptic spasms with modified hypsarrhythmia.



(a) Interictal EEG



(b) MRI of right temporal lesion

FIGURE 9: Asymmetric spasm: (a) interictal EEG showing synchronous generalized discharges consistently having maximal amplitude on the right, which corresponds to (b) right temporal focal lesion (WHO 1 ganglioglioma).

2.5. Dravet Syndrome

2.5.1. Clinical Presentation. Dravet syndrome is also known as severe myoclonic epilepsy of infancy. Febrile status epilepticus manifests in previously normal infants prior to age 1 year either as generalized tonic-clonic seizures or a hemicconvulsion involving alternating sides. Afebrile seizures of multiple types then follow and are medically refractory. Head sensitivity, both to fever and ambient temperature, is a hallmark. Antiepileptic medications such as carbamazepine, oxcarbazepine, and phenytoin exacerbate seizures. Development stagnates and may regress. Intellectual disability, impulsivity, and ataxia emerges [34].

2.5.2. Long-Term Prognosis. The prognosis for Dravet syndrome is typically poor although there is phenotypic variability. Frequent intractable seizures and recurrent refractory status epilepticus occur throughout childhood. Seizures often improve in adulthood, but nocturnal convulsive seizures continue [35]. Mortality is reported in up to 10%, and death often occurs due to seizure-related complications [36, 37].

2.5.3. Etiologies. SCN1A mutations are found in 80% of patients with Dravet syndrome although mutations in SCN1B, SCN2A, and GABRG2 have also been reported. A minority of children with clinically diagnosed Dravet syndrome have no mutation found.

2.5.4. Interictal EEG. The EEG findings in Dravet syndrome evolve with age. During the first year of life, the background EEG may be normal or show nonspecific slowing. Generalized or focal slowing may be present if the EEG is done after a prolonged seizure. The interictal epileptiform abnormalities increase between the second and fifth years of life and are typically generalized spike and polyspike and wave discharges. Multifocal or focal abnormalities are also present in the frontocentral or centrottemporal and vertex regions and likely represent fragments of diffuse discharges [38]. Photosensitivity and/or pattern sensitivity may be present in up to 40% of patients [34, 38]. In approximately 19–25% of children, generalized paroxysms and photosensitivity may decrease or disappear with age [39]. Focal and multifocal abnormalities may appear only during sleep [38].

2.5.5. Ictal EEG. The ictal EEG findings depend on the seizure type. Pseudorhythmic spike and wave discharges with periodic attenuations can be present in hemicconvulsion or focal seizures with evolution to bilateral convulsive seizures [38]. Atypical absence seizures are seen within the first year after seizure onset and may be associated with eyelid myoclonus and generalized myoclonus. The EEG shows 2–4 Hz generalized spike wave discharges [40]. Myoclonic seizures can occur in clusters associated with generalized 3 Hz or faster spike wave with frontocentral predominance. Erratic, or segmental, myoclonia involving distal extremities and areas of the face, which are more palpable than visible, are epileptic seizures even though there is no EEG correlation [34]. Tonic seizures are rare in Dravet syndrome. The ictal

EEGs in tonic seizures show a generalized fast rhythm lasting from 2 to 3 seconds.

3. Childhood Onset Epilepsy Syndromes

3.1. Electrical Status Epilepticus in Slow Wave Sleep Syndromes

3.1.1. Clinical Presentation. Continuous spike wave in sleep syndrome (CSWS) and Landau Kleffner syndrome (LKS) both present in school-aged children with developmental and behavioral regression. Regression in CSWS is more global with significant executive dysfunction. A history of brain insult or abnormal development can be present before seizure onset and regression. Children with LKS are developmentally normal and then experience a regression in receptive language called acquired auditory agnosia.

3.1.2. Long-Term Prognosis. With treatment, development and seizures improve although clinical and EEG relapses are common. As the child approaches adolescence, the seizures and EEG abnormalities in both CSWS and LKS spontaneously resolve. However, development does not normalize.

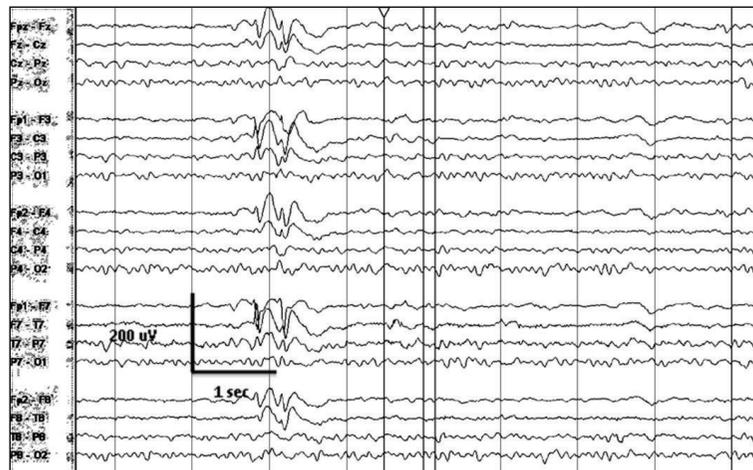
3.1.3. Etiologies. Children with LKS have normal neuroimaging and normal development prior to onset of symptoms. There is no known cause of LKS. In contrast, children with CSWS are often found to have genetic, metabolic, or structural etiologies [41].

3.1.4. Interictal EEG. Both syndromes are associated with electrical status epilepticus in slow wave sleep (ESES) defined by nearly continuous epileptiform discharges during slow wave sleep. This EEG pattern must be present to make the diagnosis.

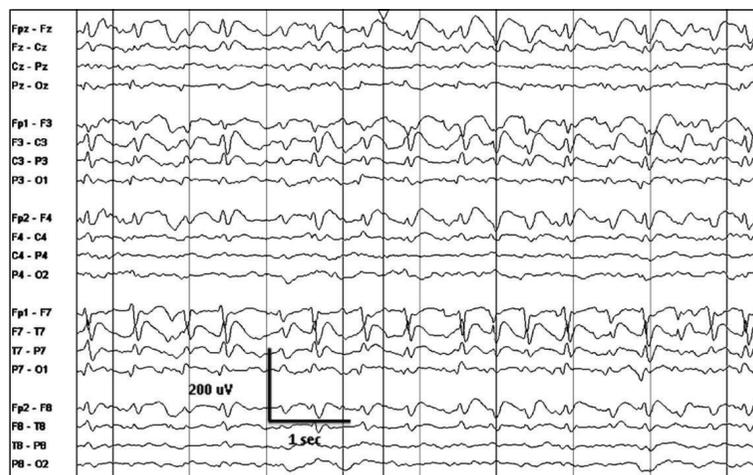
The EEG in CSWS demonstrates focal or diffuse slowing of the background with or without interictal discharges during wakefulness. Epileptiform discharges are focal, multifocal, or generalized. The epileptiform discharges in CSWS are often maximally present over the frontal regions, which may correlate with the observed executive dysfunction of these patients. There is significant activation if spike wave discharges during sleep, typically maximal over the frontal and frontocentral head regions. Furthermore, focal and multifocal discharges often have a broad distribution during sleep (Figure 10).

The EEG in LKS during wakefulness may be normal or may demonstrate focal epileptiform discharges that are maximal over the frontotemporal or temporal regions. Like the children with CSWS, there may be focal or generalized slowing of the background activity. The EEG during sleep demonstrates nearly continuous spike wave discharges that are often maximal over the temporal regions (Figure 11) [41].

3.1.5. Ictal EEG. Children with CSWS and LKS may or may not have seizures, making these unique epilepsy syndromes. The ictal EEG is similar to other focal seizures and is not diagnostic.



(a) Awake EEG in CSWS



(b) Sleep EEG in CSWS

FIGURE 10: EEG in a patient with CSWS and history of left neonatal intraventricular hemorrhage: (a) awake interictal EEG in CSWS demonstrating generalized epileptiform discharges, maximal left, and (b) asleep interictal EEG demonstrating continuous epileptiform discharges maximally present over the frontocentral head regions, maximal left.

3.2. Lennox-Gastaut Syndrome

3.2.1. Clinical Presentation. Lennox-Gastaut syndrome (LGS) manifests in children from 1 to 8 years of age. The most common seizures are tonic, atonic, and absence seizures. All seizure types may not be present simultaneously or at onset. The presence of other seizure types such as myoclonic seizures, unilateral clonic seizures, or focal seizures with or without evolution to bilateral convulsive seizures does not exclude LGS [42]. LGS can evolve from epileptic spasms. Developmental delay is present in 20–60% of patients at onset and increases to 75–95% after 5 years [43].

3.2.2. Long-Term Prognosis. The long-term prognosis for Lennox-Gastaut syndrome is poor. Refractory seizures may improve with time but do not resolve. Recurrent status epilepticus also continues. Intellectual disability continues throughout life. Those with early onset epilepsy, especially

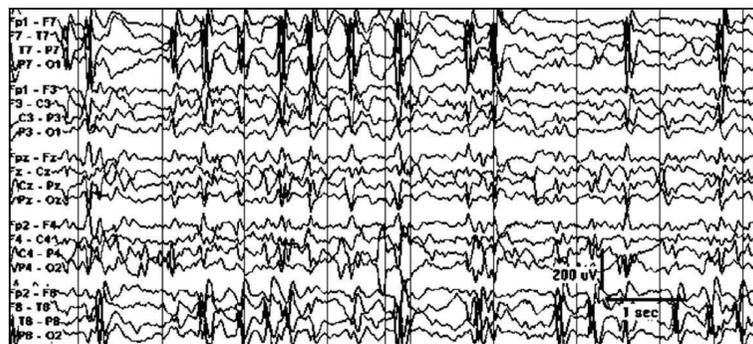
those with a prior history of West syndrome, have the worst prognosis [44].

3.2.3. Etiologies. Etiologies for LGS are heterogeneous. Up to 1/3 of children have no known cause of their epilepsy. Structural lesions are a common cause of LGS and may be due to congenital malformation so of cortical development, hypoxic-ischemic encephalopathy or other cerebrovascular events, and tuberous sclerosis complex. Genetic and metabolic disorders are also associated with LGS, but less frequently [44].

3.2.4. Interictal EEG. At seizure onset, the interictal EEG may demonstrate a slow and poorly organized background during wakefulness with normal EEG during sleep. The degree of slowing tends to correlate with severity of intellectual impairment. Diffuse slow spike wave discharges then occur in repetitive sequences but can be irregular infrequency,



(a) Awake interictal EEG in LKS



(b) Asleep interictal EEG in LKS

FIGURE 11: EEG in a nine-year old with LKS: (a) awake interictal EEG demonstrating infrequent potentially epileptiform discharges over the right temporal region and (b) asleep interictal EEG demonstrating nearly continuous discharges maximally present over the bilateral temporal regions.

amplitude, morphology, and distribution. Slow spike wave discharges (SSW) consist of a spike (<70 ms) or a sharp wave (70–200 ms), followed by a positive deflection and a sinusoidal negative slow wave of 300–500 ms (Figure 12) [44]. SSWs repeat between 1 and 4 Hz, but typically at 1.5–2.5 Hz [45]. SSWs are abundant and at times prolonged without apparent clinical changes. Hyperventilation and photic stimulation do not generally increase SSW. Focal and multifocal epileptiform discharges are seen in 14–18% of patients [44].

In adulthood, the awake EEG may be normal or show generalized slowing. Generalized fast activity persists in sleep, but the SSW are present only in a minority of adults with LGS [46]. Many EEGs evolve to show independent multifocal spike wave discharges [47].

3.2.5. Ictal EEG. The ictal EEG pattern depends on the recorded seizure type. Bursts of nearly continuous SSW may be associated with decreased responsiveness, representing atypical absence seizures. The ictal EEG shows high amplitude 1.5–2.5 Hz and is difficult to distinguish from the interictal pattern. Tonic seizures are associated with generalized voltage attenuation (electrodecremental pattern) or bursts of low-amplitude fast (15–25 Hz) activity with increasing amplitude 50–100 μ V (“recruiting” rhythm), followed by generalized delta slowing for several seconds before returning to baseline (Figure 13). Atonic seizures can be characterized

by generalized spike-wave activity, generalized polyspike-and-wave activity, generalized voltage attenuation, or runs of low- or high- voltage fast activity (Figure 14). Myoclonic seizures may show generalized spike or polyspike and wave discharge corresponding to the myoclonic jerk. In adulthood, the tonic seizures and accompanying diffuse fast rhythms continue during sleep [48].

Status epilepticus occurs in more than 2/3 of all patients with LGS. Tonic status and atypical absence status are the most common. The EEG during status epilepticus may be difficult to appreciate from the abnormal interictal pattern of abundant SSW. Ictal spike wave discharges are more persistent and the EEG becomes more desynchronous and absence of posterior background activity [42].

3.3. Myoclonic-Atonic Epilepsy

3.3.1. Clinical Presentation. Myoclonic-atic epilepsy (MAE) is also known as myoclonic-astatic epilepsy, or Doose syndrome. Seizure onset is between 7 months and 6 years in previously normally developing children. It is more common in males by twofold, except in the first year of life during which the ratio is similar. Myoclonic-atic seizures are characterized by initial vocalization or grunt, caused by quick contracture of the diaphragm, followed by atonic head or body drop. The presence of the myoclonic-atic sequence accounts for 10% of children with MAE; 50% have isolated



FIGURE 12: Slow spike and wave discharges in a four-year-old child with Lennox-Gastaut syndrome. Note the high amplitude of the generalized, anteriorly predominant, slow spike and wave discharges.

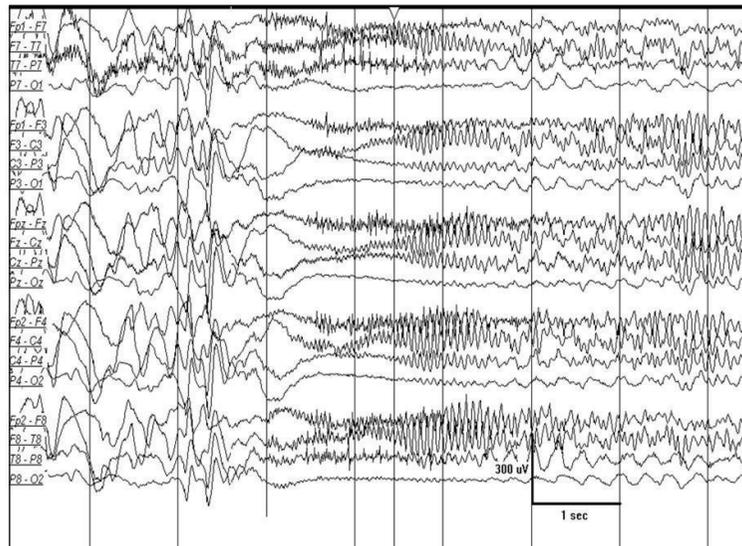


FIGURE 13: A 17-year-old man with history of autism spectrum disorder with a tonic seizure. Generalized voltage attenuation (electrodecremental pattern), bursts of low amplitude fast activity (15–25 Hz) with increasing amplitude from 50 to 100 μV with a "recruiting" rhythm.

myoclonic seizures and 30% have isolated atonic seizures [49]. Other seizure types present include absence seizures, clonic seizures, and generalized tonic-clonic seizures. Tonic seizures are only rarely present. Status epilepticus of absence seizures and myoclonic-atonic seizures is common.

3.3.2. Long-Term Prognosis. The prognosis of MAE is variable. If effective treatment is found early, some children can become seizure-free and have a good cognitive outcome. Although prognosis cannot be predicted at initial presentation, those children with status epilepticus and cognitive decline have a poorer outcome. EEG features that suggest less favorable outcome include persistence of abnormal background slowing and failure of alpha rhythm to develop.

3.3.3. Etiologies. There is no known cause of MAE identified although there may be a possible genetic link to the generalized epilepsy with febrile seizures plus (GEFS+) family [50].

3.3.4. Interictal EEG. The EEG is initially normal. Diffuse or focal theta activities have been described. Brief bursts of generalized polyspike and wave epileptiform activity at 2–5 Hz are noted. Occipital 4 Hz activity may also be seen and can be attenuated by eye opening [50]. Photoparoxysmal responses are associated with 3–7 Hz generalized spike and wave complexes.

3.3.5. Ictal EEG. All ictal EEGs demonstrate generalized spike or polyspike and wave complexes. Persistent focal EEG

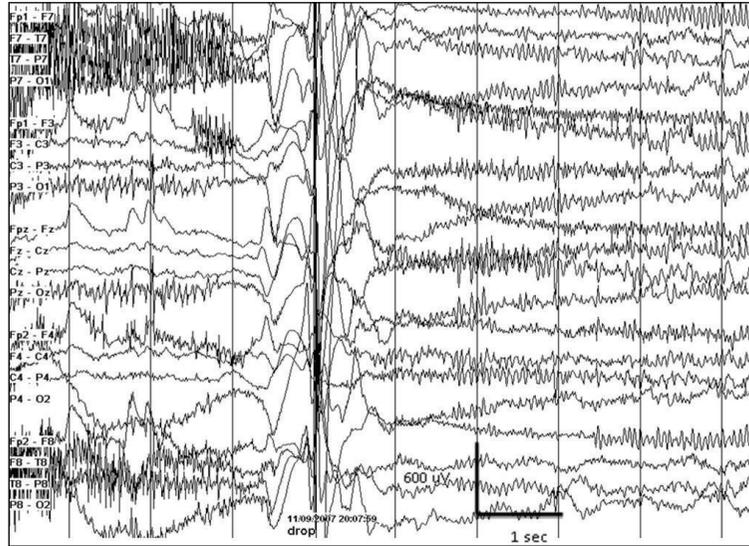


FIGURE 14: A 7-year-old girl with Lennox-Gastaut syndrome. Atonic seizure associated with generalized polyspike-and-wave, generalized voltage attenuation, and runs of low voltage fast activity.

findings are not typically seen in MAE although apparent focal abnormalities or shifting laterality may be present and are likely fragments of generalized discharges [50].

4. Epilepsy Syndromes with Variable Age of Onset

4.1. Progressive Myoclonic Epilepsies. Progressive myoclonic epilepsies are rare disorders caused by metabolic, genetic, and neurodegenerative diseases. Children can present at all ages with multiple seizure types, worsening myoclonus, and developmental regression. Long-term prognosis and mortality depend on the specific etiology. The interictal EEG in the progressive myoclonic epilepsies demonstrates generalized slowing of the background with frequent generalized and multifocal epileptiform discharges. The myoclonus is associated with a generalized spike and wave discharge on EEG. Photosensitivity is common and can increase interictal and ictal discharges. These patterns are neither specific nor sensitive for determining specific etiology [51] although there are some clinical and neurophysiologic findings that can be helpful in determining etiology.

4.1.1. Tay-Sachs. Tay-Sachs is due to hexosaminidase a deficiency and typically presents during infancy with exaggerated startle reflex to sound a developmental regression. The EEG can demonstrate fast spikes over the central head region [52].

4.1.2. Myoclonic Epilepsy with Ragged Red Fibers. Mitochondrial disorders result in metabolic energy failure. The cerebral involvement manifests as seizures. Myoclonic epilepsy with ragged red fibers is an example of a mitochondrial disease that presents with multiple neurologic signs in addition to myoclonic epilepsy, including deafness, myopathy, optic atrophy, and cerebellar ataxia. The EEG is nonspecific,

demonstrating slowing of the background with generalized and focal epileptiform discharges [51].

4.1.3. POLG1 Mutation. Mutation in the nuclear encoded mitochondrial POLG1 gene may manifest as Alpers disease or as ataxia syndromes such as myoclonus, epilepsy, myopathy, sensory ataxia (MEMSA) syndromes in older individuals. Alpers disease causes recurrent prolonged status epilepticus, hepatic failure, and cognitive decline. The EEG in Alpers disease demonstrates a slow or absent posterior dominant rhythm with multifocal and generalized epileptiform activity [53] (Figure 15). Status epilepticus is common and may have an EEG correlation of high amplitude delta activity that is maximal over the posterior head regions with superimposed epileptiform activity [54].

4.1.4. Lafora Disease. During adolescence, Lafora disease causes recurrent seizures and cognitive regression. Early in the course of Lafora disease, the generalized epileptiform discharges occur at a frequency of approximately 3 Hz. As the disease progresses, there is slowing of the background and the frequency of the discharges increases from 3 Hz up to 6–12 Hz [51].

4.1.5. Unverricht-Lundborg Disease. Similar to Lafora disease, Unverricht-Lundborg disease is also associated with adolescent onset epilepsy with cognitive regression. The EEG in Unverricht-Lundborg disease is nonspecific during wakefulness, showing the expected generalized slowing, epileptiform discharges, and photoparoxysmal response. However, the sleep EEG patterns remain essentially normal, which is not a typical finding in other progressive myoclonic epilepsies [51].

4.1.6. Neuronal Ceroid Lipofuscinosis. Neuronal ceroid lipofuscinosis (NCL) also presents in adolescence with refractory

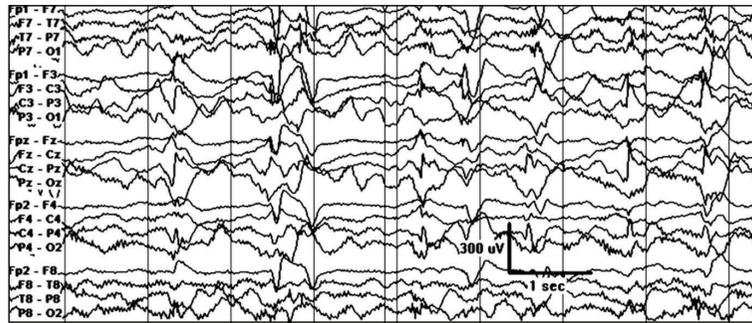


FIGURE 15: Interictal EEG in Alper's disease due to POLG1 mutation demonstrating high-amplitude generalized epileptiform discharges and suppressed background.

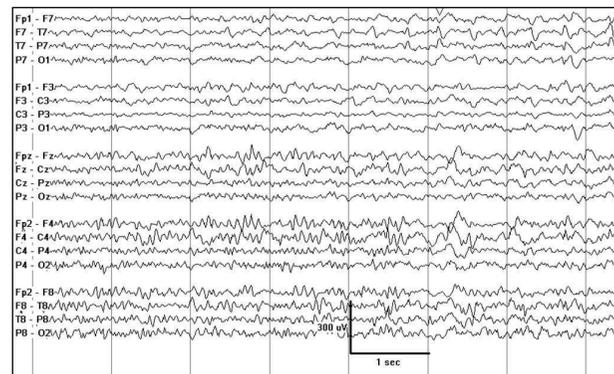
seizures and regression, as well as visual loss. As in other storage diseases, there is progressive slowing of the background activity on the EEG, leading to loss or “vanishing” of EEG activity in NCL [52]. Photosensitivity with a photoparoxysmal response below 3 Hz may also be present [55].

4.2. Immune-Mediated Syndromes. Autoimmune-mediated etiologies for epilepsy are increasingly recognized and should be suspected in patients with multifocal neurologic signs and symptoms, including intractable epilepsy, psychiatric disorder, cognitive dysfunction, movement disorders, sleep disturbance, or autonomic dysfunction with acute or subacute onset and a progressive course. There may be personal or family history of autoimmunity or symptom onset after illness or immunizations.

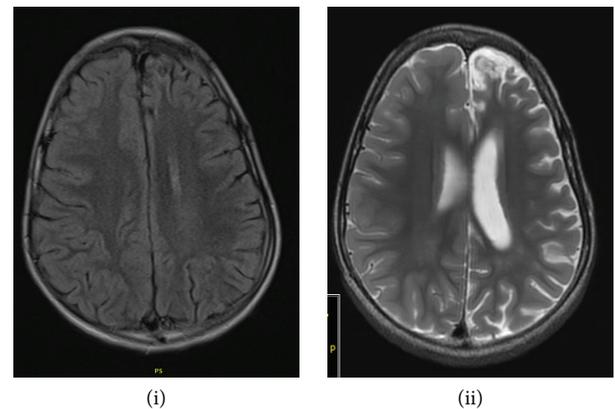
4.2.1. Rasmussen's Encephalitis. Rasmussen's encephalitis is an autoimmune-mediated progressive focal epilepsy with associated increasing contralateral hemiatrophy. The EEG may show lateralized background slowing ipsilateral to the hemiatrophy. Epilepsia partialis continua is common and may not have an EEG correlation (Figure 16).

4.2.2. Voltage-Gated Potassium Channel Complex Antibodies. Voltage-gated potassium channel (VGKC) complex antibodies are associated with intractable epilepsy and encephalopathy in children. LGI1 and CASPR2 are the two most commonly identified VGKC target antigens. The interictal EEG demonstrates nonspecific slowing of the background and multifocal or generalized epileptiform discharges. Facio-brachial dystonic seizures are characterized by brief unilateral facial grimace with concurrent ipsilateral arm dystonia that occurs many times per day and is often seen in children and adults with VGKC-related encephalopathy [56]. The ictal EEG demonstrates contralateral rhythmic frontotemporal spike wave discharges.

4.2.3. NMDA Receptor Antibodies. NMDA receptor (NMDAR) antibodies are also associated with intractable epilepsy and encephalopathy in children. The EEG in patients with NMDAR antibodies demonstrates diffuse nonspecific slowing but often does not reveal potentially epileptogenic discharges. In a minority of patients, nearly



(a) Focal left temporal interictal discharges with decreased amplitude over the left hemisphere



(b) Progressive cerebral atrophy at (i) 8 months and (ii) 15 months after seizure onset

FIGURE 16: EEG in a previously well child presenting with epilepsy partialis continua, progressive hemiparesis, and contralateral cerebral atrophy, consistent with Rasmussen's syndrome.

continuous 1–3 Hz delta activity with superimposed bursts of beta frequency fast activity is present, termed “extreme delta brush” because it is reminiscent of the spindle delta brush pattern seen in premature infants [57].

4.3. Specific EEG Findings in Other Childhood Developmental Disabilities. Rarely, neurodevelopmental syndromes are

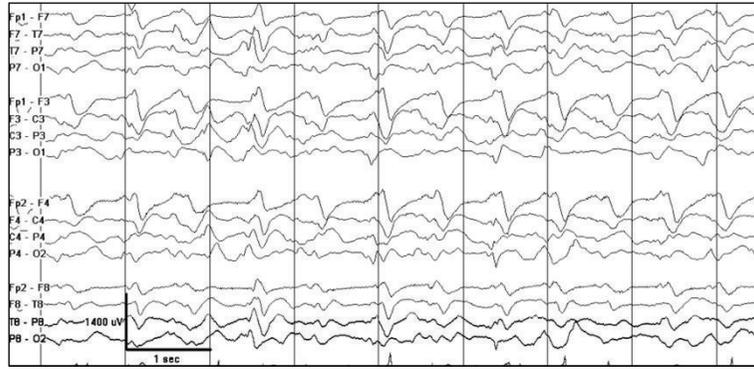
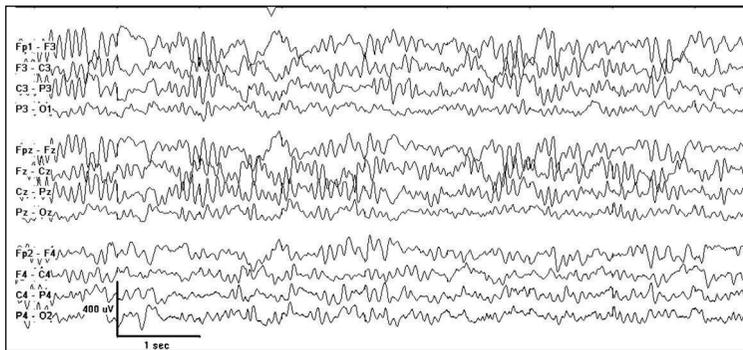
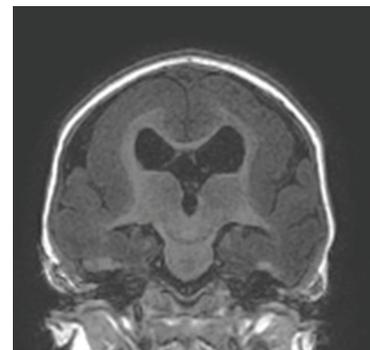


FIGURE 17: A 5 year-old girl with Angelman syndrome. The notched-delta pattern, a variant of ill-defined slow spike-and-wave complexes, in which spikes are superimposed on the ascending or the descending phase of the slow wave giving it a notched appearance.



(a) Diffuse alpha and beta activity greater than 100 μ V



(b) MRI showing lissencephaly

FIGURE 18: Lissencephaly due to *DCX* mutation in a 6 month-old male.

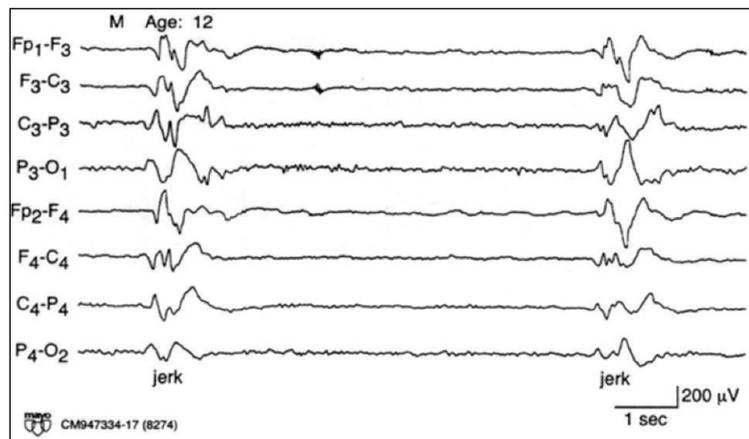


FIGURE 19: A 12-year-old boy with subacute sclerosing panencephalitis. Note high voltage, polyphasic sharp-and-slow-wave complexes, lasting from 0.5 to 2 seconds in a pseudoperiodic pattern.

associated with specific EEG patterns, both epileptiform and nonepileptiform. Recognition of these specific EEG patterns can be helpful in identifying the underlying syndrome.

4.3.1. Angelman Syndrome. Angelman syndrome is a neurodevelopmental disorder caused by absence of functional maternally inherited UBE3A gene on chromosome 15q11–q13

[58]. Children have severe developmental delay, poor, or no language acquisition, happy demeanor, stereotypies, and wide-based gait. Epilepsy and EEG abnormalities are seen in 80% of patients [59]. Generalized diffuse slowing with normal sleep patterns is seen. The notched delta pattern (Figure 17) is seen in 73% of patients with Angelman syndrome at a mean age of 5.2 years [60]. Interictal epileptiform abnormalities are focal or multifocal in distribution.

4.3.2. Lissencephaly. Lissencephaly is a severe malformation of cortical development with agyria or pachygyria. Onset of epileptic spasms may be the presenting feature that leads to diagnosis. The background EEG is nonspecific. Three reported EEG patterns are seen in lissencephaly: (1) diffuse greater than 100 μ V alpha and beta activity in all cortical regions (Figure 18), (2) alternating high amplitude >300 μ V bursts of sharp and slow waves followed by short periods of attenuation, and (3) high amplitude spike wave or sharp wave activity, without alpha or beta frequencies or attenuations. Children with anterior agyria-pachygyria with DCX mutation have diffuse moderate amplitude alpha activity, whereas those with posterior predominant cortical abnormality seen in LIS1 mutation tend to have the EEG pattern with bursts of sharp and slow waves with periods of attenuation.

4.3.3. Subacute Sclerosis Panencephalitis. Subacute sclerosis panencephalitis (SSPE) is a postmeasles encephalitis causing a degenerative process in children and adolescents. It is characterized by motor jerks and progressive intellectual deterioration. The typical EEG pattern consists of high voltage, polyphasic sharp- and slow-wave complexes, lasting from 0.5 to 2 seconds in duration and occurring repetitively in a pseudoperiodic fashion (Figure 19). The complexes are usually generalized and bisynchronous but may be asymmetric or occur in a more lateralized or focal fashion. The complexes may occur at irregular intervals initially. As the disease progresses, the complexes occur at regular intervals, typically every 4 to 15 seconds but may range up to 1 to 5 minutes. Stereotyped motor jerks or spasms occur in association with the periodic complexes. The movements may take place simultaneously with, prior to, or following the periodic complexes. The slow-wave complexes occurring in a regular and periodic fashion and having a constant relationship to motor movements make this pattern specific to SSPE [61].

5. Conclusion

When children present with new onset seizures, the long-term outcome is of great concern to parents and clinicians. Knowledge of the EEG findings supportive of specific electroclinical syndromes is important for accurate diagnosis. Classification of epilepsy electroclinical syndromes is essential particularly in epileptic encephalopathy to guide optimal treatments and counsel family regarding expected outcome.

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Review Article

Continuous Spikes and Waves during Sleep: Electroclinical Presentation and Suggestions for Management

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Received 25 March 2013; Accepted 7 July 2013

Academic Editor: Elaine Wirrell

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Continuous spikes and waves during sleep (CSWS) is an epileptic encephalopathy characterized in most patients by (1) difficult to control seizures, (2) interictal epileptiform activity that becomes prominent during sleep leading to an electroencephalogram (EEG) pattern of electrical status epilepticus in sleep (ESES), and (3) neurocognitive regression. In this paper, we will summarize current epidemiological, clinical, and EEG knowledge on CSWS and will provide suggestions for treatment. CSWS typically presents with seizures around 2–4 years of age. Neurocognitive regression occurs around 5–6 years of age, and it is accompanied by subacute worsening of EEG abnormalities and seizures. At approximately 6–9 years of age, there is a gradual resolution of seizures and EEG abnormalities, but the neurocognitive deficits persist in most patients. The cause of CSWS is unknown, but early developmental lesions play a major role in approximately half of the patients, and genetic associations have recently been described. High-dose benzodiazepines and corticosteroids have been successfully used to treat clinical and electroencephalographic features. Corticosteroids are often reserved for refractory disease because of adverse events. Valproate, ethosuximide, levetiracetam, sulthiame, and lamotrigine have been also used with some success. Epilepsy surgery may be considered in a few selected patients.

1. Introduction

Continuous spikes and waves during sleep (CSWS) is an epileptic encephalopathy, that is, a condition in which the epileptic processes themselves are thought to contribute to the disturbance in cerebral function. CSWS is characterized by (1) seizures, (2) neurocognitive regression, and (3) an electroencephalography (EEG) pattern of electrical status epilepticus during sleep (ESES) [1–6]. ESES is characterized by marked sleep potentiation of epileptiform activity in the transition from wakefulness to sleep that leads to near-continuous bilateral (or occasionally lateralized) slow spikes and waves that occupy a significant proportion of nonrapid eye movement (non-REM) sleep [2, 4].

In this review, we summarize epidemiological, etiological, clinical, and EEG features in CSWS based on available data. We also suggest an approach to manage this syndrome and

present it in the framework of a more general childhood seizure susceptibility syndrome.

2. Definitions

The terms “ESES,” “CSWS,” and “Landau-Kleffner syndrome” have been used interchangeably in the literature to refer to the EEG pattern of frequent spike-waves or to the associated epileptic encephalopathy with regression [6–8]. The EEG pattern and the associated epileptic encephalopathy are different concepts that might require differentiated names. A recent survey in North-America showed that the use of concepts in ESES and CSWS is very heterogeneous, and a common terminology is not available [9]. For the purposes of this review, we will use “ESES” when referring to the EEG pattern, “CSWS” when referring to the epileptic encephalopathy with

global regression, and “Landau-Kleffner syndrome” (LKS) when referring to the epileptic encephalopathy with mainly language regression. We use this terminology in order to give unequivocal names to the different concepts, but we acknowledge that terminology is in progress, and it may change in the future.

The main focus of this review is on CSWS, a severe epileptic encephalopathy with (1) ESES on EEG, (2) seizures, and (3) developmental regression in, at least, two domains of development. Therefore, patients with developmental regression in mainly the language domain will be reviewed under the associated condition of “Landau-Kleffner syndrome” [4]. The borders between these entities are often difficult to delineate, and conditions may be considered as different presentations of the same electroclinical spectrum [10].

3. Epidemiology

CSWS is a rare condition that occurs only in children and adolescents. In an outpatient pediatric series, 1 out of 440 (0.2%) epileptic children had CSWS [11]. In tertiary pediatric epilepsy centers, around 0.5%–0.6% of patients were diagnosed with CSWS [12, 13]. Among children and adolescents undergoing epilepsy surgery for intractable seizures, about 1–2% of patients presented with CSWS [14, 15]. The exact frequency of CSWS is difficult to assess because of inconsistent inclusion criteria and study methodologies. Gender distribution in large series and reviews shows a male-to-female ratio of 4 : 3 to 3 : 2 [2, 16–21].

4. Clinical Features

CSWS is an age-related epileptic encephalopathy in which the clinical features evolve over time. The evolving nature of this syndrome allows the recognition of several clinical events: age at seizure onset, age at neurocognitive regression, and age at seizure freedom. These clinical events provide information to identify electroclinical stages in CSWS, namely, dormant stage (from birth to epilepsy onset), prodromal stage (from epilepsy onset to regression), acute stage (from regression to seizure freedom), and residual stage (after seizure freedom) [22–24].

4.1. Seizures. A typical child with CSWS initially has normal or moderately abnormal baseline development and then presents with seizures around 2–4 years of age. Patients with structural lesions of the brain tend to have seizures earlier (around 2 years of age) than patients without lesions (around 4 years of age) [4]. Seizures during the prodromal stage occur typically out of sleep and are frequently clonic or tonic-clonic unilateral seizures that rarely progress to unilateral status epilepticus [6, 16, 25]. During the prodromal stage, two or more seizure types are seen in only 20% of patients [16]. During the acute stage, there is a marked increase in the frequency and types of seizures, which become more difficult to control [2, 6, 16, 25, 26]. Unilateral seizures become rare, while atonic seizures appear and the motor components of the seizures lead to sudden falls. Atypical absence seizures

increase in frequency and severity and may even evolve into absence status epilepticus [6, 16, 25]. The lack of tonic seizures has been classically considered a major feature of this syndrome and allows for differentiation from Lennox-Gastaut syndrome (LGS) [1, 6, 25].

4.2. Neurocognitive Regression. During the dormant stage, neurocognitive development is clinically normal in approximately two-thirds of cases [13, 25, 26]. A severe neurocognitive regression occurs around 5–6 years of age in most patients. Neurocognitive deterioration affects a wide spectrum of developmental and neurocognitive milestones in varying but often severe degrees. Regression domains include language, behavior, learning, memory, attention, social interactions, motor skills, and global intelligence [2, 3, 6, 8, 15, 17, 25, 27–30].

5. Electroencephalographic Features

During wakefulness, the EEG shows focal/multifocal spikes that increase in frequency during the acute stage. The hallmark EEG feature of CSWS is ESES. ESES is characterized by (1) marked potentiation of epileptiform discharges during non-REM sleep, leading to (2) a (near)-continuous, bilateral, or occasionally lateralized slow spikes and waves, (3) and these spikes and waves occur “during a significant proportion” of the non-REM sleep with a threshold ranging from 25% to 85% [1, 6, 15, 19–21, 25, 27, 31–35].

5.1. Evolution of ESES over Time. Abnormal EEG findings are found during the prodromal period or even the dormant stage. Findings always include potentiation of spiking during non-REM sleep. During the acute stage, interictal epileptiform activity becomes much more frequent and severe with more widespread spikes of higher amplitude associated with a more abnormal background. During sleep, the EEG pattern presents as ESES [4]. ESES typically appears about 4–8 years of age and typically remits around 8–9 years of age [8, 17, 19, 35]. The age of detection of the ESES pattern on EEG varies widely in different studies and likely reflects the varied criteria of ESES used as well as the variations of time intervals in which EEGs are performed.

5.2. Cut-Off Value. The initial definitions of ESES proposed that no less than 85% of the total duration of slow sleep should be occupied by slow spike-waves [6, 34]. This cut-off value has been followed by several authors [6–8, 15, 17, 21, 35–39], while other authors used lower cut-off percentages [19, 20, 40, 41]. The International League Against Epilepsy does not refer to any particular threshold and only requires that spike-waves be “continuous” and “diffuse” [1] leading to heterogeneous and variable use of cut-off values by the professionals caring for these children [9].

5.3. Quantification of Epileptiform Activity. The classic measure for the quantification of epileptiform activity is the spike-wave index, expressed as the percentage of sleep occupied by spike-waves. While this percentage has been widely used,

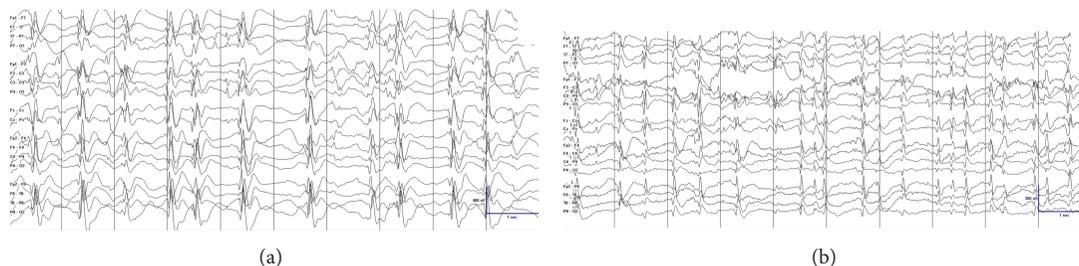


FIGURE 1: Different values in the quantification of the epileptiform activity result when using different methods of quantification. Epileptiform activity appears much more frequently in (b) than in (a). Both tracings have a 100% of epileptiform activity if the reader quantifies the epileptiform activity using spike percentage, that is, counting the percentage of 1-second bins occupied by spike-waves. However, if the reader quantifies the epileptiform activity using spike frequency, that is, the total number of individual spike-waves per unit of time (per 10 seconds in this page, per 100 seconds in a longer tracing), epileptiform activity is almost double in (b) than in (a). Note that the tracings have different voltage gains.

the exact method for calculating this value is often not specified [6, 7, 15, 17, 19, 21, 26, 35, 40]. A reproducible way to quantify epileptiform activity is to quantify the percentage of 1-second bins with at least one spike-wave in them, termed spike-wave percentage [24, 36]. Another reproducible method consists in counting the total number of spikes per unit of time, termed spike frequency [24]. A formal comparison between these two methods showed that spike frequency could better detect changes in epileptiform activity in those patients with very active epileptiform discharges (Figure 1) [24]. In addition, spike frequency lends itself better for automated quantification [42]. There is also no formal consensus on which portion of sleep is used for calculating the epileptiform activity with different periods of the night used by different authors [6, 19, 24, 35, 36, 43] and in clinical practice [9]. Regarding lateralized epileptiform activity, there is insufficient evidence to support that unilateral or focal discharges should be quantified differently than symmetric and bilateral discharges [20, 26, 39, 44].

6. Evolution over Time

CSWS evolves over time, and this evolution manifests in all three cardinal manifestations, including clinical seizures, EEG abnormalities, and neurocognitive regression. We therefore describe the evolution of this clinical presentation in these three categories.

6.1. Seizures. Seizures almost always disappear with age, even in patients with a static or progressive encephalopathy [2, 3, 6, 25, 27, 29, 41, 45, 46]. The age of seizure freedom peaks around 6–9 years of age although data on this clinical event are scarce, and the range is wide [27, 29].

6.2. Electroencephalogram Features. ESES progressively resolves with interictal epileptiform discharges during sleep substituted by a progressive return of the physiologic graphoelements and patterns of sleep. Typically, the resolution of the ESES pattern occurs around 8–9 years of age, in parallel with the timing of seizure freedom. However,

ESES can persist and be very active for a period after seizure freedom [3, 24, 25, 29].

6.3. Neurocognitive Features. The initial regression ultimately leads to a plateau in development. Some patients present with moderate improvements after seizure freedom. However, most patients remain severely impaired [2, 3, 6, 47]. The impact of interictal spikes on neurocognitive features is a matter of debate, and it is not clear whether an increased amount of epileptiform activity is associated with a worse cognitive outcome [4, 48, 49].

7. Etiology and Pathophysiology

The exact cause of CSWS is unknown, but there are two factors that have been implicated. First, an association of CSWS with early developmental lesions of the brain has been shown. Second, an increasing number of genetic associations of unclear significance have also been described.

7.1. Early Developmental Lesions. Several case reports and small series described the association between patients with the ESES EEG pattern and early developmental lesions, such as malformations of cortical development [45], or vascular insults [50–52]. Larger series also support this association. In a study of 32 patients with prenatal or perinatal thalamic lesions, sleep potentiation of epileptiform activity occurred in 29 cases (90.6%) [27]. In two large series of patients with ESES, 33 out of 67 patients (49.3%) and 18 out of 44 (40.9%) patients had an early developmental lesion [20, 53]. While these lesions may not be specific for ESES, but for epilepsy in general, a recent series compared 100 patients with ESES and 47 patients with epilepsy without ESES. Patients with ESES had a higher frequency of early developmental lesions (48% versus 19.2%; $P = 0.002$) and a higher frequency of thalamic lesions (14% versus 2.1%; $P = 0.037$). These findings are consistent with other series suggesting that approximately 40–50% of patients with ESES had an early developmental insult [20, 53, 54], with a majority having perinatal lesions of vascular etiology [20, 53, 54]. Interestingly, some authors report that certain cortical malformations may also be related

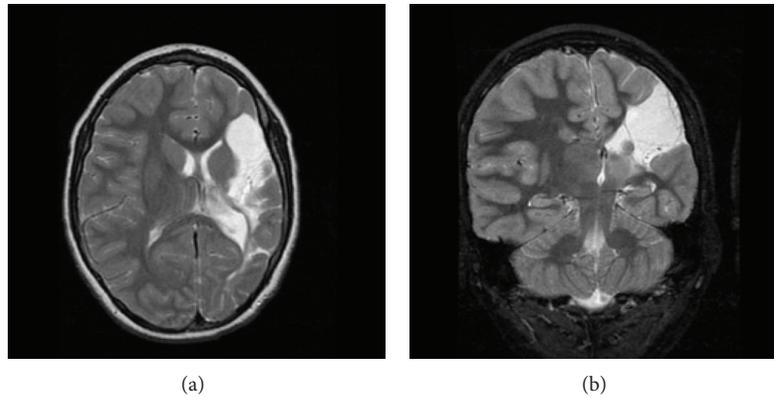


FIGURE 2: Early vascular lesions in patients with CSWS. Axial view T2 weighted in (a), coronal view T2 weighted in (b). Extensive cystic encephalomalacia affecting the left hemisphere in the distribution of the left middle cerebral artery consistent with a left middle cerebral artery infarct.

TABLE 1: Genetic factors that have been described in association with CSWS.

Study	Type of study	Association
Beumanoir et al., 1995 [104]	Case report	CSWS in two monozygotic twins
Praline et al., 2006 [105]	Case report	Two siblings with ESES and different clinical presentations
Verhoeven et al., 2012 [106]	Case report	One patient with CSWS and dysmorphic features carried a de novo 8q12.3q13.2 microdeletion
Godfraind et al., 2008 [107]	Case report	One patient with CSWS carried a G392R mutation in neuroserpin of probable pathogenic significance (the mutation led to a progressive neurodegenerative disease and CSWS)
Nakayama et al., 2012 [108]	Case series (2 patients with CSWS)	Two patients with CSWS and dysmorphic features carried an unbalanced translocation between 8p and 9p
Brolì et al., 2011 and Giorda et al., 2009 [109, 110]	Case series (2400 subjects with isolated or syndromic intellectual disability)	Five patients with CSWS carried a Xp11.22-p11.23 duplication
Kevelam et al., 2012 [40]	Case series (13 children with ESES and different clinical presentations)	Two patients with CSWS carried copy number variations in CHRNA7 and PCYT1B genes of probable pathogenic significance
Mefford et al., 2011 [111]	Case series (315 patients with different epileptic encephalopathies, 29 had CSWS or Landau-Kleffner syndrome)	One patient with CSWS carried a copy number variant in the DOK5 gene of uncertain pathogenic significance
Reutlinger et al., 2010 [112]	Case series (3 patients with ESES and different clinical presentations)	Three patients with ESES and different clinical presentations and dysmorphic features carried a deletion in 16p13.2p13.13
Atkins and Nikanorova, 2011 [66]	Case series (20 patients with ESES and different clinical presentations)	One patient with ESES (no further details on clinical presentation) carried a partial trisomy 13/21

Legend: CSWS: continuous spikes and waves during sleep. ESES: electrical status epilepticus in sleep.

to early vascular insults [55]. In particular, early developmental lesions that involve the thalamus are strongly associated with CSWS (Figure 2) [54].

7.2. Genetic Factors. Familial antecedents of seizures (including febrile seizures) are found in around 10–15% of patients with CSWS [6, 25]. Although genetic predisposition seems to play a minor role in CSWS, a growing number of case reports and small series describe associations with copy number variations and different mutations in several chromosomes

(Table 1). The etiological role of these genetic factors in CSWS is largely undefined to date. It is likely that these genetic variants are associated not with CSWS *per se*, but with different neurological conditions that result in the final common pathway of CSWS. A similar theory is suggested for hypsarrhythmia in West syndrome.

7.3. Pathophysiology. Animal models are providing insights into the basic pathophysiology of sleep-potential spiking

[56]. Cortical lesions have been found to weaken the neurotransmission between corticothalamic neurons and the reticular nucleus of the thalamus without weakening the circuit between corticothalamic and thalamocortical neurons [57–59]. Therefore, reticular neurons do not have the normal loop interaction with the corticothalamic neurons that provides a feed-forward inhibition to thalamocortical neurons [57]. In contrast, a pathological loop with thalamocortical neurons is created which promotes a robust oscillatory network in the cortico-thalamo-cortical loop [57–59]. Breaking this pathological loop by selective inhibition of the thalamocortical neurons is a promising approach that has been found to work in an animal model [59]. The deficiency of the GluA4 AMPA receptor in a *Gria4*^{-/-} mouse model similarly weakens the normal output of the reticular neurons leading to the development of spike-wave discharges [57]. It can be hypothesized that lesions in the reticular nucleus of the thalamus may also lead to a potentiation of oscillatory discharges in the cortico-thalamo-cortical network. Supporting this hypothesis, marked sleep potentiation of epileptiform activity has been found in patients with early developmental lesions affecting the thalamus [27, 54]. The only study that evaluated the specific thalamic areas that were injured showed that the reticular nucleus was the most frequently affected structure and it was involved in 91% of the cases [27].

8. Management

8.1. To Treat or Not to Treat Epileptiform Activity. The relationship of epileptiform activity in the EEG with neuropsychological function is a matter of debate. Near-continuous epileptiform discharges are considered to be related to neurocognitive regression in CSWS [6, 48, 49, 60]. Many studies demonstrate that epileptiform activity is deleterious for learning and memory under certain experimental conditions [48, 49, 60–65], indirectly supporting the option of treatment. A recent study associated epileptiform activity during ESES with activation in the thalamocortical network and deactivation in the default mode network [38]. Since these networks seem prominent in neuropsychological processes and consolidation of memory traces during sleep, it is possible that epileptic spikes may contribute to regression in CSWS. On the other hand, the impact of interictal epileptiform activity on cognitive function may not be severe enough to serve as the sole explanation for the degree of neurocognitive regression [48, 65]. Many studies suggest that long-term neurocognitive function may significantly improve if epileptiform activity in the EEG can be reduced with antiepileptic drugs [3, 6, 7, 17, 19, 49], but this effect remains to be proven. Therefore, whether to treat epileptiform activity without a direct clinical correlate and, especially, to what extent to treat EEG findings is unclear. As a rule of thumb, we always treat the patient while considering the clinical presentation as a whole, not solely the EEG or other isolated laboratory values.

8.2. Modification of the Natural Course of the Disease by Treatment. Treatment goals of CSWS include not only improved seizure control, but also a reduction in EEG abnormalities

and potentially improvement of neurocognitive function or at least prevention of further regression. There is evidence in the literature supporting a beneficial effect of treatment on seizure frequency and severity [7, 19, 26, 36, 66–70] and epileptiform activity [19, 21, 71, 72]. Several studies suggest that long-term neurocognitive function can significantly improve once epileptiform discharges are reduced, and this effect has been related to treatment with antiepileptic drugs [3, 6, 7, 17, 19, 73–77]. However, to date, there is no scientific evidence for or against treatment of interictal spikes.

8.3. Antiepileptic Drugs. The most common antiepileptic drugs used for CSWS include valproate, ethosuximide, and levetiracetam [78]. In a series of 15 patients with CSWS treated with high-dose valproate alone or with valproate and ethosuximide, 10 cases (67%) responded with long-term control of their epilepsy and partial recovery of cognitive function [19]. In a separate study, the combination of valproate and ethosuximide was effective in 2 additional patients [7]. In contrast, other series did not report similar improvements after treatment with comparable medication regimens. Valproate was reported as not effective in 28 patients [26]; valproate and benzodiazepines did not achieve any improvement in 7 patients and were associated with adverse behavioral reactions in 3 children [30], and several case reports describe no significant improvement with valproate [67, 68, 79]. Ethosuximide was also found to lack efficacy in 7 patients with CSWS [26] and to exert only a modest effect in 3 [67]. The efficacy of levetiracetam is supported by several case reports in the literature [26, 36, 66–68, 70]. The only placebo-controlled double-blind crossover study in patients with ESES showed that treatment with levetiracetam reduced epileptiform activity (from a spike index of 56 to 37) in a series of 18 patients, although 3 other patients discontinued treatment because of negative cognitive side effects [80]. Other drugs that have been reported as effective in small series include sulthiame [26, 81] and lamotrigine [45, 82]. Phenytoin, phenobarbital, and, especially, carbamazepine and oxcarbazepine are generally avoided because they have been associated with exacerbations of epileptiform discharges in patients with ESES [82–85].

8.4. High-Dose Benzodiazepines. Benzodiazepines have demonstrated efficacy in reducing epileptiform activity in the short term. Transitory resolution of the ESES pattern was observed after the administration of clonazepam [19, 21]. Diazepam has a shorter half-life than clonazepam, which can be advantageous in a condition such as CSWS where more severe epileptiform activity occurs during the night. In a series of 4 patients with CSWS refractory to valproate and ethosuximide, a short cycle of high-dose oral or intrarectal diazepam (0.5–1 mg/Kg per day for 6–7 days) was effective in the short term in two patients [19]. In a series of 15 patients with CSWS, all patients responded to the treatment with high-dose rectal diazepam [86]. High-dose oral diazepam (0.75–1 mg/Kg/day for 3 weeks) was also efficacious in 3 out of 8 (37.5%) patients, but the response was temporary [26]. In 29 patients with ESES and different clinical presentations,

the mean epileptiform activity decreased from 77% to 41% after a nocturnal administration of 1 mg/Kg of oral diazepam [72]. This reduction in epileptiform activity persisted for some months [87], but whether this reduction in epileptiform activity is accompanied by a sustained improvement in clinical features remains to be proven. Other series show that 9 out of 10 patients did not respond to valproate and benzodiazepines, and 3 patients experienced an adverse behavioral reaction [30]. Adverse effects of high-dose diazepam treatment are generally considered mild and self-limited [72, 86], but severe behavioral disinhibition and even the need for discontinuation have also been described in few children [3, 87].

8.5. Immune Modulation Therapy. Corticosteroids and intravenous immunoglobulins have shown improvement in selected cases and, in some cases, lead to complete resolution of CSWS. Once CSWS is recognized, usually during the acute phase, corticosteroid treatment should be considered. In a series of 44 children with a pattern of ESES and clinical presentations of variable severity, prolonged corticosteroid treatment (hydrocortisone 5 mg/kg/day during the first month, 4 mg/kg/day during the second month, 3 mg/kg/day during the third month, and 2 mg/kg/day during the next 9 months, followed by slow withdrawal for a total treatment duration of 21 months) led to reductions of seizures or neuropsychological improvement in 34/44 (77.3%) cases, with 34 achieving complete control of seizures and normalization of EEG abnormalities in 21 patients. The long-term remission rate was 45% [53]. However, the inclusion of milder clinical presentations could make these results difficult to compare to other series where all or most patients had clear CSWS [53]. In another series, a positive response to different corticosteroids (prednisone, methylprednisolone, or adrenocorticotrophic hormone) was observed in 11 out of 17 patients with CSWS [26]. The intramuscular administration of 0.001–0.04 mg/kg/day of adrenocorticotrophic hormone was reported to be effective in 1 out of 4 patients [19]. The side effects of corticosteroid treatments usually limit its long-term use. Only a handful of patients treated with intravenous immunoglobulins have been reported in the literature. Intravenous immunoglobulin treatment was associated with improvements in 3 out of 9 patients with CSWS [26]. In another series, the neurocognitive function of 1 out of 3 patients with CSWS improved following the administration of intravenous immunoglobulins [88]. However, there is probably a publication bias of positive results, and the high cost and risk of complications associated with immunoglobulins make their role in the treatment of CSWS unclear.

8.6. Surgical Treatment. Although classically epilepsy surgery was performed on patients with focal discharges, it has also been successfully applied to select patients with generalized discharges [89, 90]. Some patients with CSWS may also benefit from surgical treatment. Surgical interventions include multiple subpial transections (MSTs), focal resective

surgery of the epileptogenic zone, hemispherectomy and corpus callosotomy. MST consists of multiple small superficial parallel cuts in the cortex that theoretically severs only the local corticocortical connections in an attempt to disrupt local epileptic circuitry without altering the vertical neural columns and their function. It has been reported to lead to recovery of age-appropriate speech in 7 patients out of a series of 14 patients with Landau-Kleffner syndrome [89], whereas a less dramatic language improvement was found in other series [91, 92]. Two patients with CSWS secondary to neonatal stroke markedly improved after hemispherectomy [93]. In another study, two patients with CSWS secondary to early developmental lesions in the thalamus became seizure-free after a hemispherectomy in one and after an extensive corticectomy around a large porencephalic cyst in the other [27]. A study evaluated epilepsy surgery in 13 patients with CSWS secondary to different early developmental lesions who underwent various surgical procedures including anterior callosotomy (6 patients), complete callosotomy (3 patients), hemispherectomy (2 patients), and lobar resection (2 patients). Subjects achieved an overall improvement in seizure control and EEG features in most patients [8].

Improvements may be related to the type of surgery performed. The cognitive deterioration may be halted in most patients; however, while there was some cognitive recovery, patients did not return to baseline. In a series of 8 patients with CSWS secondary to perinatal infarction (7 patients) and a malformation of cortical development (1 patient), 6 patients underwent a hemispherectomy, and 2 underwent focal resection. Results included disappearance of the pattern of ESES (all 8 patients), seizure freedom (6 patients), marked improvement in seizure control (2 patients), and an overall improvement in cognitive function (in 3 out of 5 patients with neuropsychological evaluation) [15]. Patients with CSWS should undergo epilepsy surgery only after a careful evaluation of potential benefits and risks in the individual patient. A tendency toward neurocognitive improvement was found in 3 out of 5 patients with CSWS after epilepsy surgery [15]. However, data on the long-term neurocognitive outcome of surgically managed CSWS patients are not available.

8.7. General Suggestions for Managing Patients with CSWS (Figure 3). Current literature does not permit the development of an evidence-based management approach to CSWS. Most of the drugs used for CSWS are selected based on individual experience, case reports, or small case series that claim efficacy for a specific drug. Responses to treatment in uncontrolled case reports or case series should be interpreted with caution as any treatment for a disorder with a fluctuating natural course tends to be initiated at the peak of severity, so that some improvement can be attributed to the natural fluctuations of the disease. In addition, other series report a lack of efficacy for commonly used treatment options for CSWS. There is no evidence on the efficacy of the ketogenic diet in patients with CSWS. Here, we provide a practical treatment approach based on case series in the literature (Figure 3). In practice, most patients with CSWS were already

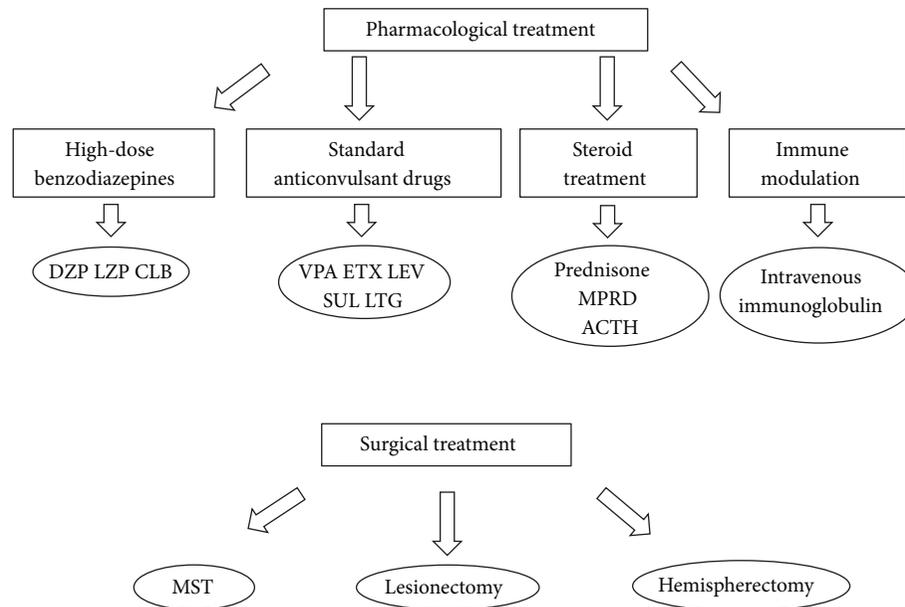


FIGURE 3: Options for the management of patients with CSWS. Options for chronic management are high-dose benzodiazepines, standard antiepileptic drugs in different combinations, and corticosteroids and immune-modulating agents. These options are considered as first choices by different authors, although standard antiepileptic drugs are generally used before the recognition of CSWS. Epilepsy surgery is reserved for few selected refractory cases. Legend: ACTH: adrenocorticotrophic hormone. CLB: clobazam. DZP: diazepam. ETX: ethosuximide. LEV: levetiracetam. LTG: lamotrigine. LZP: lorazepam. MPRD: methylprednisolone. MST: multiple subpial transection. SUL: sulthiame. VPA: valproate.

on some standard antiepileptic drug (valproate, levetiracetam, or similar) when their seizures first began and before their condition was recognized as CSWS. Once in the acute phase, standard antiepileptic drugs, corticosteroids, and benzodiazepines can be considered as first choices depending on the particular patient and the familiarity of the physician with these drugs. Several groups have reported the usefulness of benzodiazepines [19, 26, 72, 86], and a frequent protocol used at our institutions is nocturnal Diazepam 1 mg/Kg during the first night followed by 0.5 mg/Kg every following night for 1–3 months [87]. For the chronic management of CSWS and particularly for seizure control standard antiepileptic drugs such as valproate, ethosuximide, levetiracetam, sulthiame, and lamotrigine are frequently used. Polytherapy is often needed. Medication selection should be guided by presenting seizure types [7, 19, 26, 30, 36, 45, 66–68, 70, 78–82]. Other options include treatment with corticosteroids, adrenocorticotrophic hormone, or intravenous immunoglobulin [19, 26, 53, 88]. Epilepsy surgery should be considered, especially in patients with an early unilateral developmental lesion, even when the epileptiform activity on EEG is generalized [8, 15, 27, 89–93]. For the acute control of very active nighttime epileptiform discharges, high-dose benzodiazepines have been used over a period of a few months [19, 21, 26, 72, 86]. While adequate control of seizures improves the quality of life of the patients and should be pursued, it is unknown how aggressively interictal epileptiform activity in relationship with neurocognitive regression should be treated. Only prospective studies that correlate the response to treatment of interictal epileptiform

activity with the improvement in neurocognitive function will be able to answer that relevant question.

9. Related Conditions

ESES, the EEG pattern that characterizes CSWS, can be found in other electroclinical conditions. CSWS might represent the most severe end of a continuum in which Landau-Kleffner syndrome would be an intermediate condition and “benign” focal epilepsy syndromes of childhood would be at the most benign end of the spectrum.

9.1. Landau-Kleffner Syndrome. It is an age-related epileptic encephalopathy where regression occurs mainly in the language spectrum and the EEG abnormalities are more centered around the temporal-parietal regions [94]. Seizures are not a prominent part of this syndrome, and they are either infrequent or do not even occur in 20–30% of cases [3, 74]. Contrary to CSWS, structural brain lesions in LKS are an exception to the rule [94]. Most antiepileptic drugs are effective for seizure control in LKS [7, 18, 21]. Corticosteroids have been reported to markedly improve the evolution of the disease [18, 53, 77], and intravenous immunoglobulins demonstrated promising results in very few cases, although immunoglobulins are expensive and associated with potentially serious side effects [88, 95–99]. Resective surgery is not an option because the focus of epileptiform activity frequently involves eloquent cortex, including language areas. The technique of multiple subpial transections has led to

variable results [91, 92, 100]. Similar to CSWS, seizures and EEG abnormalities normalize over time, but most patients do not recover their baseline language status [76].

9.2. *“Benign” Pediatric Focal Epileptic Syndromes.* They include “Benign” epilepsy of childhood with central-temporal spikes, Panayiotopoulos syndrome, and Gastaut-type late-onset childhood occipital epilepsy. These syndromes share features such as a strong genetic predisposition, age-related appearance and disappearance of electroclinical manifestations, and a relatively “benign” clinical course. As in the previous syndromes, interictal epileptiform activity may be disproportionately severe in comparison with the seizure correlation. Neurocognitive dysfunction, if present, is mild. The individual description of each particular syndrome is beyond the scope of this review and can be found elsewhere [101, 102]. Because of their main features, “benign” pediatric focal epileptic syndromes may be considered as part of the electroclinical spectrum of CSWS [101, 102].

9.3. *Seizure (or Spikes) Susceptibility Syndrome.* CSWS, Landau-Kleffner syndrome and “benign” pediatric focal epilepsy syndromes share a series of common features: (1) an electroclinical syndrome consisting of seizures, interictal epileptiform activity, and neuropsychological deficits of different severities, (2) an age-related evolution with onset in early childhood and spontaneous improvement before puberty, (3) interictal epileptiform activity becomes markedly potentiated during non-REM sleep, (4) interictal epileptiform activity is disproportionately severe in comparison with the seizure correlate, and (5) interictal epileptiform activity frequently persists after seizure freedom. Overlap between these clinical presentations has led to the hypothesis of a common seizure susceptibility syndrome. In this syndrome, the different electroclinical presentations reflect different severities of a common underlying pathophysiology, similar to what happens with the different clinical presentations of hypsarrhythmia. A genetic or acquired disruption of the neural networks early in development would create hyperexcitable neural networks [57, 58] that, depending on its severity and localization, could manifest as different electroclinical presentations in the spectrum [27, 54, 56, 101, 103].

10. Conclusions

CSWS is an age-related epileptic encephalopathy that represents the most severe end of the childhood seizure susceptibility syndrome. Its characterizing features are (1) seizures, (2) interictal epileptiform activity that becomes prominent during sleep leading to the electroencephalogram pattern of ESES, and (3) neurocognitive regression. The etiology of CSWS is unknown, but early developmental lesions play a major role in around half of the cases. The neurocognitive outcome is generally poor, and it is currently unknown whether treatment can modify it. High-dose benzodiazepines have been used successfully to decrease very active epileptiform discharges. Polytherapy with combinations of valproate,

ethosuximide, levetiracetam, sulthiame or lamotrigine, and corticosteroids is frequently used. Epilepsy surgery can be considered in a few very selected number of patients. A better understanding of the response to treatment, the electroclinical spectrum, and the underlying pathophysiology may allow for the development of an evidence-based management approach in the future.

Conflict of Interests

The authors do not have any conflict of interests relevant to this paper to disclose.

Acknowledgments

Iván Sánchez Fernández is funded by a grant for the study of Epileptic Encephalopathies from “Fundación Alfonso Martín Escudero.” Kevin E. Chapman performs, interprets, and bills for clinical neurophysiology procedures, including EEGs, at Children’s Hospital Colorado. Jurriaan M. Peters is supported by National Institutes of Health P20 RFA-NS-12-006 and 1U01NS082320-01 Grants, by the World Federation of Neurology Grant-in-Aid Competition, and by a Faculty Development Fellowship from the “Eleanor and Miles Shore 50th Anniversary Fellowship Program for Scholars in Medicine,” Boston Children’s Hospital, Department of Neurology, 2012–2013. He performs video-EEG long-term monitoring, EEGs, and other electrophysiological studies at Boston Children’s Hospital and bills for these procedures. Chellamani Harini performs, interprets, and bills for clinical neurophysiology procedures, including EEGs, at Boston Children’s Hospital. Alexander Rotenberg performs, interprets, and bills for clinical neurophysiology procedures, including EEGs, at Boston Children’s Hospital. Dr. Rotenberg’s salary and research are supported by grants, unrelated to the present paper, from the Department of Defense, NIH NINDS, the Epilepsy Therapy Project, CIMIT, the AlRashed Family Foundation, the Fisher Family Foundation, and the Translational Research Program at Boston Children’s Hospital. He serves as an Associate Editor at the Journal of Pediatric Neurology. Tobias Loddenkemper serves on the Laboratory Accreditation Board for Long-Term (Epilepsy and ICU) Monitoring (ABRET); he serves as a Member of the American Clinical Neurophysiology Council (ACNS) and serves on the American Board of Clinical Neurophysiology and serves as an Associate Editor of Seizure. He performs Video EEG long-term monitoring, EEGs, and other electrophysiological studies at Children’s Hospital Boston and bills for these procedures and receives support from NIH/NINDS 1R21NS076859-01 (2011–2013). He is supported by a Career Development Fellowship Award from Harvard Medical School and Children’s Hospital Boston, by the Program for Quality and Safety at Children’s Hospital Boston, the Translational Research Project, and by the Payer Provider Quality Initiative. He receives funding from the Epilepsy Foundation of America (EF-213583 & EF-213882), from the Center for Integration of Medicine & Innovative Technology (CIMIT), Citizens United for Research in Epilepsy (CURE), the Epilepsy Therapy Project, and an infrastructure grant

from the American Epilepsy Society and received investigator initiated research support from Eisai Inc. and Lundbeck.

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Review Article

Diagnosis and Management of Epileptic Encephalopathies in Children

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Received 13 March 2013; Revised 4 June 2013; Accepted 18 June 2013

Academic Editor: Elaine Wirrell

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Epileptic encephalopathies refer to a group of disorders in which the unremitting epileptic activity contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone, and these can worsen over time leading to progressive cerebral dysfunction. Several syndromes have been described based on their electroclinical features (age of onset, seizure type, and EEG pattern). This review briefly describes the clinical evaluation and management of commonly encountered epileptic encephalopathies in children.

1. Introduction

The term “epileptic encephalopathy” refers to a group of disorders in which the unremitting epileptic activity contributes to progressive cerebral dysfunction. This cannot be explained by the underlying etiology alone [1]. It may be progressive or have waxing-waning course. The underlying etiology is diverse. Their clinical and electroencephalographic (EEG) features mirror the specific age-related epileptogenic reaction of the immature brain. The various syndromes of epileptic encephalopathy are tabulated in Table 1. This review will briefly discuss the diagnosis and management of these syndromes according to the age of onset.

2. Early Infantile Epileptic Encephalopathies

This group of disorders comprises Ohtahara syndrome or early infantile epileptic encephalopathy (EIEE), early myoclonic encephalopathy (EME), and malignant migrating partial seizures in infancy.

Ohtahara syndrome is a devastating epilepsy with onset ranging from intrauterine period to 3 months of age. The *tonic spasms* are the defining seizure type which are very frequent and occur in both sleep and wakeful states. Besides these,

partial and rarely myoclonic seizures may be observed. The interictal EEG shows burst suppression pattern with no sleep-wake differentiation. The bursts last for 2–6 seconds alternating with periods of suppression lasting for 3–5 seconds.

The underlying causes are heterogenous. The majority of cases are attributable to static structural brain lesions such as focal cortical dysplasia, hemimegalencephaly, and Aicardi syndrome [2, 3]. Few genetic mutations have been described but these are not specific for Ohtahara syndrome [4, 5]. These include mutations in the syntaxin binding protein-1 (*STXBP-1*) [6], Aristaless-related homeobox (*ARX*) [7], and *SLC25A22*-gene encoding a mitochondrial glutamate carrier [8]. An epileptic encephalopathy similar to Ohtahara syndrome, attributable to mutations in the *KCNQ2* gene that encodes the voltage-gated potassium channel Kv7.2, has been recently described [9]. Though the condition appears similar to Ohtahara syndrome, subtle differences include progression with reduction in seizure frequency in *KCNQ2* encephalopathy in comparison to Ohtahara syndrome which frequently evolves to West syndrome and the unusual transient basal ganglia imaging abnormalities in *KCNQ2* encephalopathy.

The medical management of seizures is not rewarding. The dietary therapy has been tried with some success. Ishii et al. reported a favourable response of ketogenic diet in

TABLE 1: Epileptic encephalopathies.

Recognized syndromes
Ohtahara syndrome
Early myoclonic encephalopathy
West syndrome
Dravet syndrome
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
Landau-Kleffner syndrome (LKS)
Proposed
Epilepsy of infancy with migrating focal seizures [15, 16]
Late infantile epileptic encephalopathy [35]
Atypical benign partial epilepsy of childhood [36]
Hypothalamic epilepsy [37]
Myoclonic encephalopathy in nonprogressive disorders [38]

a male infant with Ohtahara syndrome who had failed multiple antiepileptic drugs [10]. Neurosurgery is sometimes favourable in selected cases of cerebral malformations [11]. The prognosis is uniformly poor with survivors left with severe psychomotor retardation. There may be age-dependent evolution to West syndrome and then subsequently to Lennox-Gastaut syndrome.

Early myoclonic encephalopathy presents within the first 3 months of age and mostly within the neonatal period. The prenatal onset is known. Fragmentary, erratic myoclonia, partial seizures, and less frequently tonic spasms are seen. The interictal EEG shows burst suppression pattern more prominent during the sleep. The bursts last for 1–5 seconds with longer periods of suppression (3–10 seconds). Table 2 shows differentiating features between EEG features of Ohtahara syndrome and early myoclonic encephalopathy.

Many of the reported cases are familial. The inborn errors of metabolism such as nonketotic hyperglycinemia, organic acidemia, Menkes disease, Zellweger syndrome, molybdenum cofactor deficiency [2], pyridoxine dependency [12], and genetic factors are the most important etiologies. The structural abnormalities are rarely found [2].

These seizures are often refractory to conventional antiepileptic drugs. A sequential therapeutic trial with pyridoxine, folic acid, and pyridoxal phosphate should be instituted [13]. Limited success has been reported with ketogenic diet [14]. The prognosis is dismal. The EEG often evolves to atypical hypsarrhythmia which is transient or multifocal spike and sharp waves 3–4 months after the onset of the disease.

The diagnosis of these epileptic encephalopathies begins with an EEG which should include both the sleep and wake states. A magnetic resonance imaging of the brain must be obtained to look for structural defects. A metabolic profile including blood ammonia, arterial blood gas, lactate, blood tandem mass spectrometry, and urine organic acid analysis must be obtained to look for inherited metabolic defects. Testing for *STXBPI* mutations may be considered in

infants with Ohtahara syndrome, once brain malformations or inherited metabolic defects have been excluded [13].

Epilepsy of infancy with migrating focal seizures, is a rare, age-specific epileptic encephalopathy with a malignant course with onset in the first 6 months of age. It is characterized by a period of normal early development followed by nearly continuous migrating polymorphous focal seizure which are intractable, with subsequent psychomotor retardation and, in most children, progressive decline of head circumference percentile [15, 16].

Interictal EEGs show diffuse slowing of the background activity with multifocal epileptiform discharges. Ictal EEGs display paroxysmal discharges occurring in various regions in consecutive seizures in a given patient. They start in one region and progressively involve the adjacent areas. The area of ictal onset shifts from one region to another and from one hemisphere to the other, with occasional overlapping of consecutive seizures.

The etiology is largely unknown. *SCN1A* [17, 18] and phospholipase $C\beta 1$ (*PCB1*) [19] gene mutations have been described in few patients. The seizures are markedly pharmacoresistant to conventional antiepileptic drugs. Potassium bromide [20] and stiripentol [21] have been tried with some success. The ketogenic diet has been unsuccessful [22].

3. West's Syndrome

West's syndrome was first described by West in 1841 [23] and is characterized by epileptic spasms or "*salaam attacks*," hypsarrhythmia on EEG, and developmental delay or regression. The typical onset is between 3 and 12 months of age. The epileptic spasms are clusters of sudden, brief (0.2–2 seconds), diffuse or fragmented, and tonic contractions of axial and limb muscles. This may be accompanied by cry, laughter, or autonomic changes. It may be flexor (most common), extensor, mixed, or subtle. They usually occur in arousal and in alert states [24].

Hypsarrhythmia is the classical interictal EEG finding and is characterized by chaotic background with nearly continuous random asynchronous high-voltage slow waves and spikes arising from multiple foci (Figure 1) [25]. Many variations have been described [26]. These include increased interhemispheric synchronization, consistent voltage asymmetries, consistent focus of abnormal discharge, episodes of generalized/regional or lateralized voltage attenuation (Figure 2), primarily high-voltage bilaterally asynchronous slow wave activity with relatively little epileptiform abnormalities. Both classic and variant hypsarrhythmia have the same prognosis. The variation occurs because of sleep state, etiology, disease course, and treatment.

The EEG becomes fragmented and more synchronized during nonrapid eye movement (NREM) sleep and relatively normalizes during rapid eye movement (REM) sleep. Ictal EEG patterns are variable and may comprise classical electrodecremental pattern, high-voltage generalized slow-wave, or low-amplitude fast activity [24].

The etiology is diverse. West's syndrome has been classically classified into symptomatic (identifiable neurological insult), cryptogenic (probably symptomatic but with no

TABLE 2: EEG features of Ohtahara syndrome and early myoclonic encephalopathy.

Feature of burst-suppression pattern	Ohtahara syndrome	Early myoclonic encephalopathy
Appearance	Usually seen at the onset of the disease	Seen later; most distinct at 1–5 months of age
Disappearance	Within the first 6 months	Persists for longer periods
State in which it presents	Both sleeping and waking states	Exclusively present or enhanced during sleep
Burst-to-burst intervals	Shorter	Longer
Evolution to hypsarrhythmia	Frequent	May be a transient feature

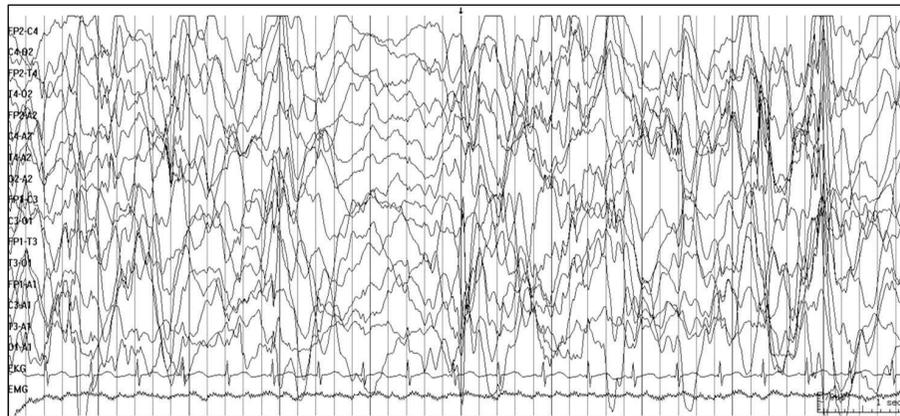
Timebase = 30 mm/s; sensitivity = 7 μ V/mm; high cut = 70 Hz and low cut = 1 Hz

FIGURE 1: EEG findings in classical hypsarrhythmia: the background is chaotic with bursts of bilateral asynchronous high-amplitude slow waves interspersed with spikes followed by electrodecremental response.

known etiology), and idiopathic (normal premorbid development and unknown etiology) forms. The classification as per new ILAE classification [1] is shown in Table 3. Recently, a genetic and biologic classification has been suggested [27]. Thus, a thorough clinical evaluation followed by appropriate neuroimaging and genetic and metabolic work-up is warranted in a child with West's syndrome.

Adrenocorticotrophin hormone (ACTH) is the drug of choice for short-term treatment of epileptic spasms. Low-dose ACTH may be equally effective as high dose ACTH [28]. Oral steroids may also be an alternative, especially in resource-constrained settings [29]. Vigabatrin is a second-line drug except in children with tuberous sclerosis complex where it is the preferred drug over ACTH. Pyridoxine and biotin trial should always be considered in refractory spasms or when clinically indicated. The ketogenic diet has also shown to be beneficial [30–32]. Resective neurosurgery may be warranted in refractory cases with unilateral or focal congenital or early acquired cortical lesions [33]. Total callosotomy may be considered in children with persistent drop attacks [34].

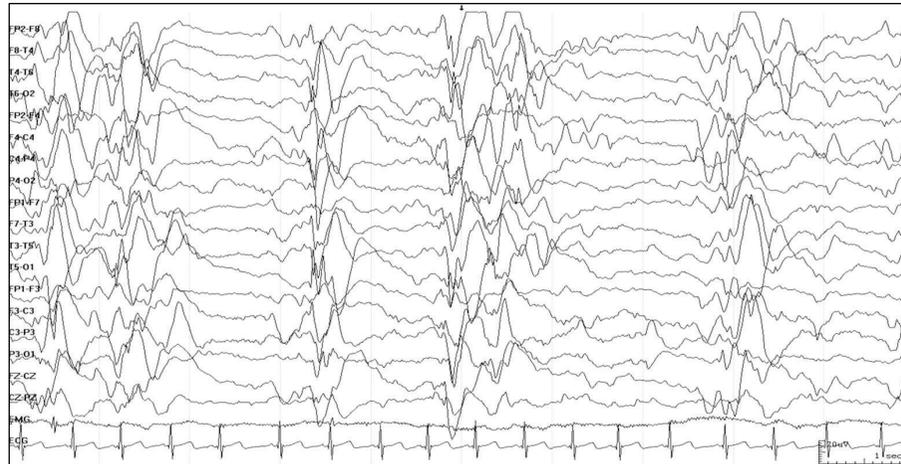
The prognosis is guarded and is governed by the underlying etiology and the treatment. The affected children are left with variable psychomotor retardation, epilepsy, or psychiatric disorders [24].

4. Late Infantile Epileptic Encephalopathy

This entity has been proposed by Nordli et al. [35, 39]. The onset is beyond one year of age with classical *myoclonic-tonic* seizures. The tonic component is longer than the infantile spasms and shorter than that seen in Lennox-Gastaut syndrome. There may be associated myoclonic seizures, epileptic spasms, and atonic seizures. The interictal EEG shows disorganized high-amplitude slow background with multifocal spikes more pronounced during the sleep. The response to the conventional antiepileptic drugs is poor with some response to hormonal therapy and ketogenic diet. The prognosis is guarded.

5. Dravet Syndrome

It was first described by Dravet in 1978 as severe myoclonic epilepsy of infancy (SMEI) [40]. The onset is usually between 5 and 8 months of age with frequent, prolonged febrile unilateral clonic convulsions with alternating pattern in a previously normal child. Nonfebrile seizures may also be present. This stage is followed by emergence of multiple seizure types (myoclonic, atypical absences and complex focal seizures) which frequently progress to status epilepticus and associated severe psychomotor deterioration. The relentless progression



Timebase = 30 mm/s; sensitivity = 7 μ V/mm; high cut = 70 Hz and low cut = 1 Hz

FIGURE 2: EEG findings in hypsarrhythmia (burst-suppression) variant: there are bursts of bilateral asynchronous high-amplitude slow waves interspersed with spikes followed by generalized voltage attenuation.

stops at around 10–12 years of age with decrease in seizure frequency and persisting neurologic sequelae [41].

The interictal EEG is normal initially. In some cases, generalized photoparoxysmal responses and rhythmic theta (4–5 Hz) activity may be seen in centroparietal areas and vertex. Soon, the EEG deteriorates with background slowing, asymmetric paroxysms of generalized polyspike/spike-slow-wave discharges and multifocal epileptiform abnormalities. Photic, pattern, and eye closure sensitivity may be present [24, 42].

The children with borderline SMEI or intractable childhood epilepsy with generalized tonic clonic seizures (ICEGTCS) may lack myoclonic seizures or generalized spike-and-wave activity [43].

Mutations in the SCN1A gene encoding the alpha-1 subunit of the sodium channel are detectable in 70–80% of patients with Dravet syndrome [44]. Other reported mutations include mutations in genes GABARG2 (encoding γ 2 subunit of GABA_A receptor), SCN1B and protocadherin 19 (PCDH19) genes [44, 45].

Seizures are usually refractory. Drugs like carbamazepine, phenytoin, and lamotrigine are contraindicated. Stiripentol in conjunction with clobazam or valproate has recently been licensed for use in Dravet syndrome [46]. Early initiation of ketogenic diet has been advocated [47]. Avoidance of hyperthermia and stress is critical.

6. Lennox-Gastaut Syndrome

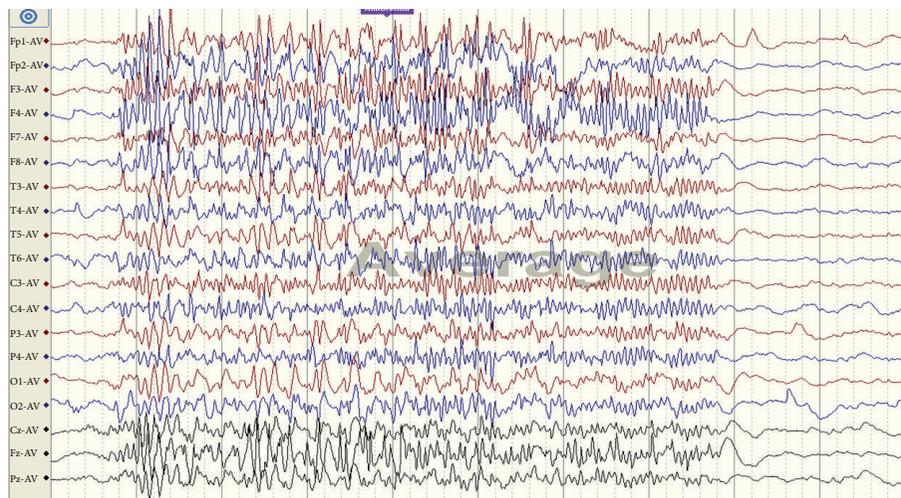
Lennox-Gastaut syndrome (LGS) is a severe form of epileptic encephalopathy with onset between 1 and 8 years of age, mainly between 2 and 5 years of age. It is characterized by intractable polymorphic seizures including tonic, atypical absence, atonic and myoclonic seizures. “Drop attacks,” tonic or atonic, seen in 50% children, are a nightmare for the family and frequently causes injuries [48]. Two-thirds of the patients may have nonconvulsive status epilepticus [49].

Twenty percent of children have history of epileptic spasms [50]. The cognitive deterioration/stagnation is common and fluctuates with the seizure frequency.

The pathognomonic interictal EEG finding is bilateral, synchronous, and slow spike-and-wave discharges (1.5–2.5 Hz) with frontocentral voltage dominance with abnormal background. Paroxysmal fast activity (Figure 3) of bilateral synchronized bursts of 10–20 Hz frontally dominant activity lasting for few seconds is also seen. It may be an ictal correlate of a tonic seizure, especially if prolonged. Focal discharges are common. NREM sleep dramatically enhances all the paroxysmal abnormalities. Other abnormalities include sleep fragmentation of the slow spike-and-wave bursts, polyspike discharges, pseudoperiodic appearance, diffuse voltage attenuation, focal and multifocal spikes and sharp waves, diffuse background slowing, abnormal sleep architecture with reduced or absent REM sleep, and severe background disorganization with a quasihypsarrhythmic pattern in some patients [51].

The etiology of Lennox-Gastaut syndrome is heterogeneous and similar to epileptic spasms (see Table 2). One-third of children have no antecedent history or evidence of cerebral pathology [24].

Lowering the frequency of serious/disabling seizures like drop attacks, minimizing daytime seizures, and minimizing adverse effects of antiepileptic drugs may be a realistic management goal in children with Lennox-Gastaut syndrome. Valproate and clobazam are the preferred drugs. Levetiracetam, rufinamide, lamotrigine, topiramate, and zonisamide are the second-line drugs. Steroids and intravenous immunoglobulins may be indicated during periods of increased seizure frequency or status epilepticus [24, 36, 52–54]. The ketogenic diet is a useful alternative and may be used early in the management [55]. Nonpharmacological therapies also include vagus nerve stimulation [56, 57], electrical stimulation of centromedian thalamic nuclei [58], and complete or partial callosotomy.



Timebase = 30 mm/s; sensitivity = 7 μ V/mm; high cut = 70 Hz and low cut = 1 Hz

FIGURE 3: Generalized paroxysmal fast activity: there are bursts of bilateral synchronous high-frequency low-amplitude activity lasting for 7 seconds with sudden onset and resolution.

TABLE 3: Classification of West syndrome.

Structural/metabolic

Pre-, peri-, and postnatal cerebral ischemia

Cerebral malformations

Neuro-infections sequelae

Neurocutaneous syndromes: tuberous sclerosis, incontinentia pigmenti

Hypothalamic hamartoma

Inborn errors of metabolism: biotinidase deficiency and other organic aciduria, phenylketonuria, mitochondrial disorders, Menkes disease, nonketotic hyperglycinemia, and antitruin deficiency

Genetic

Genetic: CDKL-5, MeCP 2, ARX, STXBP-1, SPTAN1, and PLC- β 1

Chromosomal disorders: down syndrome, 1p36 deletion, and Pallister-Killian syndrome

Unknown

The prognosis is guarded with more than 80% children having persistent epilepsy and severe neurocognitive sequelae. Normal development prior to onset of seizures, normal neuroimaging, near normal background on EEG, faster generalized spike-wave-activity, and activation of generalized spike-wave-activity by hyperventilation may predict favourable outcome [24].

6.1. Case Study 1. A 7-year-old boy, a known case of Lennox-Gastaut syndrome secondary to perinatal asphyxia, presented with flurry of seizures (tonic and atypical absences). He was on 40 mg/kg/day valproate, 3 mg/kg/day lamotrigine, and 40 mg/kg/day levetiracetam. He had partial response to modified Atkins diet in the past but had discontinued the diet due to poor compliance. In the emergency room, he was administered intravenous diazepam. After 10 minutes of diazepam administration, there was marked increase in the frequency of prolonged tonic spasms with cardiorespiratory compromise. The EEG showed frequent bursts of prolonged

generalized paroxysmal fast activity with diffuse delta waves in between.

Learning Point. Intravenous benzodiazepines may result in paradoxical precipitation of tonic status in patients with LGS and hence should be used with caution in such patients.

7. Epileptic Encephalopathy with CSWS Including LKS

7.1. Landau-Kleffner Syndrome. This syndrome was first described by Landau and Kleffner [59]. The peak onset is between 5 and 7 years of age with verbal auditory agnosia in a previously normal child. The language function continues to deteriorate and the course can be gradually progressive or fluctuating. All types of aphasia can occur. Some children may become mute. Mild behavioral abnormalities are common. Seizures occur in 75% children. They are infrequent and usually nocturnal. Semiologies may include generalized

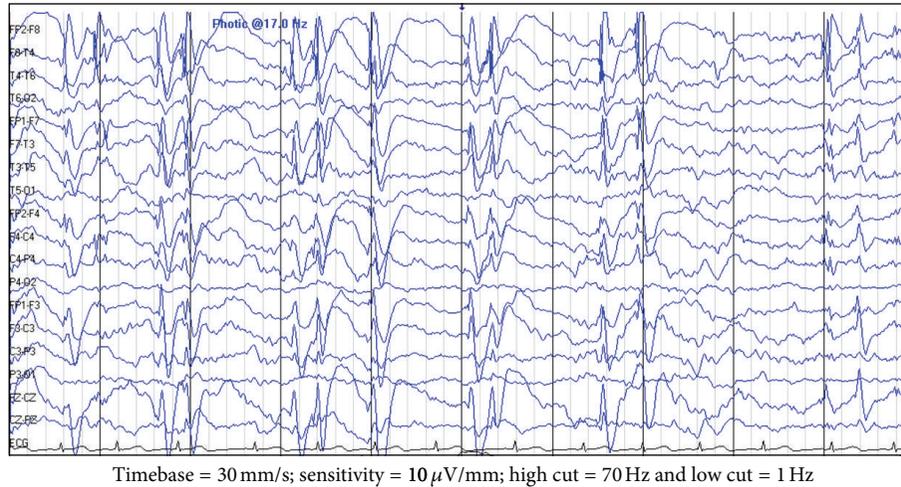


FIGURE 4: EEG findings in epileptic encephalopathy with continuous spike-and-wave during sleep: there is nearly continuous 1-2 Hz bilateral synchronized spike wave discharges during the sleep record.

tonic-clonic, focal motor, atypical absences, head drops, and subtle seizures.

The EEG is characterized by mainly posterior temporal (vertical dipole) epileptiform discharges. These discharges can be multifocal, unilateral, or bilateral and markedly activated by NREM sleep [60]. They may continue into the REM sleep, a differentiating feature from epilepsy with CSWS [24].

The main aim of the treatment is to reduce or eliminate the epileptiform discharges. Valproate, benzodiazepines, levetiracetam, ethosuximide, and sulthiame are the most effective drugs [61]. Poor responders may be treated with ACTH or prednisolone. Prolonged oral steroids may be required as relapses are common on withdrawal. Steroids may be administered early in the course of the illness. The role of intravenous immunoglobulins is unclear [62]. Favourable results have been reported with ketogenic diet in small studies [63]. For medically refractory cases, multiple subpial transection including the Wernicke area has been used with some success especially if electrophysiologic lateralization can be demonstrated [64, 65].

The seizures and epileptiform abnormalities remit by the age of 15 years. The majority of children are left with permanent language dysfunction. The earlier the onset of LKS, the worse the prognosis with regard to the language function.

7.2. Epileptic Encephalopathy with Continuous Spike-and-Wave during Sleep. The onset of this epileptic encephalopathy is between 2 months and 12 years of age with a peak at 4–7 years of age. The preceding neurodevelopment is normal in 50% children. Seizures are the presenting symptom in 80% children and neuropsychological deterioration in the rest. The children present with infrequent, nocturnal seizures (simple or complex focal, generalized tonic-clonic or myoclonic seizures). The interictal EEG during wakefulness shows focal or multifocal epileptiform discharges with

accentuation during NREM sleep [66]. The localization of discharges can be frontocentral, frontotemporal, centrottemporal, or frontal [67].

After 1-2 years, there is increase in seizure frequency with emergence of new seizure types (absence or atonic seizures, negative myoclonus). This is associated with the appearance or deterioration of neurocognitive status. The symptoms depend on the predominant site of epileptiform discharges. Mainly, frontal CSWS affects the cognitive and executive functioning, and temporal-predominant-CSWS affects the linguistic function [24]. The interictal EEG during wakefulness shows more pronounced abnormalities. During NREM sleep, EEG shows continuous/nearly continuous, bilateral, 1.5–3 Hz, frontally predominant, and spike-wave-discharges (CSWS) which may be asymmetric or focal (Figure 4). They are also known as electrical status epilepticus during sleep (ESES) [68]. The spike wave index (SWI), a measure of the frequency of spiking in the EEG tracing, is usually more than 85%. EEG during REM sleep shows disappearance of ESES pattern.

This stage is followed by clinicoelectroencephalographic remission, usually 2–7 years after the onset. The majority of the children, however, are left with residual moderate-to-severe neurocognitive deficits.

The etiology is unknown. Abnormal neuroimaging is seen in 30–59% cases [66, 69, 70] and may include cerebral atrophy, perinatal vascular insults, and cerebral malformations. The evolution from benign childhood focal epilepsies to ESES is also reported [71].

Early initiation of steroids/ACTH is usually recommended. Intravenous immunoglobulins also have shown promising results [62]. The antiepileptic drugs, used for LKS, are usually effective. Limited response has been demonstrated with ketogenic diet [72]. Epilepsy surgery may be considered in medically refractory cases with focal lesions on neuroimaging or focal EEG findings. Hemispherectomy and focal resective epilepsy surgery may be beneficial for children with ESES

with structural etiology [73]. With the encouraging results in the children with LKS, multiple subpial transections may be beneficial for the cognitive impairment and behavioural problems seen in epileptic encephalopathy with continuous spike-and-wave during sleep [74].

8. Atypical Benign Partial Epilepsy of Childhood

This syndrome is also known as *LGS transient* or *pseudo-Lennox syndrome*. The onset is at 2–6 years of age in previously normal child with clusters of atonic and nocturnal focal “Rolandic-like” seizures. Variable cognitive involvement may be seen during periods of active seizures. The interictal EEG shows centroparietal spikes (horizontal dipole) and generalized spike-and-wave discharges. The centroparietal spikes may be seen in trains and may be associated with frontocentral and centroparietal spikes [75]. The interictal magnetoencephalography has localized the clusters of spike sources around the Rolandic-sylvian fissures [76]. This is in contrast to the findings in Rolandic epilepsy where the clusters of spike sources have been localized along the Rolandic region with orientation vertical to the central sulcus [77].

Similar condition may be induced by lamotrigine or carbamazepine in few children with rolandic and Panayiotopoulos syndromes [78, 79]. Some authors consider it as a mild form of epilepsy with continuous spike-and-wave during sleep (CSWS) [36]. It is still debatable whether this entity is a separate clinical entity or part of a continuum related to rolandic epilepsy [80].

The features like an earlier age of onset, frequent atonic seizures, more frequent and prolonged focal seizures, and prominent associated behavioural problems may differentiate this entity from rolandic epilepsy [75].

Seizures are usually refractory to conventional treatment but usually remit by adolescence. The long-term neurocognitive outcome is usually favourable [24, 48].

8.1. Case Study 2. A 5-year-old, developmentally normal boy presented with multiple episodes of atypical absences, atonic seizures, and nocturnal focal seizures for the last 3 months. He had mild behavioural complaints. The examination was unremarkable. A diagnosis of possible LGS was made, and the boy was initiated on valproate and clonazepam. An interictal EEG revealed normal background with frequent centro-temporal spikes. The diagnosis was revised to atypical benign partial epilepsy in view of the clinic EEG features.

Learning Point. LGS may be a clinical differential of atypical benign partial epilepsy. However, the lack of tonic seizures or developmental delay and normal awake EEG background activity differentiates atypical benign partial epilepsy from LGS.

9. Conclusions

Epileptic encephalopathies start at an early age and manifest with seizures, which are usually intractable, aggressive EEG

paroxysmal abnormalities and severe neurocognitive deficits. The clinicoelectroencephalographic features are age related and depend on the structural and functional maturity of the brain. Their recognition and appropriate management are critical.

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Review Article

Metabolic Causes of Epileptic Encephalopathy

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Received 22 February 2013; Accepted 16 April 2013

Academic Editor: Giannennaro Coppola

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Epileptic encephalopathy can be induced by inborn metabolic defects that may be rare individually but in aggregate represent a substantial clinical portion of child neurology. These may present with various epilepsy phenotypes including refractory neonatal seizures, early myoclonic encephalopathy, early infantile epileptic encephalopathy, infantile spasms, and generalized epilepsies which in particular include myoclonic seizures. There are varying degrees of treatability, but the outcome if untreated can often be catastrophic. The importance of early recognition cannot be overemphasized. This paper provides an overview of inborn metabolic errors associated with persistent brain disturbances due to highly active clinical or electrographic ictal activity. Selected diseases are organized by the defective molecule or mechanism and categorized as small molecule disorders (involving amino and organic acids, fatty acids, neurotransmitters, urea cycle, vitamers and cofactors, and mitochondria) and large molecule disorders (including lysosomal storage disorders, peroxisomal disorders, glycosylation disorders, and leukodystrophies). Details including key clinical features, salient electrophysiological and neuroradiological findings, biochemical findings, and treatment options are summarized for prominent disorders in each category.

1. Introduction

Inherited metabolic epilepsies are disorders that, while individually rare, are in aggregate a substantial clinical portion of child neurology, as well as a complex field of knowledge for physicians, investigators, and students to tackle. A subset of these disorders can lead to the development of epileptic encephalopathy, that is, a brain disturbance due to highly active clinical or electrographic ictal activity. The epileptologist may view these from the viewpoint of syndromic phenotypes such as early myoclonic encephalopathy, early infantile epileptic encephalopathy, infantile spasms, and myoclonic epilepsies. They have various degrees of treatability at present, with some requiring prompt diagnosis and intervention to avoid otherwise catastrophic outcomes. Careful consideration of metabolic disorders in patients presenting with epileptic encephalopathy is therefore warranted, and to this end, we hope a review may be helpful.

This paper provides an overview of inborn metabolic errors associated with epileptic encephalopathy, summarizing key clinical features and underlying biochemistry, salient electrophysiological and neuroradiological findings,

and primary treatment options where appropriate. Examples of specific disorders are discussed, with full listings of the multiple enzyme defects and diseases in particular categories presented in tables. The range of inherited metabolic disorders has been organized by the category of molecules or the biochemical process involved: for example, small molecule disorders include dysfunction involving amino, organic, or fatty acids, neurotransmitters, the urea cycle, vitamers and cofactors, and disorders of the mitochondria. Large molecule diseases cover defects in glycosylation, lysosomal and peroxisomal function, and leukodystrophies.

2. Small Molecule Disorders

2.1. Amino and Organic Acid Disorders. Amino acidopathies and organic acidemias, resulting from disorders in amino or fatty acid catabolism, present with seizures and cognitive, behavioral, or motor disturbances resulting from the accumulation of toxic intermediaries, or possible structural damage [1]. Some may induce an epileptic encephalopathy. Seizure types and EEG findings vary, though myoclonic epilepsies predominate, and diffuse background slowing is

a common EEG finding. More typical EEG findings in metabolic encephalopathies are burst suppression, hypsarrhythmia, and generalized spike-wave discharges. Table 1 lists the protean disorders along with the enzyme defect and metabolites detected on diagnostic studies.

2.1.1. Methylmalonic Acidemia and Cobalamin Deficiencies.

The finding of elevated methylmalonic acid can be caused by a number of distinct disorders including defects in the vitamin B12-related enzymes cobalamin A, B, C, or D and methylmalonyl CoA mutase (MUT). Early myoclonic encephalopathy, as well as other epilepsies and epileptic encephalopathies, has been associated with this finding. The most common methylmalonic acidemia involving cobalamin is cobalamin C deficiency (Figure 1); individuals may present in infancy or early childhood with seizures and progressive encephalopathy. Patients presenting with status epilepticus have also been reported. Treatment with hydroxycobalamin is effective, including prenatal supplementation in affected families but may not reverse existing neurological injury in delayed diagnoses [3].

2.1.2. *Propionic Acidemia.* Propionic acidemia (PA) is caused by defects in the enzyme propionyl CoA carboxylase and commonly presents with lethargy, vomiting, metabolic acidemia, and sometimes hyperammonemia [4]. A severe presentation of this disease in infancy with infantile spasms and hypsarrhythmia is reported [5]; myoclonic and generalized seizures are common in early childhood and infancy and typically evolve into mild generalized and absence seizures later in life [6].

2.1.3. *Ethylmalonic Acidemia.* Ethylmalonic encephalopathy is usually lethal in infancy or early childhood and has a severe presentation including seizures, brain structural malformations, neurodevelopmental regression, pyramidal and extrapyramidal symptoms, chronic diarrhea, and dermatological findings including petechiae and acrocyanosis. MRI has shown frontotemporal atrophy, enlargement of the subarachnoid spaces, and basal ganglia T2-weighted hyperintensities [7]. EEGs may worsen over time, with multifocal spike and slow waves and background disorganization [8].

2.1.4. *3-Hydroxy-3-Methylglutaric Acidemia.* When untreated, dysfunction of the enzyme 3-hydroxy-3-methylglutaryl CoA lyase (which cleaves 3-hydroxy-3-methylglutaryl CoA into acetyl CoA and acetoacetate) leads to metabolic acidosis with absent ketone production, lactic acidemia, hypoglycemia hepatomegaly, and lethargy, possibly progressing to coma and death. Seizures are linked in most cases to lactic acidemia or hypoglycemia and are associated with multifocal spike-wave discharges on EEG [8]. Some presentations show particular association with white matter lesions, dysmyelination, and cerebral atrophy on neuroimaging [9, 10].

2.1.5. *Glutaric Acidemia.* Dysfunction of the enzyme glutaryl CoA dehydrogenase prevents the metabolism of tryptophan, hydroxylysine, and lysine, resulting in increased

urine glutaric acid metabolites. This is a cerebral organic acidopathy, with predominantly neurological symptoms featuring macrocephaly, increased subarachnoid spaces, and progressive dystonia and athetosis with striatal injury [11]. Seizures can be a presenting sign and are seen during acute encephalopathic events [12, 13]. EEGs show background slowing with generalized spike-and-wave and mixed multifocal discharges [8, 14]. Therapy using a low-protein diet (especially low lysine and tryptophan), carnitine supplementation, and aggressive emergency management can significantly improve the outcomes. The antiepileptic valproate should be avoided, however, because it is believed to affect acetyl CoA/CoA ratios and may exacerbate metabolic imbalance [13].

2.1.6. *3-Methylglutaconic Acidurias.* Five subtypes of 3-methylglutaconic aciduria (MGA) have been categorized (Table 1); all are cerebral organic acidopathies resulting from defects in the leucine catabolic pathway. Neurological and developmental symptoms are central in all five types although seizures are prominent mainly in Type I. Patients with Type I MGA present with leukoencephalopathy and epileptic encephalopathy with psychosis and depression, in addition to ataxia, optic atrophy, and sensorineural hearing loss. These are often accompanied by systemic issues including cardiomyopathy, liver and exocrine pancreatic dysfunction, and bone marrow failure [15]. EEGs show diffuse slowing and white matter lesions can be seen on MRI, usually in a supratentorial location [8, 15, 16].

2.1.7. *Canavan Disease.* Canavan disease is primarily a disease of demyelination. It is thought to be caused by brain acetate deficiency resulting from a defect of N-acetylaspartic acid (NAA) catabolism [17]. Accumulation of NAA, a compound thought to be responsible for maintaining cerebral fluid balance, can lead to cerebral edema and neurological injury. Presentation of Canavan disease includes progressive epileptic encephalopathy with developmental delay, macrocephaly, leukodystrophy, and optic atrophy [18, 19]. Seizures often begin in the second year of life, and treatment is primarily supportive, including antiepileptic medications.

2.1.8. *D- and L-2-Hydroxyglutaric Aciduria.* D-2-Hydroxyglutaric aciduria results from the loss of enzyme function in either D-2-hydroglutaric dehydrogenase or hydroxyacid-oxoacid transhydrogenase, which metabolizes GHB (gamma-hydroxybutyrate). Though presentations vary, severe cases manifest in the neonatorum with encephalopathy, intractable epilepsy, and cardiomyopathy. Seizures are present in almost all cases, and MRI findings have included signal alterations in the basal ganglia and diencephalon, as well as agenesis of the corpus callosum.

The enantiomer, L-2-Hydroxyglutaric aciduria, is a disorder of alpha ketoglutarate synthesis. It presents with neurodevelopmental delay, generalized seizures, and progressive ataxia. Multifocal spike-waves and burst suppression can be seen on EEGs [20, 21], and characteristic MRI findings include cerebellar atrophy, subcortical white matter loss, and

TABLE 1: Amino acidemias and organic acidopathies.

Disorder	Defective enzyme	Diagnostic metabolites
Propionic acidemia (PA)	Propionyl CoA carboxylase	Propionylcarnitine (C3; P)* Methylcitrate (U)* 3-Hydroxypropionic acid (U)
Methylmalonic acidemia (MMA)	Methylmalonic mutase Cobalamin A Cobalamin B	Methylmalonic acid (P, U) Propionylcarnitine (C3; P) Methylcitrate (U) 3-Hydroxypropionic acid Methylmalonic acid (P, U)
Methylmalonic acidemia with homocysteinuria, cobalamin C/D	Cobalamin C Cobalamin D	Propionylcarnitine (C3; P) Methylcitrate (U) Total homocysteine (P) 3-Hydroxypropionic acid (U)
Isovaleric acidemia (IVA)	Isovaleryl dehydrogenase	Isovaleric acid (U) Isovalerylcarnitine (C5; P)
3-Methylcrotonylglycinuria (3MCC)	3-Methylcrotonyl CoA carboxylase	3-Hydroxyisovaleric acid (U) 3-Methylcrotonylglycine (U) Hydroxyisovalerylcarnitine (C5OH; P)
3-Hydroxy-3-methylglutaryl CoA lyase deficiency	3-Hydroxy-3-methylglutaryl CoA Lyase	Hydroxyisovalerylcarnitine (C5OH; P) 3-Hydroxy-3-methylglutaric acid (U) 3-Methylglutaconic acid (U)
Malonic aciduria	Malonyl CoA decarboxylase	Malonate (U)
2-Methyl-3-hydroxybutyryl CoA dehydrogenase deficiency	2-Methyl-3-hydroxybutyryl CoA dehydrogenase	2-Methyl-3-hydroxybutyrate (U) Tiglylglycine (U) C4 C5
Ethylmalonic encephalopathy	Branched chain Keto-dehydrogenase	Ethylmalonic acid (U) Methylsuccinic acid C4–C6 acylglycines (P) C5:1 (P)
Beta-ketothiolase deficiency	3-Methyl acetoacetate thiolase	2-Methyl-3-hydroxybutyrate (U) Tiglylglycine (U) 2-Methyacetacetate (U) Propionylcarnitine (C3; P) Hydroxyisovalerylcarnitine (C5OH; P)
Biotinidase deficiency and Holocarboxylase synthetase deficiency	Biotinidase Holocarboxylase synthetase	Biotinidase enzyme deficiency (P) Lactate (P, U) 3-Methylcrotonylglycine (U) Methylcitrate (U) 3-Hydroxypropionic acid (U)
2-Methyl butyryl CoA dehydrogenase	2-Methyl butyryl CoA dehydrogenase	2-Methylglycine (U) Isovalerylcarnitine (C5; P) Glutaric acid (U)
Glutaric acidemia I	Glutaryl CoA dehydrogenase	3-Hydroxyglutaric acid (U) Glutaryl carnitine (C5-DC; P)
3-Methylglutaconic acidurias	3-Methylglutaconyl CoA hydratase (Type I) Barth (Type II) Costeff (Type III) Type IV Type V	3-Methylglutaconic acid (U) Hydroxy-isovalerylcarnitine (P)
Canavan disease	Aspartoacylase	N-Acetylaspartic Acid (U)
L-2-Hydroxyglutaric aciduria	L-2-Hydroxyglutarate dehydrogenase	L-2-Hydroxyglutaric Acid (U) Lysine (CSF)
D-2-Hydroxyglutaric aciduria	D-2-Hydroxyglutarate dehydrogenase Hydroxy-oxoacid transhydrogenase	D-2-Hydroxyglutaric acid (U)
4-Hydroxybutyric Aciduria	Succinate semialdehyde dehydrogenase	Gamma-hydroxybutric acid (U)
Fumaric aciduria	Fumarate hydratase	Fumarate (U)

TABLE I: Continued.

Disorder	Defective enzyme	Diagnostic metabolites
Maple syrup urine disease (MSUD)	Branched chain Keto-dehydrogenase	Leucine (P) Alloisoleucine (P) Dicarboxylic acids (U)
Dihydrolipoamide dehydrogenase	MSUD III	Leucine (P) Alloisoleucine (P) Dicarboxylic acids (U) Lactic acid (P, U)
Phenylketonuria (PKU)	Phenylalanine hydratase (PAH)	Phenylalanine (P) Low tyrosine (P)

(P): plasma, (U): urine. Adapted from Pearl [2].

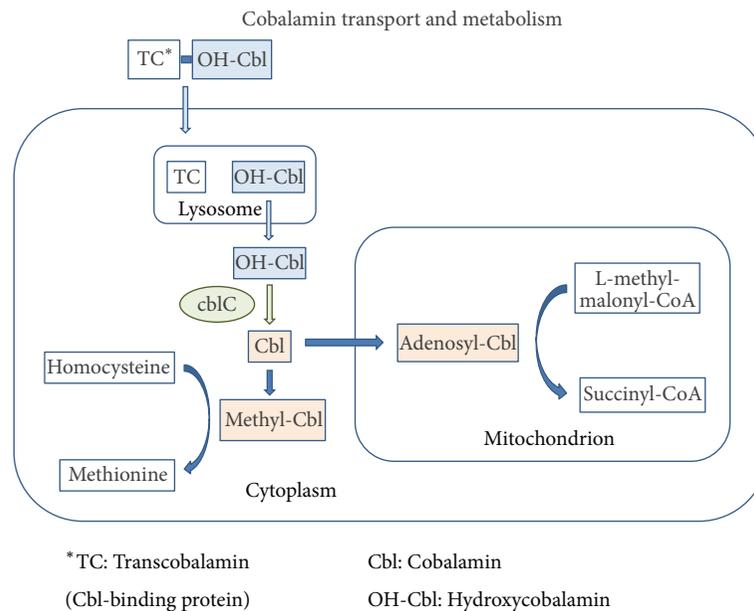


FIGURE 1: Cobalamin transport and metabolism. Hydroxycobalamin (OH-Cbl) enters the cell bound to transcobalamin (TC), a binding protein. The hydroxycobalamin-transcobalamin complex is broken down inside the lysosome, and the enzyme cobalamin C (CblC) removes the hydroxyl group to generate free cobalamin (Cbl), which is synthesized via additional steps into methyl- and adenosyl-cobalamin.

symmetric T2-weighted hyperintensities in the cerebellar dentate nuclei, globus pallidi, and thalami.

2.1.9. Fumaric Aciduria. Seizures are a prominent feature in fumaric aciduria, due to a defect in the conversion of fumarate to malate. The disorder can present prenatally with polyhydramnios and cerebral ventriculomegaly and manifests in infancy and early childhood with epilepsy, serious neurodevelopmental delay, macrocephaly, opisthotonus, and vision loss. Status epilepticus is well reported. Diffuse polymicrogyria, decreased white matter, large ventricles, and open opercula are seen on neuroimaging [22].

2.1.10. Maple Syrup Urine Disease and Dihydrolipoamide Dehydrogenase Deficiency. Dysfunction of the enzyme branched-chain 2-keto dehydrogenase (BCKD) in maple syrup urine disease (MSUD) prevents normal degradation of the branched-chain amino acids leucine, isoleucine, and valine, leading to toxic accumulation of metabolites.

Neurological symptoms present in infancy and include cerebral edema, seizures, lethargy, vomiting, and “bicycling” movements [23]. Seizures are related to the cerebral edema and hyperlycinemia, and these symptoms can progress to coma and death. The EEG may show a characteristic comb-like rhythm (Figure 2). Treatment focuses on removing leucine from blood with dialysis or by reversing catabolism through feeding.

Dihydrolipoamide dehydrogenase deficiency, sometimes referred to as MSUD Type III, is due to a defect in a subunit of BCKD, as well as 3 other essential enzymes. The disorder leads to metabolic acidosis and neurological injury, and patients can present with hypoglycemia, absent ketones, elevated liver transaminases, and seizures [24]. The disorder is often fatal at an early age, representing multienzyme failure.

2.2. Disorders of GABA Metabolism. Seizures are an important problem in disorders of the synthesis or degradation of gamma-aminobutyric acid (GABA), the brain’s primary inhibitory neurotransmitter. The most common of

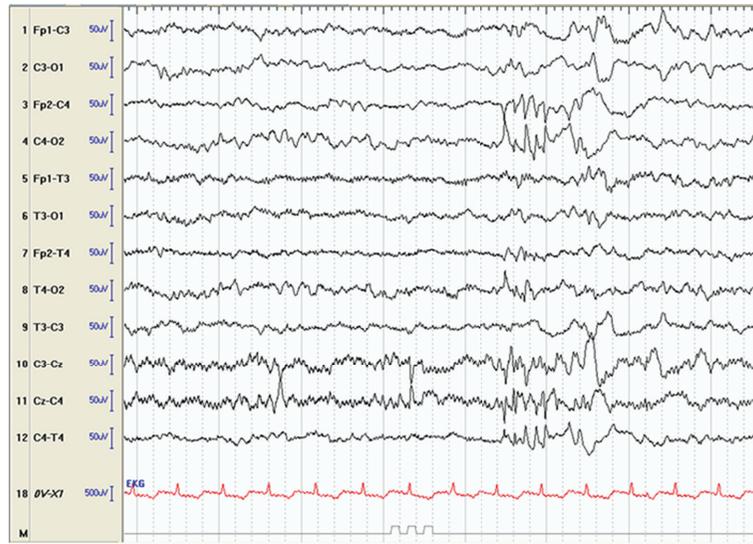


FIGURE 2: EEG of 4-day-old infant with MSUD shows comb-like rhythm over the right central (C4) area. (sensitivity 7 mcv/mm, HFF 70 Hz, time constant 0.5 sec, 8 sec epoch). Pearl [2].

these is succinic semialdehyde dehydrogenase (SSADH) deficiency, though GABA-transaminase deficiency—while extremely rare—features a more severe, progressive epileptic encephalopathy. Both are inherited metabolic disorders affecting GABA degradation.

2.2.1. Succinic Semialdehyde Dehydrogenase Deficiency (4-Hydroxybutyric Aciduria). Deficiency of the enzyme succinic semialdehyde dehydrogenase (SSADH) results in increased systemic and CSF levels of GABA and its catabolite, 4-hydroxybutyric acid (GHB). Patients present with neurodevelopmental delay, expressive language impairment, hypotonia, hyporeflexia, ataxia, and behavioral disorders that commonly include obsessive compulsive and attention deficit hyperactivity disorders. Over 50% of individuals with SSADH deficiency will develop seizures, most commonly tonic-clonic and atypical absence seizures [25]. Recurring status epilepticus and sudden unexpected death in epilepsy patients (SUDEP) have been reported, the latter associated with escalating seizure frequency and severity [26]. MRIs show increased T2-weighted signals in the globus pallidus, cerebellar dentate nucleus and subthalamic nucleus, and variably cerebral and cerebellar atrophy [27]. EEGs typically show generalized spike-wave activity although some may have partial features and variable hemispheric lateralization (Figure 3). Treatment is currently limited to antiepileptic and behavioral medications. While valproate is generally avoided due to its ability to inhibit any residual enzymatic activity, its use has been associated with improvement in some patients with challenging epilepsy including epileptic encephalopathy.

2.3. Fatty Acid Oxidation Disorders. Severe seizures can be a presenting sign of defects in fatty acid beta-oxidation, a biochemical process that produces alternatives source of acetyl-CoA and ketone bodies for energy. Fatty acid oxidation

(FAO) disorders (Table 2) are a large category of diseases that particularly endanger the CNS and other organ systems that have high energy demands. Metabolic decompensation can be triggered by physiological stressors such as fasting, fever, or physical exertion, and symptoms can appear at any age. Acute crises resemble Reye syndrome, with cardiomyopathy and arrhythmia, as well as rhabdomyolysis and hypoketotic hypoglycemia [28, 29].

Blood and urine laboratory tests are informative towards a diagnosis, particularly if done while the patient is symptomatic. Treatment is dependent on clinical presentation and include avoidance of fasting with frequent low-fat and carbohydrate-rich intake for nonsymptomatic patients and moderation of physical stress in combination with medium-chain triglyceride (MCT) supplementation for patients symptomatic with myopathy. Patients in metabolic crisis require close management in an inpatient setting, with immediate reversal of the catabolism [30, 31].

2.4. Mitochondrial Diseases. Epilepsy is a common secondary feature of mitochondrial disease, and disorders in this category (Table 3) have been associated with severe epileptic encephalopathy. Seizures can be a logical consequence of mitochondrial dysfunction: deficient energy generation disrupts the active maintenance of neuronal membrane potential, and seizure-induced cellular hyperactivity adds further oxidative stress to already deficient ATP generation. Up to 60% of patients with mitochondrial disease develop seizures, and many of these can be refractory to treatment [32]. Myoclonic epilepsies are the most commonly reported, but almost all seizure types have been seen, and individual patients can often show multiple types.

2.4.1. POLG1 Disease. Mutations in the gene *POLG1*, which facilitates mitochondrial DNA replication, have been linked

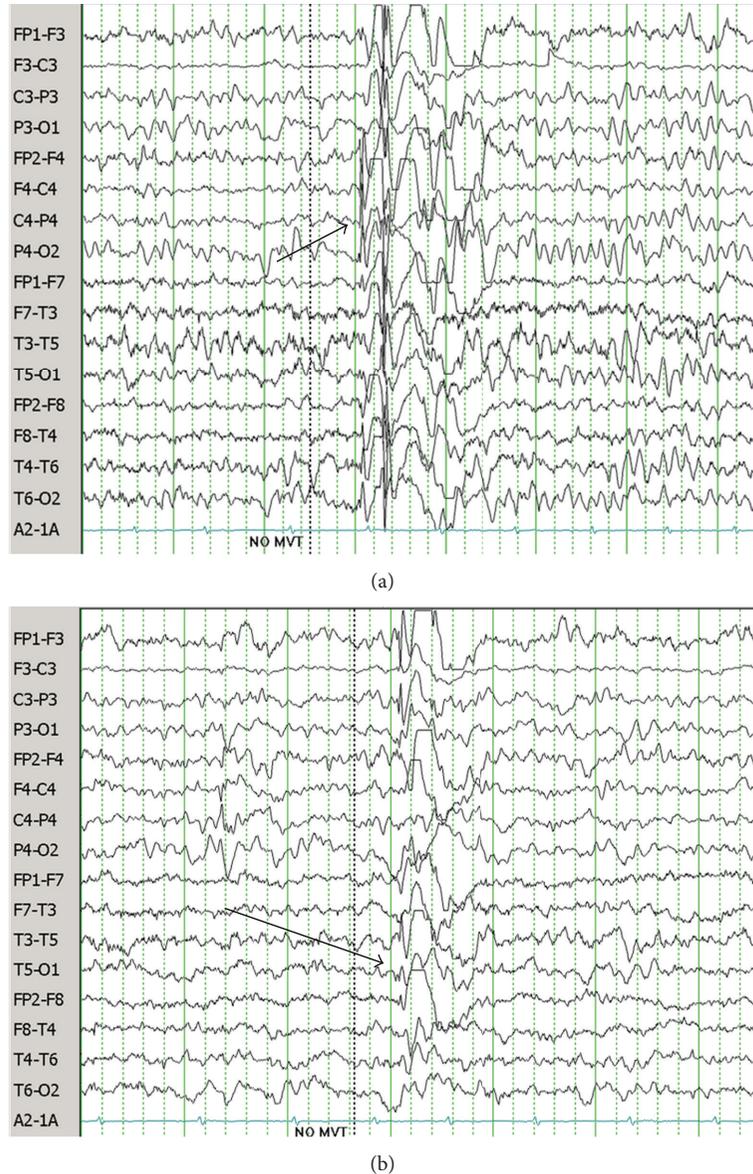


FIGURE 3: (a) EEG of 3-year-old female with SSADH deficiency. Note diffuse spike-wave paroxysm with lead-in over right hemisphere. (b) Same recording as top, showing left-sided spike-wave paroxysm. Pearl [2].

to a range of disease phenotypes, the most prominent being Alpers' disease [33] (Figure 4). Alpers-Huttenlocher disease is a rapidly progressive encephalopathy, causing intractable epilepsy and diffuse neuronal degeneration. Partial complex and myoclonic seizures are most common, although the disorder can evolve to include multiple seizure types [34]. The use of valproate is contraindicated; it has been associated with liver failure in patients with POLG1 mutations, as well as epilepsia partialis continua.

A syndrome of myoclonic epilepsy myopathy sensory ataxia (MEMSA) has also been seen in patients with mutations in POLG1. Seizures, usually focal and often refractory, begin in young adulthood, though other symptoms including sensory neuropathy and cerebellar ataxia may occur in

adolescence. Over time, individuals develop cognitive decline and myopathy [35].

2.4.2. Myoclonic Epilepsy with Ragged Red Fibers (MERRF). Myoclonic epilepsy with ragged red fibers (referring to the appearance of affected muscle cells) is a progressive epilepsy syndrome associated with prominent myoclonus, cognitive decline, optic atrophy, hearing loss, and myopathy [36]. It is associated with mtDNA mutations, and symptoms usually become noticeable in adolescence or young adulthood [37]. EEG findings include focal discharges, atypical spike- or sharp- and slow-wave discharges, and suppression of this activity during sleep [38].

TABLE 2: Fatty acid oxidation disorders and biochemical characteristics.

Disorder	Biochemical characteristics
Carnitine uptake defect (CUD) (Primary/systemic carnitine deficiency, carnitine transporter OCTN2 deficiency)	↓↓↓ Carnitine (P)
Carnitine palmitoyltransferase I deficiency (CPT 1A)	↑ Ammonia (P) ↑ Liver enzymes (ALT, AST)
Carnitine palmitoyltransferase II deficiency (CPT II) (i) lethal neonatal (ii) infantile (iii) myopathic	↑ C12–C18 acylcarnitines (P) ↑ Ammonia (P) ↑ Liver enzymes (ALT, AST)
Carnitine-acylcarnitine translocase deficiency (CACT)	↑ Creatine kinase (P) ↑ Long chain acylcarnitines (P) ↓ Free carnitine (P)
Mitochondrial trifunction protein deficiency (TFP) (i) Isolated long chain Acyl-CoA Dehydrogenase deficiency (LCHAD)	Hypoketotic hypoglycemia
Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)	Hypoglycemia (ketotic or nonketotic)
Medium chain acyl-CoA dehydrogenase deficiency (MCAD)	Hypoketotic hypoglycemia
Medium chain 3-ketoacyl-CoA thiolase deficiency (MCKAT)	Ketotic lactic aciduria C6–C12 dicarboxylic aciduria
Short chain acyl-CoA dehydrogenase deficiency (SCAD)	↑ Ethylmalonic acid (U) Hyperinsulinemic hypoglycemia
Medium/short chain acyl-CoA dehydrogenase deficiency (M/SCHAD)	↑ 3-Hydroxybutylcarnitine ↑ 3-Hydroxy butyric acid (U) ↑ 3-Hydroxy glutaric acid (U)
Glutaric acidemia Type II	Hypoglycemia Metabolic acidosis
2,4-Dienoyl-CoA reductase deficiency	2-Trans,4-Cis-decadienylcarnitine (P, U)
Acyl-CoA dehydrogenase 9 deficiency (ACAD9)	Persistent lactic acidosis

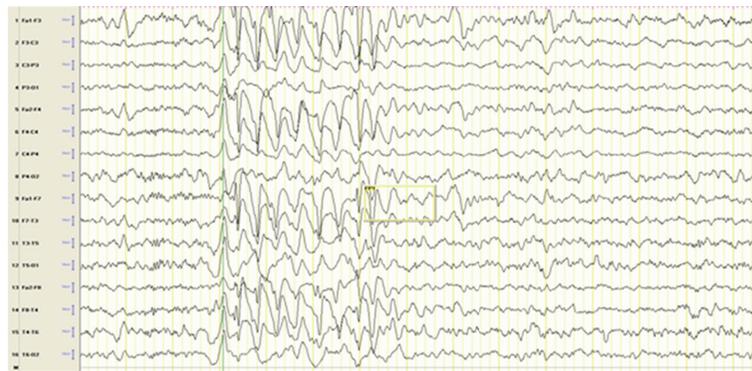


FIGURE 4: 7-year-old boy diagnosed with Alpers' syndrome presented with encephalopathy, tonic-clonic seizures and myoclonic seizures. EEG shows high amplitude anterior poorly formed 2-3 Hertz sharp and slow activity. Pearl [2].

2.4.3. Leigh Syndrome. Leigh syndrome, also known as subacute necrotizing encephalomyopathy, can be seen in disorders involving mitochondrial DNA (as well as nonmitochondrial disorders). Individuals present with neurologic regression with worsening hypotonia, spasticity, and brainstem failure as the disease progresses. Neuroimaging may show bilateral, symmetric lesions in the basal ganglia, thalami, midbrain, and brainstem as well as cortical and cerebellar atrophy

[39]. Focal and generalized epilepsy are associated with this phenotype, and *epilepsia partialis continua*, as well as infantile spasms and hypsarrhythmia, has been described [40].

2.5. Cerebral Folate Deficiency. Cerebral folate deficiency can be a common end result of diverse metabolic and genetic conditions (Table 4). A suspected pathology in primary CFD

TABLE 3: Mitochondrial disorders and epilepsy.

Category of disorder	Syndrome
Mitochondrial complex deficiencies	(i) Complex I deficiency (ii) Complex II deficiency (iii) Complex III deficiency (iv) Complex IV deficiency (v) Complex V deficiency
Mitochondrial DNA disorders	(i) mtDNA depletion syndromes (a) POLG1 disease (1) Alpers-Huttenlocher disease (2) Childhood onset epilepsy partialis continua (EPC) (3) Myoclonic epilepsy myopathy sensory ataxia (MEMSA) (ii) mtDNA deletion syndromes (a) Kearns-Sayre syndrome (KSS) (b) Chronic progressive external ophthalmoplegia (CPEO) (iii) Myoclonic epilepsy with ragged-red fibers (MERRF) (iv) Myoclonic epilepsy, lactic acidosis, and stroke (MELAS)
Other associated syndromes	Leigh syndrome

involves impaired transport of folate across the choroid plexus into the central nervous system. This may be due to one of multiple causes, including loss of function mutations in the folate FR1 receptor, blocking autoantibodies to the folate receptor, or disrupted uptake due to valproic acid. Secondary folate deficiency can also be seen in inborn metabolic diseases, such as Rett syndrome, 3-phosphoglycerate dehydrogenase deficiency (a congenital serine biosynthesis disorder), and mitochondrial disorders such as Kearns-Sayre or Alpers disease [41–44].

Primary cerebral folate deficiency (CFD) is characterized by normal blood but low CSF levels of 5-methylhydrofolate (5-MTHF), the physiologically active form of folate. The common phenotype includes epilepsy, along with neurodevelopmental delay (or regression) and dyskinesias. Individuals with blocking autoantibodies to folate receptors present in early childhood with intractable generalized tonic-clonic seizures. In some cases, treatment with high doses of folinic acid (as opposed to folic acid, which has poor blood-brain barrier entry) has been reported to ameliorate seizures and improve neurological function [45].

2.6. Serine Synthesis Defects. Lserine, a nonessential amino acid, is synthesized from 3-phosphoglycerate by the sequential activity of three enzymes, each with associated disorders (Table 5). The majority of patients with serine deficiencies are affected by an abnormality in the first step, 3-phosphoglycerate dehydrogenase. The clinical phenotype, which includes congenital microcephaly and psychomotor retardation with refractory seizures and hypsarrhythmia, is nonspecific, likely leading practitioners to suspect in utero processes such as TORCH (Toxoplasmosis, Syphilis, Rubella, Cytomegalovirus, Herpes simplex, HIV) or static perinatal difficulties. MRI findings in infantile onset patients have revealed cortical and subcortical atrophy, as well as delayed myelination [46]. Juvenile onset has also been reported, with presentation at school age with absence seizures and moderate developmental delay [47]. Supplementation with

oral serine and glycine has been reported to significantly improve seizures, spasticity, behavior, and feeding, as well as white matter volume and myelination [48, 49].

2.7. DEND Syndrome (Developmental Delay, Epilepsy, and Neonatal Diabetes). A syndrome that combines the problems of developmental delay, epilepsy, and neonatal diabetes is an epileptic channelopathy associated with mutations in potassium channel and sulfonylurea receptor genes [50]. These mutations permanently “lock in” the K_{ATP} channel in an open state, leading to insufficient insulin release and severe hyperglycemia within the first six months of life [51–53]. Clinical manifestations include neurodevelopmental delay, dysmorphic features, hypotonia, and seizures starting as early as the neonatorum. Infantile spasms with hypsarrhythmia, as well as severe tonic-clonic and myoclonic epilepsies, are reported. Neonatal hyperglycemia in DEND can be managed with insulin or sulfonylureas, but the latter is capable of bypassing the defective regulation of K_{ATP} channels and may have better efficacy for the neurological phenotype [50, 54, 55].

2.8. Hyperinsulinism-Hyperammonemia (HI-HA). HI-HA is a syndrome of congenital hyperinsulinism and hyperammonemia that has been related to activating mutations affecting GDH (glutamate dehydrogenase), a participant in the insulin secretion pathway. These defects cause GDH to become insensitive to inhibition, resulting in excess ammonia production and insulin release and neurological sequelae from hypoglycemic insults and hyperammonemia [56]. The clinical constellation of generalized epilepsy, learning disorders, and behavior problems, in the context of hypoglycemia (both postprandial and fasting) and persistent hyperammonemia, is characteristic.

Hypoglycemic seizures may be the first apparent indication. However, some patients have been observed to experience paroxysms, accompanied by generalized electroencephalographic features, without hypoglycemic episodes.

TABLE 4: Cerebral folate deficiencies.

	Disorder or mechanism
Primary cerebral folate deficiency	Folate receptor FR1 defect due to autoantibodies Folate receptor FR1 defect due to (FOLR1 gene) mutation
Disorders with secondary cerebral folate deficiency	Aicardi-Goutieres syndrome Alpers syndrome Isolated Rett syndrome Kearns-Sayre syndrome Mitochondrial complex I encephalomyopathy Valproic acid complications

TABLE 5: Serine synthesis defects.

Disorder	Epilepsy and neuroimaging features	Response to treatment with L-serine and glycine
3-Phosphoglycerate dehydrogenase deficiency	Infantile phenotype: (i) intractable seizures (ii) MRI: hypomyelination and delayed myelination	Infantile phenotype: (i) Seizure control or significantly lowered frequency (ii) Increased white matter volume
	Juvenile phenotype: (i) absence seizures (ii) MRI: no abnormalities	Juvenile phenotype: (i) Seizure control (ii) Prevention of neurological abnormalities
Phosphoserine Aminotransferase deficiency	Symptomatic patient: (i) intractable seizures (ii) MRI: generalized atrophy, including cerebellar vermis and pons, white matter abnormalities	Symptomatic patient: (i) No clinical response to treatment
	Presymptomatic patient: (i) MRI: no abnormalities	Presymptomatic patient: (i) Prevention of all neurological abnormalities
Phosphoserine phosphatase deficiency	Single case, details not reported	Not reported

Adapted from Pearl [2].

This suggests that epilepsy in HI-HA may not be due solely to low CNS glucose availability [57–59]. HI-HA is manageable with a combination of dietary protein restriction, glucagon, antiepileptic medications, and diazoxide, a K_{ATP} channel agonist that inhibits insulin release [60].

2.9. Glucose Transporter 1 Deficiency. Glucose transporter type I (Glut-1) facilitates the passage of glucose across the blood-brain barrier, and its dysfunction in the developing brain leads to the development of a metabolic encephalopathy. CSF shows hypoglycorrhachia associated with normal plasma glucose and low-to-normal CSF lactate, measured in a fasting state. A wide array of phenotypes has been associated with this disorder, but 90% of affected children develop epilepsy (of various types, including absence, focal, generalized myoclonic, clonic, tonic, and nonconvulsive status epilepticus) [61]. Microcephaly, ataxia, and psychomotor delay may be present [62], but patients may also suffer from epilepsy without any accompanying motor or cognitive

deficiencies. Haploinsufficiency (of the SLC2A1 gene) is correlated with the severity of symptoms [63]. EEG findings vary and may be normal, but usually include either focal or generalized slowing or attenuation, or spike-and-wave discharges (generalized, focal, or multifocal). Neuroimaging results may demonstrate diffuse atrophy.

Glucose transporter I deficiency has emerged as the leading metabolic indication for the ketogenic diet, a dietary therapy that replaces glucose with ketone bodies as the primary biochemical energy source. Response is rapid, even in the case of formerly refractory seizures, and treatment should be maintained long term. Additionally, there are certain compounds known to inhibit Glut-1, including phenobarbital, diazepam, methylxanthines (theophylline, caffeine), and alcohol, which should be avoided [64].

2.10. Pyridoxine, Folinic Acid, and Pyridoxal-5'-Phosphate Dependent Epilepsies. There are various epileptic encephalopathies related to vitamin B6 metabolism (Table 6), and

TABLE 6: Pyridoxine and pyridoxal-5'-phosphate-dependent Epilepsies.

	Pyridoxine- or folinic-acid-dependent epilepsies (PDE)	Pyridoxal-5'-phosphate (PLP-) dependent epilepsy
Deficient enzyme	Antiquitin (ATQ)	Pyridox(am)ine phosphate oxidase (PNPO)
Blood chemistry	Normal, but hypoglycemia and lactic acidosis have been reported	Hypoglycemia and lactic acidosis common
Vanillic acid (Urine)	Absent	Present
Pipelicolic acid (blood, CSF)	↑	Normal
AASA* (blood, urine, CSF)	↑	Normal
Neurotransmitter metabolites (CSF)	(Possible) ↑ 3-Methoxytyrosine	↑ L-DOPA, 3-Methoxytyrosine ↓ Homovanillic acid, 5-Hydroxyindoleacetic acid
Clinical signs	Postnatal refractory seizures, gastrointestinal symptoms, encephalopathy with hyperalertness, sleeplessness	Fetal distress and in utero fetal seizures, postnatal refractory seizures and encephalopathy

*AASA: alpha-amino adipic semialdehyde. Adapted from Pearl [2].

pyridoxine-dependent epilepsy (PDE) is the prototype, resulting from a loss of the biologically active pyridoxal-5'-phosphate (PLP) due to a dysfunction of the protein antiquitin (*ALDH7A1*) [65]. PDE normally presents within the first hours following birth with serial refractory seizures responsive to pyridoxine administration. Improvement is significant and usually rapidly appreciable on EEG [66]. Variants of the disorder that respond to folinic acid instead of, or in addition to, pyridoxine have also been described, as well as atypical cases with long asymptomatic periods or presenting later in infancy (i.e., weeks or months following birth) [67, 68].

PNPO, or pyridox(am)ine phosphate oxidase, deficiency is a distinct disorder involving refractory seizures responsive not to pyridoxine but to its biologically active form, pyridoxal-5'-phosphate (PLP) [69, 70]. This disorder is due to a defect in the enzyme PNPO, which synthesizes PLP from precursors pyridoxine-P and pyridoxamine-P [71]. Patients may present prenatally with fetal seizures and premature birth and if untreated can progress to status epilepticus and death. Laboratory and genetic testings are available to confirm these diagnoses (Table 6); trials of systemic pyridoxine administration require close cardiorespiratory monitoring.

2.11. Urea Cycle Disorders. The urea cycle (Figure 6), the metabolic mechanism for nitrogen detoxification and removal, is facilitated by six enzymes and a mitochondrial transporter and carrier, each being susceptible to dysfunction (Table 7). In the event of an enzyme or transport defect, the resulting hyperammonemia can lead to overwhelming encephalopathy, often accompanied by seizures and hypotonia that may be exacerbated by metabolic stresses such as fever or infection [72]. EEG monitoring should be initiated early in the course of acute treatment, as seizure activity is thought to be related to hyperammonemic crises or structural damage, and subclinical electrographic

seizures are reported. Males with OTC deficiency typically present in the neonatorum and with high mortality, whereas female heterozygotes can vary in the severity and timing of presentation depending on hepatic lyonization [72].

The goals of therapy during metabolic crisis are removal of ammonia through hemodialysis, nitrogen scavenging with agents including sodium benzoate and sodium phenylacetate [73], and reversal of catabolism. Immediate antiepileptic therapy is indicated for optimizing treatment; valproate, however, may interfere with the urea cycle and precipitate metabolic crises [74]. Maintenance therapy of urea cycle defects hinges on the restriction of protein intake while providing sufficient essential amino acids. Orthotopic liver transplant may be curative, but cannot reverse existing neurologic injury.

2.12. Creatine Biosynthesis and Transport Deficiencies. Half of the body's daily requirement of creatine is synthesized from arginine and glycine by the enzymes AGAT (arginine:glycine amidinotransferase) and GAMT (guanidino acetate methyl transferase). A specific creatine transporter, CT1, encoded by an X-linked gene, facilitates the uptake into tissues. Patients with deficiencies in creatine synthesis or transport present with early developmental delay, seizures, neurologic regression, intellectual disability, autistic behavior, hypotonia, and movement disorders. Females with heterozygous mutations of the creatine transporter gene may be symptomatic with more moderate intellectual disability, learning and behavior problems, and epilepsy [75].

Approximately half of individuals with GAMT deficiency, and most males with creatine transporter deficiency, develop epilepsy [76]. Patients with GAMT deficiency have abnormal MRI signals of the globus pallidus and background slowing and generalized spike-and-wave discharges on EEG. Individuals with creatine transporter deficiency present with generalized and partial epilepsy, with EEG usually reported

TABLE 7: Urea cycle defects and biochemical characteristics.

Defective enzyme or component	Citrulline	Arginine	Ammonia	Additional biochemical characteristics
Ornithine transcarbamylase	↓	↓	↑	↑ Glutamine Normal orotic acid
Carbamoylphosphate synthetase I (CPSI)	↓	↓	↑	↑ Glutamine ↑ Orotic acid
N-acetyl glutamate synthase (NAGS)				Reduced CPSI activity (NAGS is a vital cofactor)
Argininosuccinate synthase (ASS)	↑↑ (10–100x normal)	↓	↑	
Argininosuccinate lyase (ASL)	↑	↓	↑	↑ Argininosuccinic acid (unique to ASL deficiency)
Arginase (ARG1)			Normal in absence of metabolic stress	
Ornithine transporter mitochondrial I (ornithine translocase deficiency)			↑	↑ Homocitrulline ↑ Ornithine
Citrin (solute carrier family 5) deficiency	↑			

Adapted from Pearl [2].

as showing generalized polyspike or multifocal epileptiform discharges [77, 78].

Laboratory identification using urine creatine metabolites (Table 8) is necessary to distinguish the three disorders [79]. In the case of creatine synthesis disorders, treatment with oral creatine supplementation can improve seizures and neurological function, and arginine restriction and ornithine supplementation are utilized in GAMT deficiency. Creatine transport disorders, however, are not significantly amenable to therapy other than with traditional antiepileptic medications.

2.13. Glycine Encephalopathy. Glycine encephalopathy is an inherited disorder of glycine degradation resulting from defects in the mitochondrial glycine cleavage system (GCS). The excitatory effects of glycine on the cortex and forebrain, mediated by *N*-methyl-*D*-aspartate (NMDA) receptors, lead to excess intracellular calcium accumulation and subsequent neuronal injury with intractable seizures [80]. Based on age at presentation and clinical outcomes, different categories of glycine encephalopathy (GE) can be distinguished. The majority of patients present with a severe neonatal-onset form, with primarily myoclonic and intractable seizures, hypotonia, apnea, and coma [81]. Outcomes are generally poor, particularly in the presence of brain malformations such as corpus callosum hypoplasia. There are attenuated forms, lacking congenital malformations, with a better outcome.

Laboratory analyses reveal elevated plasma and CSF glycine, as well as an increased CSF to plasma glycine ratio. EEG findings include multifocal epileptiform activity, hypsarrhythmia, and burst-suppression patterns (Figure 5) [82]. Treatment with benzoate and a low-protein diet may reduce glycine levels in plasma, and combined antiepileptic treatment is necessary for most individuals.

2.14. Sulfide Oxidase Deficiency/Molybdenum Cofactor Deficiency. Sulfite oxidase deficiency due to molybdenum cofactor deficiency (MOCOD) and isolated sulfite oxidase deficiency (ISOD) are inherited disorders of the metabolism of sulfated amino acids [83]. They typically present in the first days of life with poor feeding following an uneventful pregnancy and delivery. Seizures, primarily myoclonic or tonic-clonic, begin in the first few weeks of life; they can be refractory to therapy and may develop into status epilepticus [84]. Signs of encephalopathy with opisthotonus, apnea, prolonged crying, and provoked erratic eye movements or myoclonias can be seen, and up to 75% of patients will have slight dysmorphism including widely spaced eyes, small nose, puffy cheeks, and elongated face [85].

EEG findings include burst suppression patterns and multifocal spike-wave discharges [86], and neuroimaging results are usually profoundly abnormal, including diffuse cerebral edema evolving into cystic lesions and brain atrophy within weeks [87]. Low total plasma homocysteinemia is associated with both ISOD and MOCOD, and hypouricemia due to secondary xanthine dehydrogenase deficiency can be indicative of MOCOD. Therapy has historically been symptomatic, with combination or monoantiepileptics.

2.15. Homocysteinemias. Disorders involving homocysteine metabolism, specifically methionine and cystathionine synthesis, are characterized by elevated urine and serum homocysteine in the context of neurological symptoms. The spectrum of neurological dysfunction in homocysteine metabolism disorders is wide, including epilepsy, encephalopathy, peripheral neuropathy, ataxia, microcephaly, and psychiatric disorders. Cystathionine beta-synthetase (CBS) deficiency is the most common of the homocysteinemias, with severe defects involving multiple systems due to the essentiality of homocysteine and methionine to normal

TABLE 8: Creatine synthesis defects.

Defective enzyme or component	Urine Creatine	Urine GAA (guanidinoacetate)	Creatine/creatinine ratio	treatment
AGAT (arginine : glycine amidinotransferase)	↓	↓	Normal	(i) Amenable to creatine therapy
GAMT (guanidine acetate methyl transferase)	↓	↑	Normal	(i) Amenable to creatine therapy; (ii) Dietary restriction of arginine, with ornithine supplementation (iii) Antiepileptics may be necessary for seizure control
Creatine transporter	↑	Normal (may be slightly increased in males)	↑	(i) Antiepileptics for seizure control (ii) Creatine supplementation is ineffective

TABLE 9: Biochemical characteristics and treatment of homocysteine metabolism disorders.

Defective enzyme	Homocysteine (U, P)	Additional biochemical characteristics	Treatment
Cystathionine beta-synthase (CBS)	↑	↑ Methionine ↓ Cysteine	Pyridoxine, B12, folate Methionine-restricted diet Cysteine supplementation betaine
Methionine synthase (MTR)	↑	Normal or ↑ Folate Normal or ↑ Cobalamin	High-dose hydroxycobalamin
Methylene tetrahydrofolate reductase (MTHFR)	↑	↓ Methionine	High-dose betaine Methionine supplementation

* (U): urine, (P): plasma.

biochemical function. Focal seizures, stroke, neurodevelopmental delay, and cognitive deficiency, as well as psychosis are common neurological findings. Marfan-like skeletal symptoms, connective tissue abnormalities in the optic lens, and vasculopathies causing thrombosis and multiorgan infarcts may also be present. Treatment and biochemical findings in CBS, as well as other homocysteine disorders are summarized in Table 9.

Autosomal recessively inherited deficiency of methylene tetrahydrofolate reductase (MTHFR) may present in early infancy with severe epileptic encephalopathy [88]. The presentation with hypotonia, lethargy, feeding difficulties, and recurrent apnea may progress from seizures to coma and death. Infantile spasms may also be the presenting feature, with evolution to multiple seizure types including the Lennox-Gastaut syndrome. Status epilepticus, both clinical and subclinical, has been reported. Progressive microcephaly and global encephalopathy may ensue as seizures continue, but there is evidence for reversibility with treatment comprised principally of the methyl donor betaine [89].

2.16. Purine and Pyrimidine Defects. Disorders of purine and pyrimidine metabolism may present with epileptic encephalopathies (Table 10), including adenylosuccinase (adenylosuccinate lyase) deficiency which has a broad phenotypic spectrum including neonatal seizures [90]. Lesch-Nyhan disease, or X-linked hypoxanthine-guanine phosphoribosyltransferase deficiency, may result in epileptic seizures, but these can be difficult to distinguish from the extrapyramidal manifestations, specifically dystonic spasms, tremor, and

myoclonus. Generalized tonic-clonic seizures are the most commonly reported epilepsy type in the literature [91, 92]. Treatment with allopurinol is essential for hyperuricemia and may provide some antiepileptic effect. Antiepileptic drug choices must weigh the possibility of exacerbating underlying behavioral irritability with levetiracetam and others. Topiramate and zonisamide are avoided due to the risk of nephrolithiasis.

3. Large Molecule Disorders

3.1. Disorders of Glycosylation. Disorders of protein glycosylation, due to defects in the synthesis of N- and O-linked glycoproteins, are characterized by multiple organ system dysfunction, developmental delay, hypotonia, and epilepsy. Certain of these disorders are associated with severe encephalopathy, particularly those involving alpha-dystroglycan, a protein component of the extracellular matrix, essential to muscle integrity. These are known as dystroglycanopathies.

3.1.1. Walker-Warburg Syndrome. Walker-Warburg syndrome (WWS) is a severe dystroglycanopathy which can present at birth or prenatally with hydrocephalus and encephaloceles on imaging. Seizures and significant structural abnormalities (e.g. cerebellar atrophy, hypoplasia of the corpus callosum), migrational defects (type II lissencephaly), hypomyelination, and ophthalmologic defects are seen. Life expectancy is less than three years [93, 94].

TABLE 10: Purine and pyrimidine metabolism disorders involving epilepsy.

Disorder	Defective enzyme	Biochemical characteristics	Seizure characteristics
Lesch-Nyhan Disease (LSD)	hypoxanthine-guanine phosphoribosyl transferase	↑ Uric acid	Predominantly generalized tonic-clonic, developing in early childhood
Adenylosuccinase deficiency	Adenylosuccinate lyase	↑ succinylaminoimidazole carboxamide riboside ↑ succinyladenosine	Neonatal seizures Severe infantile epileptic encephalopathy

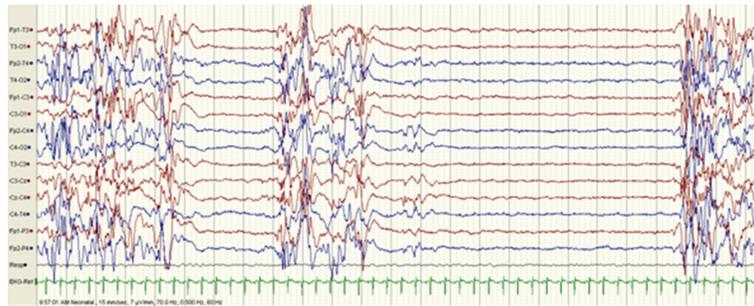


FIGURE 5: EEG of term infant with glycine encephalopathy shows burst-suppression pattern. Pearl [2].

3.1.2. Fukuyama Congenital Muscular Dystrophy. Fukuyama congenital muscular dystrophy (FCMD) classically presents in the neonatorum or even prenatally (poor fetal movement) with frequent seizures and severe brain abnormalities (migration defects, cobblestone lissencephaly, delayed myelination, hypoplasia of the pons, cerebellar cysts). By the age of 3, most patients develop epilepsy. Muscular degeneration and cardiac involvement are progressive [95, 96].

3.2. Lysosomal Storage Disorders. Lysosomal storage disorders (LSD) are a major category of diseases that involve defects in lysosomal enzyme function, lysosomal biogenesis, activation, trafficking, or membrane transporters. Over two-thirds of LSDs are neurodegenerative and some are associated with epileptic encephalopathy. Table 11 lists lysosomal storage disorders by subgroup, and prominent examples are covered below.

3.2.1. Neuronal Ceroid Lipofuscinoses (NCLs). Neuronal ceroid lipofuscinoses are genetically heterogeneous neurodegenerative disorders associated with defects in transmembrane proteins and are characterized by the accumulation of autofluorescent lipopigments in lysosomes. The symptoms include cognitive decline, seizures, vision loss, and motor impairment, though age of onset and clinical course vary [97]. The development of epilepsy can indicate a more severe clinical course, though myoclonic seizures should be distinguished from myoclonus, which is also a frequent and sometimes progressive feature of this disorder [98]. Generalized cerebral and cerebellar atrophy can be seen on neuroimaging [99].

3.2.2. Sphingolipidosis and Gaucher Disease. Defects in the degradation of sphingolipids, an essential component of

myelin sheaths and neuronal tissue, lead to progressive neurodegeneration, epilepsy, peripheral neuropathy, extrapyramidal symptoms, and characteristic “cherry-red spots.” Subtypes (II and III) of Gaucher Disease, which result from a deficiency in glucocerebrosidase, can cause devastating and rapid neurological deterioration. Neuroimaging is usually normal in patients with Gaucher Disease, but EEG can show several abnormalities including polyspikes with occipital predominance sensitive to photostimulation, diffuse slowing with high-voltage sharp waves during sleep, and multifocal spike-and-wave paroxysms [100, 101].

3.2.3. Gangliosidosis and Tay-Sachs Disease. Tay-Sachs disease is an example of defects involving the degradation of gangliosides, which are vital signaling, transport, and regulatory proteins in the lysosomal membrane. Seizures typically begin within the first year of life and worsen in frequency and severity. They are difficult to control with antiepileptics and can acutely and rapidly progress; in these cases, EEG and clinical deterioration can follow until death [102].

3.3. Peroxisomal Diseases. As a participant in cellular detoxification, lipid metabolism, as well as myelin, neuronal function, migration, and brain development [103], peroxisomes are essential for neuronal health. Nearly all peroxisomal disorders (Table 12) are known to impair neurological function, though peroxisomes are present in almost all eukaryotic cells, and consequently its associated diseases will also manifest in multiple organ systems. Seizures occur particularly in the neonatal period and may be a result of cortical migration defects. Symptomatic treatment using anticonvulsants is the predominant therapy [104, 105].

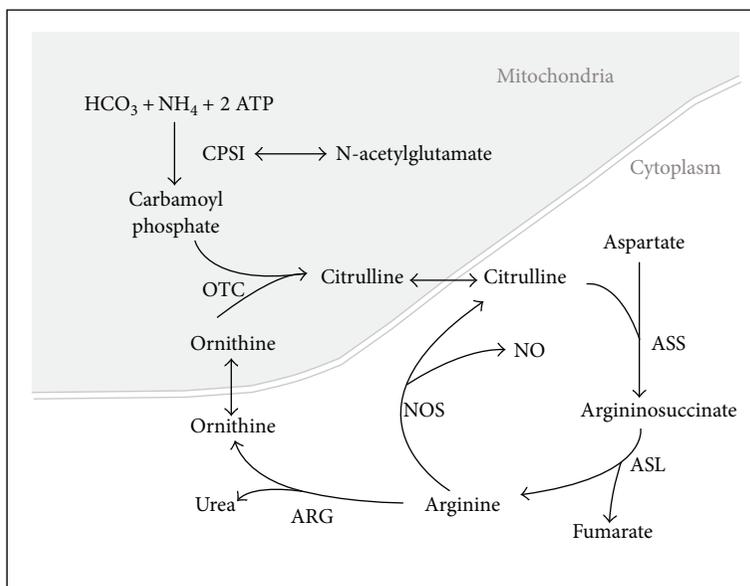


FIGURE 6: The urea cycle. The urea cycle is a pathway of cytosolic and mitochondrial proteins involved in the conversion of ammonia (NH_4) to urea for excretion via the kidneys. The enzymes in the pathway are as follows: carbamoylphosphate synthetase (CPS1), ornithine transcarbamylase (OTC); argininosuccinic acid synthase (ASS); argininosuccinic acid lyase (ASL); arginase I (ARG); nitric oxide synthase (NOS). Pearl [2].

3.3.1. Rhizomelic Chondrodysplasia Punctata. Rhizomelic chondrodysplasia punctata is a peroxisomal biogenesis disorder characterized by white matter abnormalities including inflammatory demyelination and noninflammatory dysmyelination, as well as cerebellar degeneration and loss of Purkinje cells, leading to profound intellectual deficiency. Almost all patients develop seizures, with nonspecific EEG findings. Neurological defects and degeneration are severe, and most individuals do not survive the first two years of life [106].

3.4. Leukodystrophies. Genetic leukoencephalopathies, or inherited white matter disorders, are diseases that primarily affect myelinated structures in the brain and peripheral nervous system. The majority of leukodystrophies primarily feature motor dysfunction rather than encephalopathy, particularly early on in the development of the disease. Epilepsy, however, can be a prominent symptom in certain classic leukodystrophies (Table 13) such as Alexander's disease. This is associated with defects in the GFAP gene encoding astrocyte intermediate filaments. Early onset forms of Alexander's disease (Type I) frequently feature seizures, particularly associated with fever, that are difficult to control. The clinical course of type I Alexander's disease is normally progressive neurodegeneration involving megalencephaly, psychomotor retardation, and spastic paraplegia [107].

4. Conclusion

Epileptic encephalopathies represent a challenging area of pediatric neurology and epilepsy and have a broad differential diagnosis [108]. There are protean inborn errors of

metabolism which may lead to epileptic encephalopathies. They have various degrees of treatability at present, with some requiring prompt diagnosis and intervention to avoid otherwise catastrophic outcomes. The epileptologist may view these from the viewpoint of syndromic phenotypes. In general, early myoclonic encephalopathy and myoclonic seizures represent a classic epilepsy syndrome and seizure type, respectively, associated with inborn errors of metabolism. Yet, the phenotypic spectrum of epilepsy caused by hereditary metabolic disorders is wide and includes refractory neonatal seizures, early infantile epileptic encephalopathy (syndrome of Ohtahara), infantile spasms, and progressive myoclonic epilepsies, as well as syndrome variations such as early onset absence epilepsy in glucose transporter deficiency. A careful approach to metabolic disorders is helpful to consider the various diseases that may present and develop into an epileptic encephalopathy.

The small molecule disorders include amino and organic acidopathies such as maple syrup urine disease, homocysteinemia, multiple organic acid disorders, and cobalamin deficiencies. Dietary intervention is key in preventing encephalopathy in maple syrup urine disease and glutaric aciduria, and hydroxycobalamin has a therapeutic role starting in prenatal intervention in cobalamin C deficiency. Neurotransmitter and fatty acid oxidation disorders may result in epileptic encephalopathies, and mitochondrial disorders present with a range of epilepsy phenotypes, including intractable epilepsy and epilepsia partialis continua in polymerase gamma mutations. Cerebral folate deficiency appears to result from a variety of causes but primary deficiency, associated with mutations of the folate receptor or blocking antibodies, has a phenotype of intractable generalized tonic-clonic seizures in infancy which may respond to folinic acid.

TABLE II: Lysosomal storage disorders.

Storage materials	Diseases	Primary defect
Lipids	Niemann Pick C	Intracellular cholesterol transport
Monosaccharides	Free sialic acid storage disease (i) infantile free sialic acid storage disease (ISSD) (ii) intermediate salla disease (iii) mild form (salla disease)	Lysosomal transport protein sialin
Mucopolidoses	Mucopolidosese (i) type II (I cell disease) (ii) type III (pseudo Hurler polydystrophy) (iii) type IV	N-acetylglucosamine-1-phosphotransferase N-acetylglucosamine-1-phosphotransferase Receptor-stimulated cat ion channel (mucolipidin)
Mucopolysaccharidoses (MPS)	MPS	
Dermatan, heparan sulfate	(i) type IH (Hurler)	L-iduronidase
Dermatan, heparan sulfate	(ii) type II (Hunter)	Iduronate-sulfatase
Heparan sulfate	(i) type III A (Sanfilippo type A) (ii) type III B (Sanfilippo type B) (iii) type III C (Sanfilippo type C) (iv) type III D (Sanfilippo type D)	Heparan-N-sulfatase N-acetyl- α -glucosaminidase α -glucosaminide-acetyl-CoA transferase N-acetylglucosamine-6-sulfatase
Dermatan, heparan, chondroitin sulphate	(i) type VII (Sly)	β -Glucuronidase
Multiple enzyme defects	Multiple sulfatase deficiency Galactosialidosis	Sulfatase-modifying factor-1 (SUMF1) β -Galactosidase and neuraminidase secondary to defect of protective protein, cathepsin A
Neuronal ceroid lipofuscinosis (NCL)	NCL (i) congenital (ii) infantile (INCL) (iii) late infantile (LNCL) (iv) juvenile (JNCL) (v) adult (ANCL) (vi) Northern epilepsy (NE)	Cathepsin D (CTSD) Palmitoyl-protein thioesterase-1 (PPT1) Tripeptidyl peptidase 1 (TPP1) A transmembrane protein Ceroid lipofuscinosis neuronal protein 3 (CNT3) Ceroid lipofuscinosis neuronal protein 8 (CLN8)
Oligosaccharidoses (glycoproteinoses)	Alpha-mannosidosis Beta-mannosidosis Fucosidosis Schindler disease Aspartylglucosaminuria (AGU) Sialidosis (i) severe infantile (ii) mild infantile (mucopolidosis I) (iii) adult	α -Mannosidase β -Mannosidase α -Fucosidase α -N-acetylgalactosaminidase Aspartylglucosaminidase α -Neuraminidase α -Neuraminidase α -Neuraminidase
Sphingolipidoses		
Ceramide	Farber disease	Ceramidase
Galactocerebroside	Globoid Cell Leukodystrophy (GLD or Krabbe disease) (i) infantile (ii) late infantile (iii) adult	β -Galactocerebrosidase

TABLE 11: Continued.

Storage materials	Diseases	Primary defect
Gangliosidoses	(iv) Saposin A deficiency	Sphingolipid activator protein A (SAPA)
	GM1 gangliosidoses	β -Galactosidase
	(i) infantile	
	(ii) late infantile	
	(iii) adult	
	GM2 gangliosidoses	β -Hexosaminidase
Glucocerebroside	(i) Sandhoff disease	β -Hexosaminidase A and B (α -subunit)
	(ii) Tay Sachs	β -Hexosaminidase A (β -subunit)
	(iii) GM2 activator deficiency	β -Hexosaminidase activator
	Gaucher disease	β -Glucocerebrosidase
	(i) type II	
Sphingomyelin	(ii) type III	
	(iii) Saposin C deficiency	Sphingolipid activator protein C
	Niemann-Pick	Sphingomyelinase
Sulfatide	(i) type A	
	(ii) type B	
Multiple sphingolipids	Metachromatic leukodystrophy (MLD)	Arylsulfatase A
	(i) late infantile	
	(ii) juvenile	
	(iii) adult	
Multiple sphingolipids	(iv) Saposin B deficiency	Sphingolipid activator protein B
	Prosaposin deficiency (pSap)	Precursor of Sphingolipid activator protein

Adapted from Pearl [2].

TABLE 12: Peroxisomal disorders.

Biogenesis disorders	Single enzyme disorders	Contiguous gene syndrome
Zellweger spectrum disorders (ZSD)	X-linked adrenoleukodystrophy (X-ALD)	Contiguous ABCD1 DXS1357E deletion syndrome (CADD5)
	Acyl-coA oxidase deficiency	
	Bifunctional protein deficiency (D-BP)	
	Alkyl-DHAP synthase deficiency	
	DHAP-alkyl transferase deficiency	
	Adult Refsum disease (classic)	
	Rhizomelic chondrodysplasia punctata (RCDP)	
	Glutaric aciduria type III	
Rhizomelic chondrodysplasia punctata (RCDP)	Acatlasemia	
	Hyperoxaluria type I	

Adapted from Pearl [2].

TABLE 13: Leukodystrophies including epilepsy as a manifestation.

Disorder
Alexander's disease
Globoid cell leukodystrophy (Krabbe disease)
X-linked adrenoleukodystrophy
Hereditary diffuse leukoencephalopathy with spheroids
Metachromatic leukodystrophy

Disorders of serine synthesis may respond to pre- and postnatal supplementation with serine and glycine. There are several

potassium channelopathies involving the pancreas and brain, presenting either with neonatal diabetes or hypoglycemia, specifically (developmental delay, epilepsy, and neonatal diabetes) DEND and (hyperinsulinism-hyperammonemia) HI-HA with specific therapeutic implications. Glucose transporter deficiency appears to be the prototype of transport defects causing epilepsy and having specific therapy, in this case being the ketogenic diet to supply an alternative brain fuel to glucose, and the disorders related to the pyridoxine vitamers, specifically pyridoxine and pyridoxal-5-phosphate, require prompt identification and therapy to avert a catastrophic outcome. Autosomal recessively inherited deficiency

of MTHFR may be reversible with use of betaine, whereas other small molecule defects causing epileptic encephalopathy, for example, glycine encephalopathy and sulfite oxidase deficiency, have no specific therapy at this time.

Large molecule disorders involve a complex constellation of disorders of glycosylation, lysosomal storage diseases, and peroxisomal disorders. Those including severe epilepsy include Walker-Warburg syndrome, Fukuyama congenital muscular dystrophy, gangliosidoses such as Tay-Sachs and Sandhoff diseases, and the neuronal ceroid lipofuscinoses. While epilepsy represents significant gray matter involvement in neurological disease, seizures can be a prominent aspect of leukodystrophies such as Alexander's disease. The epileptologist should consider these hereditary disorders in the investigation of patients with epileptic encephalopathies, leading to specific diagnostic steps and, in some cases, potential therapeutic maneuvers to address the metabolic defect.

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Review Article

The Role of Epilepsy Surgery in the Treatment of Childhood Epileptic Encephalopathy

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Received 19 February 2013; Revised 25 March 2013; Accepted 29 March 2013

Academic Editor: Giangennaro Coppola

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Children with epileptic encephalopathy often have global impairment of brain function and frequent intractable seizures, which contribute further to their developmental disability. Many of these children have identifiable brain lesion on neurological imaging. In such cases, epilepsy surgery may be considered as a treatment option despite the lack of localized epileptic pattern on electroencephalogram (EEG). In this paper, we summarize the clinical features of epileptic encephalopathy syndromes and review the reported literature on the surgical approach to some of these disorders.

1. Introduction

Epileptic encephalopathy is defined as a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function [1]. The report of the International League Against Epilepsy (ILAE) Task Force on Classification and Terminology includes eight syndromes under epileptic encephalopathies. One common feature among these epilepsy syndromes is the suboptimal response to treatment with antiepileptic medications. This invited the utilization of epilepsy surgery in selected patients who have structural brain lesion believed to be the cause of epilepsy.

In this paper, we briefly review the clinical features of different epileptic encephalopathy syndromes and summarize the reported literature on the surgical approach and management of some of these disorders.

2. Classification of Epileptic Encephalopathies

According to the age of onset, epileptic encephalopathy syndromes may be divided into two main groups.

2.1. Infantile Epileptic Encephalopathies

2.1.1. Ohtahara Syndrome. First described in 1976 by Ohtahara, Ohtahara Syndrome is characterized by tonic seizures and burst suppression pattern on EEG [2]. Symptoms develop earlier than other forms of epileptic encephalopathies within the first 3 months of life, usually in the first 10 days. Etiology is unclear but it generally accompanies structural brain anomalies. Seventy-five percent of cases turn into West syndrome within 3 to 6 months, and some of these turn into Lennox-Gastaut syndrome. Seizures are resistant to treatment and generally have a poor prognosis.

2.1.2. Early Myoclonic Encephalopathy. Has an early onset within the first few months of life in the form of erratic, fragmentary, or massive myoclonic seizures. Frequency varies from occasional to almost continuous myoclonus. Infants have severe delay in development, hypotonia, and disturbed alertness, sometimes with vegetative state. EEG is characterized by a burst-suppression pattern. Erratic myoclonus does not generally have an ictal EEG counterpart. Etiology remains often unknown. Some inborn errors of metabolism

were suggested such as nonketotic hyperglycinemia, propionic acidemia, molybdenum cofactor deficiency, and methylmalonic acidemia. Cerebral malformations can also cause early myoclonic encephalopathy, but more often they produce Ohtahara syndrome [3]. The prognosis is poor since there is no effective therapy.

2.1.3. West Syndrome. It usually occurs in the first year of life and consists of the triad of infantile spasms, developmental deterioration, and hypsarrhythmia pattern on EEG [4]. There is a broad range of potential causes, including cerebral malformations, infection, hemorrhage, hypoxic ischemic injury, metabolic disorders, and genetic conditions, such as Down syndrome [5]. No clear etiology is found in approximately 25–40% of cases. Adrenocorticotropin hormone (ACTH) and vigabatrin are widely used for treatment with variable degrees of success depending on the etiology. The ketogenic diet was found to be helpful in some cases [6]. Focal cortical resection or hemispherectomy may be considered for cases that are lesional and medically intractable [7]. The developmental prognosis depends partially on the etiology; normal development was described in 51% of cryptogenic cases versus only 6% of symptomatic cases.

2.1.4. Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome). It presents typically with frequent myoclonic seizures in the first year of life. They are often associated with fever and involve one side of the body although both sides of the body may be involved [8]. During the second year of life seizures become more persistent and no longer occur in association with fever. The early development of affected children is usually normal, but during the second year of life developmental regression occurs affecting mainly language and cognitive skills. On EEG there are spike and wave or polyspike discharges, which may be generalized or regional. 35–40% of patients have mutation of the SCN1A gene [9]. Seizures are very resistant to antiepileptic drugs. A combination of sodium valproate with either topiramate or stiripentol may be the most helpful. A short course of prednisolone and the ketogenic diet may also be helpful. Children with Dravet syndrome continue to have severe developmental disabilities and learning difficulties requiring full educational support.

2.2. Childhood Epileptic Encephalopathies

2.2.1. Lennox-Gastaut Syndrome (LGS). It is characterized by multiple seizure types, mental retardation or regression, and characteristic findings on EEG with paroxysms of fast activity and generalized slow spike and wave discharges (1.5–2 Hz). Seizure onset is usually at 1–8 years, peaking between 3 and 4 years. The most common seizure types are tonic, atonic, and atypical absence seizures, but myoclonic and generalized tonic-clonic seizures can be observed [10, 11]. According to etiology it is divided into cryptogenic or symptomatic. Symptomatic cases may be secondary to hypoxic ischemic encephalopathy, congenital brain malformation, vascular malformation, genetic conditions like tuberous sclerosis, trauma, brain tumor, or perinatal meningoencephalitis [12]. Antiepileptic medications, ketogenic diet, and hormonal therapies are used

in treatment with variable success. Surgical treatment has been suggested for patients with structural brain lesions as discussed below.

2.2.2. Electrical Status Epilepticus during Slow Sleep (ESES). It is a disorder that includes clinical manifestations of variable seizure types, deterioration of neuropsychological functions, and typical EEG pattern of continuous spikes and waves during slow sleep [13]. The age of onset ranges between 2 months and 12 years, with a peak around 3 to 5 years. Etiology is often unclear. Brain MRI shows diffuse or unilateral atrophy in 33% of cases [14]. Seizures may become self-limited and disappear in the midteens. However, many of affected children do not return to normal levels, particularly in the verbal area and attention [15].

2.2.3. Landau-Kleffner Syndrome (LKS). It is also known as acquired epileptic aphasia since this is the main clinical feature of this syndrome in addition to the presence of frequent spikes in the temporal or centrottemporal region activated during sleep. Onset is between 2 and 7 years in children with previously normal development [16]. It is more common in males. The presence of normal development in premorbid period is an important feature; however, preexisting language anomaly was described in 13% of cases [17]. Many therapeutic modalities have been tried with variable success. Among these are anticonvulsants, corticosteroids, IV immunoglobulin, ketogenic diet, and surgical intervention with multiple subpial transactions (MSTs) [18].

3. Surgical Approach to Children with Epileptic Encephalopathy

Epilepsy surgery was originally introduced as a treatment modality for patients who had localized epileptiform discharges on EEG. These findings are important clues to the cortical region that has to be removed to stop the seizures, and they remain a cornerstone of selection for surgery in most cases. However, over the years and with the advances achieved in neuroimaging, workers in this field developed more comprehensive approach to these patients, and the plan for epilepsy surgery nowadays is built on data gathered from EEG, magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission-computed tomography (SPECT), neurologic examination, and seizure semiology [19]. The level of concordance between these different sources of data correlates with postsurgical seizure freedom rates.

EEG in patients with epileptic encephalopathy due to congenital or early acquired brain lesion may sometimes reveal diffuse or bilaterally distributed multifocal epileptiform activity. “The exception to the rule” for surgical candidacy despite generalized or bilateral multifocal EEG features is based on the experience gained during infancy and early childhood, when the age-related pattern of hypsarrhythmia may manifest in response to a variety of diffuse or focal brain insults or lesions [7]. Furthermore, it has been noted that localized cortical abnormalities may occasionally cause generalized epilepsies such as Lennox-Gastaut

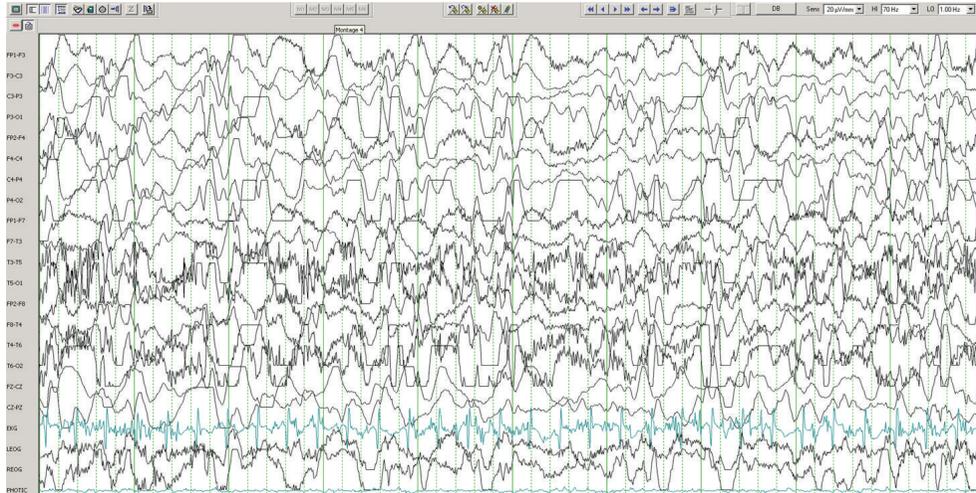


FIGURE 1: EEG prior to surgery showing generalized hypsarrhythmia.

syndrome [19]. The exact mechanisms behind these phenomena are unknown, but the generalized and contralateral epileptiform discharges may be a manifestation of potentially reversible secondary epileptogenesis resulting from an interaction between the early lesion and the developing brain [20] although further research is needed to refine this understanding.

Based on the above, it has been proposed that infants and young children with intractable epilepsy and focal brain lesion may be candidates for epilepsy surgery despite the presence of generalized EEG seizures and a diffuse pattern of multifocal or bilateral epileptiform discharges [7, 21, 22].

3.1. Case Illustrations. The following two examples illustrate the successful utilization of epilepsy surgery in such clinical scenarios.

Case 1. A 7-month-old infant girl was born at full term after uncomplicated pregnancy and normal delivery and presented with increasing number of epileptic spasms at age 3 months. She had an initial normal development. EEG confirmed the presence of hypsarrhythmia pattern (Figure 1). Brain MRI showed vascular malformation in the left temporal lobe (Figure 2). Conventional antiepileptic treatment was initially tried using adrenocorticotropin hormone (ACTH) then topiramate. This resulted in partial control of her spasms. Then at age of 11 months it was determined that surgical resection of the left temporal vascular lesion would be beneficial since the child failed medication therapy and the vascular malformation carries a risk of intracranial hemorrhage (Figure 3). The child became seizure-free after surgery despite weaning off all antiepileptic medications 6 months later. Developmentally she made remarkable progress after the cessation of her seizures. Three years after surgery she remains seizure-free and developing normally for her age.

Case 2. A 9-year-old ambidextrous girl presented with intractable epilepsy since age 2 years. Since the onset of her



FIGURE 2: Axial T2-WI MRI scan demonstrating congenital vascular malformation in the left temporal lobe.



FIGURE 3: Postoperative axial T2-WI MRI scan at the same level after left temporal lobe resection.

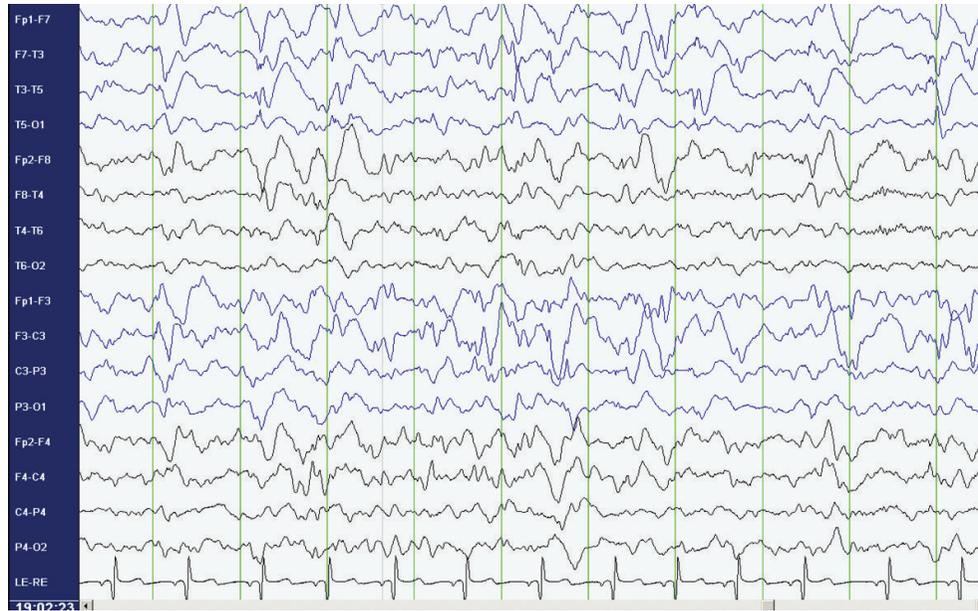


FIGURE 4: EEG prior to surgery showing multifocal sharp waves in the left and right temporal and frontal regions, maximal on the left side.

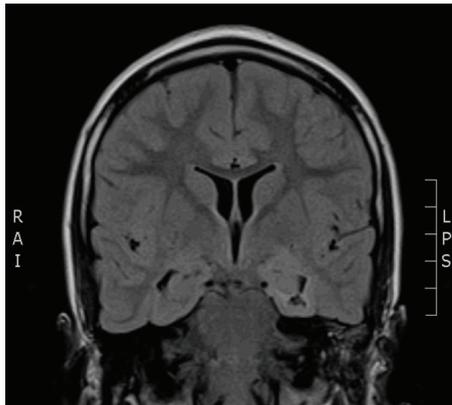


FIGURE 5: Coronal FLAIR MRI scan demonstrating the left mesial temporal lesion.

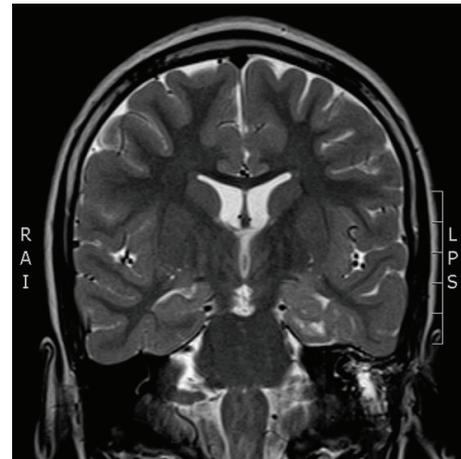


FIGURE 6: Coronal T2-WI MRI scan demonstrating the left mesial temporal lesion.

seizures she had global delay of her development affecting mainly communication, social, and cognitive skills. Despite treatment with large number of antiepileptic medications she continued to have 5–10 seizures daily. Her seizures start with an aura (sensation of fear) followed by tonic posturing of the upper body with eyes and head deviation to the right side, and then she has clonic jerking of the right arm and leg. Some of her seizures involve left hand dystonic movement and secondary generalization. Interictal EEG showed multifocal sharp waves in the left and right temporal and frontal regions. However, majority of sharp waves were in the left temporal region (Figure 4). Ictal onset was in the left frontotemporal region in three of the recorded seizures. The other two seizures were difficult to lateralize on scalp EEG. Brain MRI showed nonenhancing lesion in the left mesial temporal

region, which was hyperintense on T2 images (Figures 5 and 6).

Even though scalp EEG provided an evidence of multifocal bilateral epileptic process, the decision was made to proceed with left mesial temporal resection based on the following: (1) the presence of left mesial temporal lesion, (2) majority of epileptic activity was recorded from the left temporal region, (3) seizures were resistant to treatment with antiepileptic medications, and (4) patient's severe epilepsy caused significant global cerebral dysfunction, and she was not expected to have further deficit as a result of the planned surgery. The resection was done without any major complications (Figure 7). The pathology showed ganglioglioma

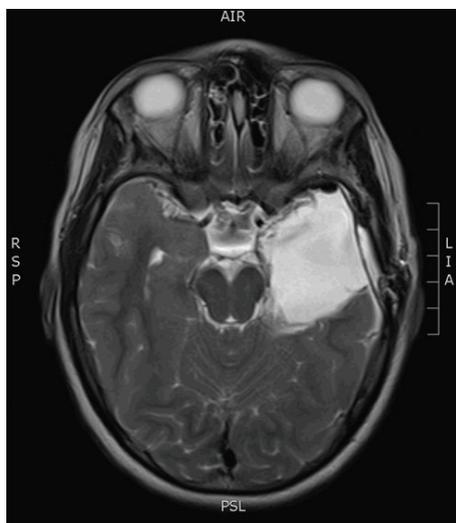


FIGURE 7: Postoperative axial T2-WI MRI scan at the same level after left temporal lobe resection.

(WHO grade I). On her four-month followup after surgery, the patient remained seizure-free, and she had remarkable improvement of her level of function.

4. Surgical Outcome of Children with Epileptic Encephalopathy in the Literature

In 2007, Wyllie et al. reported 50 pediatric patients with intractable epilepsy since early in life, developmental delay, and congenital or early acquired brain lesion on MRI [23]. They had focal surgical resection or hemispherectomy despite abundant generalized or bilateral multifocal epileptiform discharges on preoperative EEG. Postsurgically, 72% of these patients achieved seizure freedom, 16% had marked improvement, 12% were not improved. Interestingly, the authors reported no significant differences in the rate of seizure-free outcome in association with age at seizure onset or surgery, presence of hemiparesis, or focal clinical features during seizures, type of lesion, or surgery type. In these cases, the consideration of epilepsy surgery is usually influenced by multiple factors including the presence of a unilateral or strongly asymmetric congenital or early-acquired lesion on neuroimaging, the severity of the refractory epilepsy, the low risk of incurring a new postoperative neurologic deficit, and in some patients the presence of localizing clinical features during seizures. The most striking age-related finding in this cohort was the age at occurrence of brain lesions. 90% of the lesions were congenital, perinatal, or acquired during infancy, predominantly malformations of cortical development, or cystic encephalomalacia.

Lee et al. analyzed data of 27 children who had Lennox-Gastaut syndrome and underwent resective epilepsy surgery despite the presence of abundant generalized or generalized-contralateral maximal and multifocal epileptiform discharges on preoperative EEG [24]. 85% of these patients had identifiable lesions on brain MRI. At a mean of 33-month postoperative followup, 60% were seizure-free and another 15%

had infrequent seizures. Interestingly, two out of four patients without brain abnormalities on MRI became seizure-free after resective surgery was performed on the basis of electrophysiologic studies and concordant results in other multimodal neuroimages. Most, 73%, of the reported patients showed an increase in developmental quotient after seizures declined.

A more recent study by Liu et al., of 18 patients with Lennox-Gastaut syndrome treated surgically showed similar results [25]. The authors reported good seizure outcome when majority of epileptiform discharges were ipsilateral to the brain lesion despite the presence of contralateral ictal discharges. Also they noted a better intellectual outcome with younger age at surgery or shorter interval between onset of seizures and resective operation [25].

Several other studies have indicated that, in carefully selected patients, early surgery during infancy or childhood may reduce serious social, psychological, and educational consequences of uncontrolled seizures and maximize functional recovery [26–30].

Considering the overall clinical picture in epileptic encephalopathy syndromes, one might raise the concern that the generalized or bilateral multifocal epileptiform discharges could be evidence that the lesion seen on neuroimaging is only “the tip of the iceberg” of a more diffuse epileptic process. This concern is supported by the presence of global developmental delay, the diffuse nature of some of the early brain insults such as perinatal intraventricular hemorrhage or infection with infarction, and in many cases the absence of focal clinical features during seizures. Features that may overcome this concern included the catastrophic nature of the epilepsy experienced by these devastated patients, the lack of good response to currently available nonsurgical treatments, the relatively low risk for new postoperative deficits in patients with preexisting hemiparesis, limited language development and/or poor functional level, and the characteristics of the lesion on preoperative MRI [23].

5. Conclusions

Early reports of successful surgery for selected children with infantile spasms and hypsarrhythmia were met with skepticism [31], but subsequent experience with similar clinical scenarios was supportive of this approach [7, 19, 21–25]. In catastrophic cases of epileptic encephalopathy, indications for surgery and assessment of its results require different rules from those that apply to adults and older children [32]. Epilepsy surgery in carefully selected patients may be effective in controlling seizures and improving neurological function despite the lack of localized epileptic pattern on EEG. It is expected that this new paradigm for pediatric epilepsy surgery will be refined in the future by additional clinical experience and further studies.

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