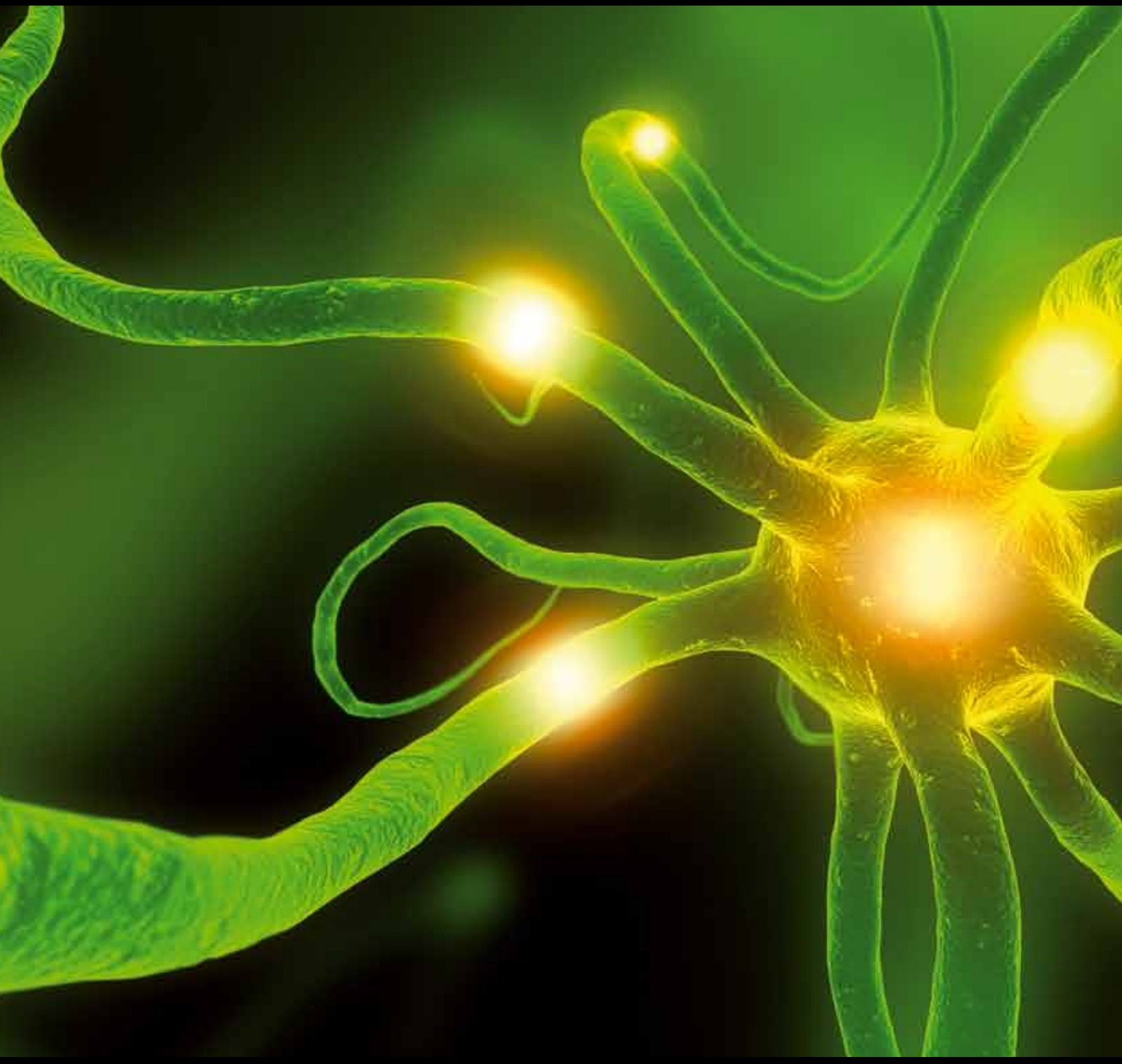
Epilepsy Research and Treatment

Epileptic Encephalopathy

Guest Editors: Nicola Specchio, Rod C. Scott, and Colin Ferrie



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Editorial Board

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Editorial

Epileptic Encephalopathy

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Epileptic encephalopathies are conditions in which epileptic activity itself is postulated to contribute to severe cognitive and behavioural impairments above and beyond what might be expected from the underlying pathology alone.

The term has been used in two ways: (1) as a generic classification term for epilepsies with severe cognitive and behavioural outcomes and (2) as a pathophysiological process. We argue that the term is not synonymous with "severe epileptic syndrome". Epileptic encephalopathy can complicate many different epileptic conditions. In some it is an almost constant feature (e.g., Lennox-Gastaut syndrome), in others expected but not invariable (e.g., West syndrome) whilst in yet others it may or may not occur with almost equal frequency (e.g., Doose syndrome). Epileptic encephalopathy very occasionally complicates otherwise benign epilepsies (e.g., benign rolandic epilepsy). Epileptic encephalopathy is a dynamic condition that may persist over time causing increasingly severe functional effects or else it may improve and remit, either spontaneously or with treatment which suppresses the proposed causative epileptic activity.

Fundamental to the concept of epileptic encephalopathy is that the cognitive and other problems which characterise it result from epileptic activity, rather than being a consequence of any underling cerebral pathology (whether genetic, structural, metabolic inflammatory, etc.) which may itself be causing the epilepsy. However, all spontaneous epileptic phenomena in humans are a function of some kind of brain disease (genetic through to structural) and therefore it is likely that all cognitive impairments in children with epilepsy are at least in part a function of aetiology.

When a brain disorder gives rise to both epilepsy and cognitive and behavioural problems, it should not be classed as an epileptic encephalopathy, but rather as an "epileptogenic encephalopathy". The crucial difference being that the cognitive and behavioural problems are not a consequence of the epilepsy, but of the cerebral pathology. However, in epileptogenic encephalopathies seizures may aggravate cognitive and behavioural problems and thus treatment of seizures may improve outcomes.

Some disorders, mostly genetically determined and characterised by the onset of seizures in the first months of life and with developmental stagnation are best considered as "early onset epilepsies with encephalopathy" rather than epileptic encephalopathy. Both the epilepsy and the encephalopathy appear to be symptoms of a known or unknown genetic defect and there is no evidence that epileptic activity is primarily responsible for the developmental stagnation. Examples of this include disorders associated with CDKL5, SCN1A, and PCDH19 mutations.

This special issue contains five papers on epileptic encephalopathy. The paper by S. Khan and R. Al Baradie is a review of the clinical and neurophysiological features of the most common epileptic encephalopathies occurring in infancy and childhood whilst the paper by Z. Kural and A. F. Ozer examines current approaches to treatment of childhood and adult epileptic encephalopathies. They emphasise that an appropriate differential diagnosis of epileptic seizures and "infraclinical epileptic discharges" are crucial to the management of seizures, epileptic discharges and the related cognitive regression.

E. Sheppard and S. Lippé examine the possible consequences of prolonged and recurrent status epilepticus on cognitive development. They correlate the occurrence and severity of epileptic encephalopathy with risk factors such as aetiology, duration and frequency and age at onset of seizures. D. Brazzo et al. explore a specific type of epileptic encephalopathy (status epilepticus during sleep), including the pathophysiological mechanisms underling the condition and the insights which may come form the use of new and emerging imaging techniques.

In the paper J. Ricardo-Garcell et al. examine associated risk factors that can contribute to the cognitive impairment in patients with epileptic encephalopathy. Prematurity and severe asphyxia were often responsible of neurodevelopmental delay. In such cases distinguishing the role of epilepsy from the underlying brain pathology in causing the encephalopathy is very difficult.

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Research Article

Epileptic Encephalopathies: An Overview

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Epileptic encephalopathies are an epileptic condition characterized by epileptiform abnormalities associated with progressive cerebral dysfunction. In the classification of the International League Against Epilepsy eight age-related epileptic encephalopathy syndromes are recognized. These syndromes include early myoclonic encephalopathy and Ohtahara syndrome in the neonatal period, West syndrome and Dravet syndrome in infancy, myoclonic status in nonprogressive encephalopathies, and Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and epilepsy with continuous spike waves during slow wave sleep in childhood and adolescences. Other epileptic syndromes such as migrating partial seizures in infancy and severe epilepsy with multiple independent spike foci may be reasonably added. In this paper, we provide an overview of epileptic encephalopathies including clinical neurophysiological features, cognitive deterioration, and management options especially that these conditions are generally refractory to standard antiepileptic drugs.

1. Introduction

Epileptic encephalopathy is defined as a condition in which epileptiform abnormalities are believed to contribute to the progressive disturbance in cerebral function, but this definition may be ambiguous [1]. The report of the International League Against Epilepsy (ILAE) Task Force on classification and terminology includes 8 syndromes under epileptic encephalopathies: early myoclonic encephalopathy, Ohtahara syndrome, West syndrome, Dravet syndrome, myoclonic status in nonprogressive encephalopathies, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and epilepsy with continuous spike waves during slow-wave sleep [1]. To these syndromes, the migrating partial seizures in infancy and severe epilepsy with multiple independent spike foci may be reasonably added [2].

A common feature is that these disorders are usually refractory to standard antiepileptic drugs (AEDs) [3]. As a result, more aggressive use of AEDs considered effective in suppressing interictal epileptiform discharges (e.g., benzodiazepines, valproic acid, and lamotrigine), immunomodulatory therapies (e.g., corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis), ketogenic diet, and surgical options is often considered [3]. In this paper, epileptic encephalopathies will be dealt with in the following concept: a particular group of usually age-related and extremely intractable epilepsies with characteristic generalized minor seizures and massive epileptic EEG abnormalities, both of which cause stagnation or deterioration in mental and cognitive functions in addition to the preexisting developmental deficit due to organic brain damage [1–3].

2. Epileptic Encephalopathy Syndromes in Infancy

2.1. Early Infantile Epileptic Encephalopathy (Ohtahara Syndrome). Ohtahara syndrome is the earliest form of the age-dependent neonatal epileptic encephalopathies and was first described by Ohtahara and colleagues in 1976 [4]. It is often defined as "Early Infantile Epileptic Encephalopathy (EIEE) with burst-suppression" or "early myoclonic encephalopathy (EME)" [4]. Symptoms appear within the first 3 months of birth and usually within the first 10 days. Often symptoms will appear with the first few hours after birth, and in some cases mothers have felt possible seizures activity in utero. Onset is acute in previously normal children [4].

Main seizure pattern is tonic spasms; other patterns include tonic/clonic, clonic, myoclonic, atonic, absences, partial, complex partial (with or without secondary generalization), gelastics, and Jacksonians. Seizures can appear in clusters or singly and patterns are likely to change with time. It is not uncommon for patterns to reappear at a later stage [4]. EEG pattern is characterized as burst suppression during both waking and sleeping states. This means that the EEG (electroencephalogram) tends to show periods of very little electrical brain activity followed by a burst of high spiky activity before returning to very low activity again. Sometimes, one side of the brain seems to be affected more than the other [5]. Seizures are intractable; although in some cases they can be improved through treatment. In general prognosis is poor with severe psychomotor retardation and significant learning difficulties. Frequently cases will progress to West syndrome or partial epilepsy (usually during infancy). Later a much smaller number develops to Lennox-Gastaut syndrome. Psychomotor development may be slightly better if the infants do not develop West or Lennox-Gastaut syndrome. Half of the children are likely to die in infancy or childhood [5, 6]. Although the disorder in incurable, much can be done to improve the lives not only of the children but also of the families. Seizure control is the main aim and will be attempted either through optimized dosages of anticonvulsants such as vigabatrin (Topamax), Dilantin, Zonegran, and Phenobarbitone, or through steroid therapies using ACTH and Prednisone. AEDs can be taken in either mono- or polytherapies. The quest for seizure control can be a slow and frustrating process. There is also the possibility of utilizing such treatments as the ketogenic diet, the VNS, or more invasive surgery, such as a partial resection or complete hemispherectomy. Physiotherapy and occupational therapies can help improve motor skills, while hippotherapy can help improve general mobility, strength, and endurance [7].

2.2. Early Myoclonic Encephalopathy. Early myoclonic encephalopathy, an epileptic syndrome with onset either in the neonatal period or the first months of life, is characterized by erratic, fragmentary, or massive myoclonus, partial seizures, and late tonic spasms. The prognosis is severe. Early myoclonic encephalopathy is characterized clinically by the onset of erratic or fragmentary myoclonus. Other types of seizures, including simple partial seizures, massive myoclonia, and tonic spasms, can also occur. Erratic, partial myoclonus usually appears as the first seizure, even as early as a few hours after birth. The myoclonus usually involves the face or extremities and may be restricted to an eyebrow, a single limb, or a finger. The jerks occur when infants are awake or asleep, and they are often described as "erratic" because they shift typically from one part of the body to another in a random, asynchronous fashion.

Frequency varies from occasional to almost continuous. In addition to limited partial myoclonus, generalized myoclonus may also be observed occasionally in some cases. Partial seizures are frequent and occur shortly after erratic myoclonus. The semiology of partial seizures is subtle, consisting, for instance, of eye deviation or autonomic phenomena such as apnea or flushing of the face. Tonic seizures are reported frequently and can occur in the first month of life or afterwards; they may occur both in sleep and wakefulness. From a clinical standpoint, the child presents a diffuse tonic contraction, usually extending to the extremities. Real epileptic spasms are rare and generally appear later. Neurologic abnormalities are constant: very severe delay in psychomotor acquisitions, marked hypotonia, and disturbed alertness, sometimes with vegetative state. Signs of peripheral neuropathy may also occur in rare cases [8]. Early myoclonic encephalopathy is believed to have various prenatal etiologies that often remain unknown. Some conditions, such as inborn error of metabolism, can produce the clinical and EEG picture typical of early myoclonic encephalopathy such as nonketotic hyperglycinemia, D glyceric acidemia, propionic acidemia, molybdenum cofactor deficiency, and methylmalonic acidemia. Few patients present with a clinical picture similar to early myoclonic encephalopathy with atypical burst-suppression pattern that recover completely after pyridoxine therapy. Some malformative disorders can also cause early myoclonic encephalopathy, but more often they produce Ohtahara syndrome [9]. In early myoclonic encephalopathy, EEG is characterized by a "burst-suppression" pattern with bursts of spikes, sharp waves, and slow waves, which are irregularly intermingled and separated by periods of electrical silence (Figure 1). The EEG paroxysms may be either synchronous or asynchronous over both hemispheres. There is no normal background activity. The burst-suppression pattern usually evolves into atypical hypsarrhythmia or into multifocal paroxysms after 3 to 5 months of life. Erratic myoclonus does not generally have an ictal EEG counterpart. Partial seizures have EEG characteristics similar to those of neonatal fits. The CT and MR findings vary and are related to etiology. The brain may be either grossly normal or have asymmetrical enlargement of one hemisphere, dilatation of the corresponding lateral ventricle, or cortical and periventricular atrophy [10]. Considering the inborn error of metabolism reported above, the serum levels of amino acids should be determined, especially glycine and glycerol metabolites and organic acids, as well as the amino acids in the cerebrospinal fluid [4, 8, 9]. The prognosis for early myoclonic encephalopathy is poor and there is no effective therapy for early myoclonic encephalopathy [9, 10].

2.3. Infantile Spasms (West Syndrome). West syndrome usually occurs in the first year of life and consists of the triad of infantile spasms, developmental deterioration, and a hypsarrhythmia pattern on EEG [11]. The epileptic spasms are brief, generalized seizures involving extension and/or flexion axially, and of the extremities. An individual spasm lasts for seconds, often longer than typical myoclonic seizures, though not as long as most tonic seizures. The spasms may be subtle and may be isolated at onset, typically clustering later in the course. Several clusters per day, particularly in drowsiness, are characteristic [11, 12]. Hypsarrhythmia, the typical interictal EEG finding, consists of a disorganized

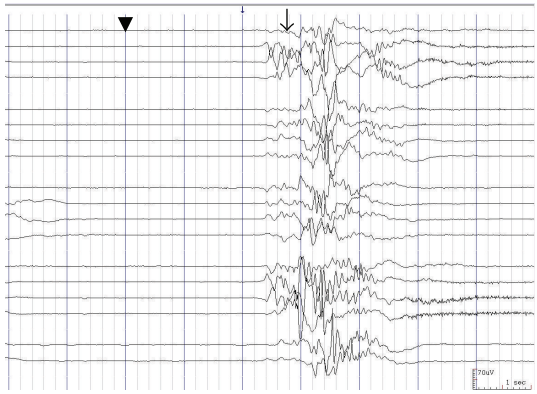

Figure 1: EEG is characterized by a "burst-suppression" pattern with bursts of spikes, sharp waves, and slow waves (arrow), which are irregularly intermingled and separated by periods of electrical silence (arrow head).

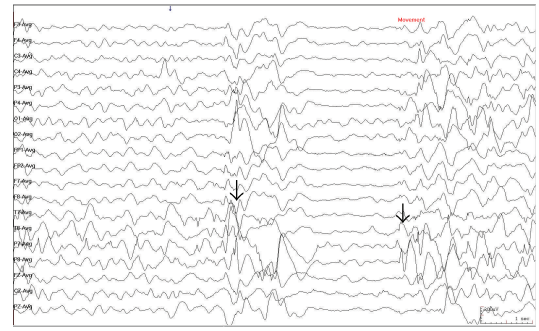

Figure 2: Hypsarrhythmia, the typical interictal EEG finding, consists of a disorganized pattern with asynchronous, very high amplitude slowing and frequent multifocal spike and sharp wave discharges (arrows).

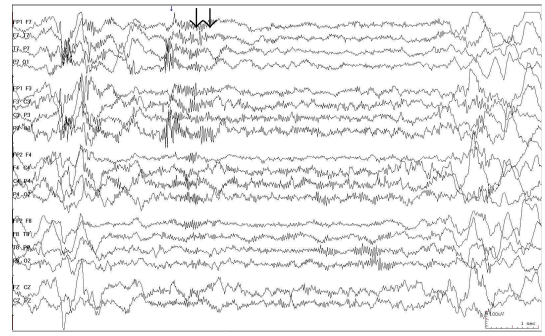

Figure 3: The ictal EEG in West syndrome typically reveals a generalized slow wave followed by diffuse voltage attenuation (electrodecrement), which may associate with a spasm or be only electrographic without clinical correlate (arrows).

pattern with asynchronous, very high amplitude slowing and frequent multifocal spike and sharp wave discharges (Figure 2). The ictal EEG typically reveals a generalized slow wave followed by a diffuse voltage attenuation (electrodecrement) (Figure 3), which may associate with a spasm or be only electrographic (without clinical correlation) [12]. No clear etiology is found in approximately 40% of cases. 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 [12, 13]. Variation in studying methodologies prohibits a clear recommendation for first line treatment; however, ACTH and vigabatrin are usually used in practice. Corticosteroids may be less efficacious than ACTH, although they are effective. Vigabatrin may be more efficacious in tuberous sclerosis. Other agents that are efficacious include valproate, levetiracetam, topiramate, zonisamide, lamotrigine, and benzodiazepines [11]. The ketogenic diet is helpful in most cases [12]. Focal cortical resection or hemispherectomy may be considered for cases that are lesional and medically intractable [11–13]. Development remains unaffected only in a minority. Most children experience slowing, plateauing, or regression of their developmental trajectory. The developmental prognosis partially depends on the etiology. No specific AED has been shown to affect long-term developmental outcome. An extensive literature review revealed that 16% had normal development, and 47% had continued seizures at an average followup of 31 months. When classified by etiology, normal development was described in 51% of cryptogenic cases versus only 6% of symptomatic cases. Approximately 17% of cases evolved into Lennox-Gastaut syndrome [12].

2.4. Malignant Epilepsy with Migrating Partial Seizures in Infancy. Onset of this rare syndrome occurs in the first year of life and may occur in the neonatal period. It is characterized by frequent partial seizures of multifocal onset, with autonomic or motor involvement. The seizures increase in frequency and may become near continuous. Clinical semiology of the seizures include lateral head and eyes deviation, focal clonic seizures of the eyes, face or limbs, unilateral or bilateral focal tonic seizures, automatic movements such as chewing, mastication, autonomic features such as apnea, salivation or facial flushing and secondary generalized tonic clonic seizures. The interictal EEG reveals multifocal epileptiform activity and slowing, diffuse slowing of the background activity. A few patients may have a normal EEG. Then the EEG background activity became slow with fluctuating asymmetry between different recordings. Initially sleep-waking cycle can be identified; spindles are rare and asymmetric. The ictal EEG confirms multifocal onsets, which may shift from seizure to seizure. In most cases, there is no clear etiology or structural problems, suggesting that genetic factors may be causative or contributory. Seizures are often difficult to control with standard AEDs. Bromides, stiripentol, and clonazepam may be helpful in some cases. Developmental regression is common, and death has been reported in infancy and childhood in severe cases [14].

2.5. Myoclonic Status in Nonprogressive Encephalopathies. This rarely reported disorder has onset in infancy or early childhood, with onset usually during the first year of life. Seizures typically begin with partial motor seizures, although

myoclonic status may occur at onset. Myoclonic absences, massive myoclonias, and rarely generalized or hemiclonic seizures may occur. Myoclonias may be multifocal and occur with startles. Myoclonic status epilepticus may be recurrent. Motor abnormalities and movement disorders are common. The interictal EEG consists of multifocal epileptiform discharges and background slowing. Epileptiform discharges are potentiated in sleep, in some cases similar to an ESES pattern. Ictal EEG recording may demonstrate generalized slow spike and wave, or an absence pattern, depending on the seizure type. A genetic cause is identifiable in approximately half of children, including Angelman syndrome and 4p-syndrome. Other reported causes include hypoxic-ischemic injury and cortical dysplasia. Episodes of myoclonic status may respond to benzodiazepines. AEDs that may be efficacious include valproate with ethosuximide or clobazam. Children have a poor prognosis, experiencing developmental regression and eventual severe mental retardation. The repeated episodes of myoclonic status may contribute to cognitive deterioration [15].

2.6. Severe Myoclonic Epilepsy in Infancy (SMEI) Dravet Syndrome. This is an uncommon form of childhood epilepsy. Out of 500 children with epilepsy, only one, or at most two, child is likely to have this form of epilepsy. It is also called Dravet syndrome. The epilepsy starts with seizures which may not initially differ from those associated with feverish illnesses. This syndrome tends to develop during the second year of life. It may not be possible to make this diagnosis until the child is two, three, or even four years old. The seizures begin in the first year of life. They are most often associated with high temperatures and often just involve one side of the body, although both sides of the body may be involved. The seizures are characterized by jerking rather than stiffness and jerking. They often recur quite frequently in the first year of life. However, at this time it is not easy to differentiate these children from others with febrile convulsions who get better and who do not go on to develop other types of seizure. During the second year of the life of children with SMEI, seizures become more frequent and persistent, are often more obviously partial (involving one part of the body), and no longer occur when a child has a high temperature but at any time of day and night. In addition to the partial seizures are the myoclonic jerks. Often the children are photosensitive (have seizures brought on by flashing lights). Seizures may also sometimes be brought on by hot environments or hot showers or baths. The early development of affected children is usually normal but once the myoclonic seizures and partial seizures start in their second year of life, children may lose skills or their developmental progress may slow down. The child's speech and language may be particularly affected. The electroencephalogram (EEG) which records the electrical activity in the brain is usually normal early in this condition. Later, by the time the child is 18 months old, there is evidence of epileptic activity with spike and wave or polyspike discharges, which occur either as single event or in bursts. These may be generalized involving the whole brain or occurring just from on small area of the brain. Some children show EEG evidence of sensitivity to flashing lights but this does not occur in all. Brain scans are usually normal. More recently a specific genetic abnormality, called a "mutation", has been found in at least 70 per cent of children with SMEI. This mutation is known as the "SCN1A" mutation. It is likely that other mutations will also be found in children with SMEI. The mutation can be looked for in a simple blood test and this has been very helpful in making or confirming a diagnosis of this epilepsy syndrome. SMEI is very resistant to anti-epileptic drugs. Phenobarbital, sodium valproate (Epilim), and lamotrigine (Lamictal) are usually tried first. However, lamotrigine may actually make the myoclonic seizures worse in many children. Other options include a medication called stiripentol, topiramate (Topamax), clonazepam (Rivotril), and clobazam (Frisium). A combination of sodium valproate with either topiramate or stiripentol may be the most helpful. A short course of a steroid (called prednisolone) and the ketogenic diet may also be helpful. Because children with SMEI always have learning difficulties, they will also need full educational assessment and support [16, 17].

3. Epileptic Encephalopathy Syndromes in Childhood

3.1. Lennox-Gastaut Syndrome LGS. Childhood epileptic encephalopathy, or Lennox-Gastaut syndrome (LGS), is a devastating pediatric epilepsy syndrome constituting 1–4% of childhood epilepsies. The syndrome is characterized by multiple seizure types; mental retardation or regression; abnormal findings on electroencephalogram (EEG), with paroxysms of fast activity and generalized slow spike and wave discharges (1.5–2 Hz) (Figure 4). The most common seizure types are tonic-axial, atonic, and absence seizures, but myoclonic, generalized tonic-clonic, and partial seizures can be observed (see clinical presentation). An EEG is an essential part of the workup for LGS. Neuroimaging is an important part of the search for an underlying etiology. LGS can be classified according to its suspected etiology as either idiopathic or symptomatic. Patients may be considered to have idiopathic LGS if normal psychomotor development occurred prior to the onset of symptoms, no underlying disorders or definite presumptive causes are present, and no neurologic or neuroradiologic abnormalities are found. In contrast, symptomatic LGS is diagnosed if a likely cause can be identified as being responsible for the syndrome. Population-based studies have found that 70–78% of patients with LGS have symptomatic LGS. Underlying pathologies in these cases include encephalitis and/or meningitis, tuberous sclerosis, brain malformations (e.g., cortical dysplasias), birth injury, hypoxia-ischemia injury, frontal lobe lesions and trauma. Overall, LGS accounts for 1–4% of patients with childhood epilepsy but 10% of patients with onset of epilepsy when younger than 5 years. The prevalence of LGS in Atlanta, GA, USA, was reported as 0.26 per 1000 live births. LGS is more common in boys than in girls. The prevalence is 0.1 per 1000 population for boys, versus 0.02 per 1000 population for girls (relative risk, 5.31). The

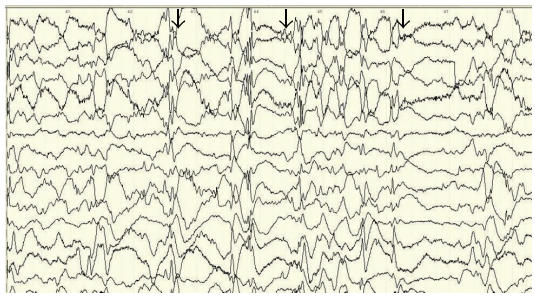

Figure 4: EEG in Lennox-Gastaut syndrome with paroxysms of fast activity and generalized slow spike and wave discharges (1.5–2 Hz) (arrows).

mean age at epilepsy onset is 26–28 months (range, 1 d to 14 y). The peak age at epilepsy onset is older in patients with LGS of an identifiable etiology than in those whose LGS has no identifiable etiology. The difference in age of onset between the group of patients with LGS and a history of West syndrome (infantile spasm) and those with LGS without West syndrome is not significant. The average age at diagnosis of LGS in Japan was 6 years (range, 2–15 y). Epidemiologic studies in industrialized countries (e.g., Spain, Estonia, Italy, and Finland) have demonstrated that the proportion of epileptic patients with LGS seems relatively consistent across the populations studied and similar to that in the United States. The prevalence of LGS is 0.1–0.28 per 1000 population in Europe. The annual incidence of LGS in childhood is approximately 2 per 100,000 children. Among children with intellectual disability, 7% have LGS, while 16.3% of institutionalized patients with intellectual disability have LGS. Long-term prognosis overall is unfavorable but variable in LGS. Longitudinal studies have found that a minority of patients with LGS eventually could work normally, but 47–76% still had typical characteristics (mental retardation, treatment-resistant seizures) many years after onset and required significant help (e.g., home care, institutionalization). A variety of therapeutic approaches are used in LGS, ranging from conventional antiepileptic agents to diet and surgery. Unfortunately, much of the evidence supporting these approaches is not robust, and treatment is often ineffective. The medical treatment options for patients with LGS can be divided into the following 3 major groups: The medical treatment options for patients with LGS include the use of antiepileptic drugs such as valproic acid and benzodiazepines such as clonazepam, nitrazepam and clobazam, vigabatrin, zonisamide, lamotrigine, topiramate and rufinamide proven effective by double-blind placebo-controlled studies (e.g., lamotrigine, topiramate, felbamate, and rufinamide). The ketogenic diet may be useful in patients with LGS refractory to medical treatment. Surgical options for LGS include corpus callosotomy, vagus nerve stimulation, and focal cortical resection [18–21].

3.2. Electrical Status Epilepticus during Slow Sleep (ESES). A disorder in which sleep induced an EEG pattern characterized by "subclinical" spikes and waves occurring almost continuously during slow sleep and appearing every night for a variable length of time in children was reported under the title of "subclinical electrical status epilepticus induced by sleep in children". The disorder was later termed "electrical status epilepticus during sleep" [22]. The clinical manifestations of this syndrome include a status heterogeneous epileptic disorder, deterioration of neuropsychological functions associated with or independent from the epileptic disorder, and deterioration of motor functions. The typical EEG pattern of continuous spikes and waves during slow sleep (Figures 5 and 6) is also an essential and absolute feature for the recognition of the syndrome. The age at which the first seizure occurs ranges between 2 months and 12 years, with a peak around 4 and 5 years. This event can be preceded by either normal psychomotor development or abnormal signs indicating preexisting encephalopathy such as hemiparesis, hemiplegia, spastic quadriplegia, diffuse hypotonia, and ataxia. The seizure types occurring in the disorder can be both partial and generalized. They include unilateral or bilateral clonic seizures, generalized tonic-clonic seizure, absences, partial motor seizures, complex partial seizures, or epileptic falls. They may occur during wakefulness or sleep. Tonic seizures, however, never occur. The first seizures are reported to be nocturnal and of unilateral type in almost one-half of the cases reported. At onset, the frequency of seizure attacks is low. At the time of discovery of the typical nocturnal EEG pattern, however, the epileptic seizures frequently change in severity and frequency. Absences and epileptic falls herald the appearance of continuous spikes and waves during slow sleep and seizure frequency increases, both during wakefulness and sleep. About 60% of patients also exhibit several types of seizures [22, 23]. The characteristic feature of this disorder is the appearance of continuous spike-wave discharges on the EEG during slow sleep. Most researchers assert that more than 85% of NREM sleep is occupied by spike-wave discharges; however, quantitative studies of different sleep stages and of temporal evolution of this EEG disturbance have not been carried. The typical EEG changes appear 1 year to 2 years after the first seizure and are associated with behavioral deterioration. Focal and generalized interictal spikes occur before this time and persist during wakefulness and REM sleep after the appearance of continuous spike waves during slow-wave sleep [24]. The cause of electrical status epilepticus during slow sleep is unknown. Long-lasting persistence of continuous spike waves during sleep is postulated to be responsible for the neuropsychiatric abnormalities in electrical status epilepticus during slow sleep; secondary bilateral synchrony is the mechanism underlying continuous spikes and waves during slow sleep. In this respect the apparent generalized seizures (absences, tonic-clonic attacks) occurring in this condition have in fact a focal onset as demonstrated by interhemispheric peak latencies of their EEG correlates, phase reversal of spikes on unilateral frontal regions, and studies of coherence and phase analyses. A localized metabolic abnormality has been also revealed by means of PET studies. Therefore, although electrical status epilepticus during slow sleep is currently classified among the epilepsies undetermined whether focal

or generalized, consistent data support the view that this syndrome is to be included in the domain of localization-related epilepsies, of cryptogenic or symptomatic nature [23–25]. Electrical status epilepticus during slow sleep is a rare order. One study revealed an incidence of 0.5% among 12,854 children evaluated during a 10-year period. There is no obvious gender preponderance [23]. The seizures in electrical status epilepticus during slow sleep are self-limited and disappear in the midteens. The good seizure outcome is independent of the etiology and is observed also in cases with cortical malformations such as multilobar polymicrogyria. The characteristic EEG patterns during slow-wave sleep also disappear at approximately the same time, but focal interictal spikes may persist. Improvement in language dysfunction, mental retardation, and psychiatric disturbances generally occurs but it is variable and individualized. The majority of affected children never return to normal levels, particularly in the verbal area and attention [25, 26]. Epileptic seizures may or may not respond to a variety of drugs including benzodiazepines, valproate, ethosuximide, carbamazepine, and phenytoin. Despite of the fact that the seizures may be refractory to therapy for months to years, the long-term prognosis of epilepsy is favorable with the disappearance of seizures in all cases. Only benzodiazepines and adrenocorticotrophic hormone have been reported to suppress the electrical status and perhaps to improve language function. However, the positive effects are often transient [23]. In individual cases, chronic oral treatment with clobazam, lorazepam, and clonazepam associated with other antiepileptic drugs usually valproate seemed to have a long-lasting effect. Short cycles (3 to 4 weeks) of relatively high doses of diazepam (0.5 mg/kg) following a rectal diazepam bolus of 1 mg/kg have also been reported to be effective. At the present time, the combined use of benzodiazepines and valproate is considered the treatment of choice in this condition. On the other hand, polytherapy should be avoided. A detailed evaluation of antiepileptic regimens in 88 patients demonstrated that the reduction in polytherapy coincided with an improvement of the syndrome. It was also suggested that the drug overload and some medications (such as carbamazepine) could play a role in the maintenance of continuous spikes and waves during slow sleep. In cases of electrical status epilepticus during sleep with severe language impairment, a progressive and long-lasting improvement of the language function has been obtained applying the surgical procedure of multiple subpial transections of the region of focal epileptic discharges [27].

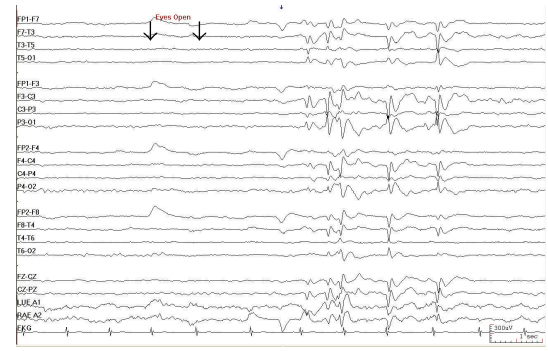

Figure 5: Electrical status epilepticus during slow sleep (ESES), disappearance of spike waves with eye opening (arrows).

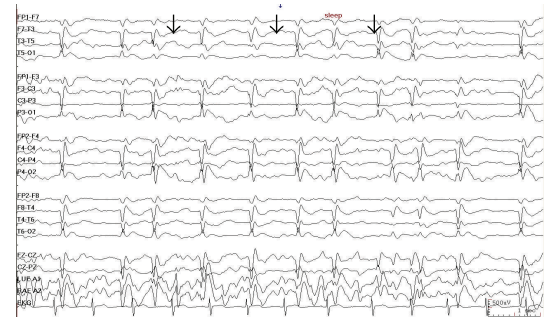

Figure 6: Electrical status epilepticus during slow sleep (ESES), continuous spike-wave discharges on the EEG during slow sleep (arrows).

3.3. Acquired Epileptic Aphasia Landau-Kleffner Syndrome (LKS). Acquired epileptic aphasia typically develops in healthy children who acutely or progressively lose receptive and expressive language ability coincident with the appearance of paroxysmal electroencephalographic (EEG) changes [28].

In most cases described in detail, a clearly normal period of motor and language development occurs before acquired epileptic aphasia symptoms appear. However, in the last 2-3 decades, several reported cases have been difficult to classify, because the patients' presenting symptoms appear to have variants of those originally described. In one case, expressive language deteriorated instead of receptive language, whereas in another case, a brief period of normal language development (single words) was followed by language regression with abnormal EEG findings. Acquired epileptic aphasia must be differentiated from autism with minimal language regression, especially when it is associated with isolated EEG abnormalities. Many current researchers classify acquired epileptic aphasia as part of the syndrome of electrical status epilepticus of sleep (ESES) [25]. Whether seizures and epileptiform discharges cause language dysfunction in acquired epileptic aphasia (AEA) is disputed. Aphasia and electroencephalographic (EEG) abnormalities might have a common cause (e.g., a left temporal brain astrocytoma or head injury). Some authors speculate that reinforcement of synaptogenesis mediates the neurologic deficits in acquired epileptic aphasia and that epileptiform discharges during a critical period of synaptic reinforcement or pruning in turn mediate the reinforcement of synaptogenesis [28]. In affected children, aphasia usually appears at age 4–7 years, and there is a slight male predominance (male-to-female ratio, 1.7 : 1). However, symptom onset has been described in patients as young as 18 months and in those as old as 13 years. This discussion excludes the congenital cases with typical electroencephalographic (EEG) patterns and little or no language development; in such cases,

the precise age of onset can never be determined. Long-term outcome studies of patients with acquired epileptic aphasia are limited by the lack of uniformity in diagnostic criteria. About half the patients have some fluctuation in aphasia, and the fluctuations usually occur over several months. On occasion, aphasia may worsen for as long as 7 years after the disease onset [29]. The treatment of acquired epileptic aphasia is far from standard, and many therapeutic modalities have been tried with variable success. Among these are anticonvulsant drugs, corticosteroids (e.g., adrenocorticotropin hormone (ACTH)), ketogenic diet, and surgical intervention with multiple subpial transections (MSTs). The calcium channel blocker nicardipine has been used in the treatment of acquired epileptic aphasia. In the initial report of 4 patients that suggested the use of nicardipine for acquired epileptic aphasia, nicardipine was given in association with anticonvulsant medications (carbamazepine, valproic acid) and corticosteroids (3 of 4 cases). However, cessation of nicardipine was associated with acute speech deterioration. The dose of nicardipine was 1 mg/kg/d or 60 mg/d for large patients. A few case reports have demonstrated that intravenous gamma globulin may be useful in acquired epileptic aphasia, but repeated doses may be necessary [30]. Many commonly used anticonvulsant agents effective against partial or generalized seizures have been used in acquired epileptic aphasia with variable success. Phenobarbital, carbamazepine, and phenytoin are often ineffective in halting the electroencephalographic (EEG) discharges, and aphasia may worsen the electrographic activity. In a few cases, the drugs may actually worsen the picture, especially in patients with drop seizures and atypical absences. Valproic acid, ethosuximide, and benzodiazepines alone or in combination have been partially or transiently effective in some cases. Benzodiazepines, especially clobazam (in Europe) and midazolam, have been most effective when given intravenously (IV). Both the impracticality of this mode of administration and its short-lived effect have limited its use. Diazepam 0.5 mg/kg given rectally (PR) at bedtime is sometimes effective. This treatment is used in 4- to 6-week courses on and off to avoid tachyphylaxis. The Boston Children's Hospital Epilepsy Group has used continuous diazepam 0.5–0.3 mg/kg given orally (PO) in acquired epileptic aphasia for periods up to 1 year. Several studies have shown levetiracetam to be beneficial when used as monotherapy in the treatment of electrical status epilepticus of sleep (ESES), continuous spike wave in slow-wave sleep (CSWS), and benign idiopathic focal epilepsies in childhood. In a recent study, Kramer et al. found clobazam and levetiracetam to be the most efficacious antiepileptic drugs in the treatment of ESES. In a case report, felbamate 45 mg/kg/d was successful in treating seizures and aphasia. However, the high frequency of aplastic anemia and liver dysfunction with this drug limits its use [31, 32].

4. Conclusions

Epileptic encephalopathies are severe brain disorders of early age that manifest with (1) electrographic EEG paroxysmal activity that is often aggressive, (2) seizures that are usually multiform and intractable, (3) cognitive, behavioral and neurological deficits that may be relentless, and (4) sometimes early death. The concept of "epileptic encephalopathies" is based on the assumption that aggressive ictal (seizure) and electrical (electrographic) epileptogenic activity during brain maturation is the main causative factor of progressive cognitive and neuropsychological deterioration or regression. Conversely, this deleterious epileptic activity is a specific age-related brain reaction of excessive neocortical excitability to different pathological conditions, which are focal or diffuse, of symptomatic or idiopathic cause. This age-related epileptogenic reaction is peculiar to the immature brain and varies significantly in accordance with the stage of brain maturity at the time that this occurs. Thus, EEG demonstrates primarily burst-suppression patterns in the neonatal period, hypsarrhythmia in infancy, and slow generalized spike-wave discharges (GSWDs) in early childhood. With advancing age, the seizure and electrographic epileptogenic features may evolve from one to another age-related stage that is from burst suppression to hypsarrhythmia and then to slow GSWD. All epileptic encephalopathies have a tendency to abate, discontinue, or even stop in adolescence but often with serious neurocognitive residuals.

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Research Article

Epileptic Encephalopathies in Adults and Childhood

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Epileptic encephalopathies are motor-mental retardations or cognitive disorders secondary to epileptic seizures or epileptiform activities. Encephalopaties due to brain damage, medications, or systemic diseases are generally not in the scope of this definition, but they may rarely accompany the condition. Appropriate differential diagnosis of epileptic seizures as well as subclinical electroencephalographic discharges are crucial for management of seizures and epileptiform discharges and relative regression of cognitive deterioration in long-term followup. Proper antiepileptic drug, hormonal treatment, or i.v. immunoglobulin choice play major role in prognosis. In this paper, we evaluated the current treatment approaches by reviewing clinical electrophysiological characteristics of epileptic encephalopathies.

1. Introduction

Epileptic encephalopathy is described as epilepsy with ictal and interictal epileptiform anomalies (clinical and EEG) and progressive cerebral dysfunction according to the classification and terminology criteria of International League against Epilepsy (ILAE) [1–3]. The following are syndromes meeting the criteria: Dravet syndrome, Doose syndrome, ESES (electrical status epilepticus of slow sleep) or CSWSS (continuous spike waves of slow sleep), Landau-Kleffner syndrome, Lennox-Gastaut syndrome, Ohtahara syndrome, and West syndrome [4]. Severe epilepsy with multiple independent spike foci is recently included in this group [2, 4].

Steroid-sensitive epileptic encephalopathies such as Hashimoto encephalopathy, progressive myoclonus epilepsies, and neonatal epileptic encephalopathies are not classified in this group but are worth mentioning [5–10].

2. Dravet Syndrome or Severe Myoclonic Epilepsy of Infancy

An important group of epileptic encephalopathies that are resistant to treatment, a severe myoclonic epilepsy of childhood, first described by Dravet in 1978, is characterized with recurrent febrile and/or afebrile, hemiclonic or generalized seizures, and status epilepticus. Child's development stops or retards after the onset of seizures [11–14]. Prevalence is unknown. The incidence is 0.5–1/40.000 and develops in 3–5% and 6.1–8.2% of all epilepsies in the first year and within the 3 years of life, respectively. Male-female ratio is 2 : 1. The most common cause is SCN1A mutations or deletions (35%) [11, 15–17]. Consequences in patients who reached adulthood and were observed for long term as well as neuropathology of the disease are unknown.

Patients with family history of febrile convulsion or epilepsy are reported to consist 25–71% in various patient series. Incidence is also significant in identical twins. GEFS is (+) in most of the cases. Ten percent of the cases are asymptomatic and SCN1A mutation is reported in their mildly affected family members. The possible genes involved are shown to be SCN1B, GABRG2, PCDH19, SCN2A, and 2q SCN [12, 18–26]. On the other hand, the association of SCN9A with febrile convulsions and Dravet's syndrome is also emphasized [27].

Common characteristics of Dravet's syndrome in animal models and patient groups are increased interictal epileptiform discharges or epileptic seizures due to sensitivity to increased body temperature and increased seizure frequency and severity due to aging [12, 13, 26, 28]. The abovementioned characteristics refer to juvenile form of Dravet's

syndrome and are based on solid evidence from several studies. Sufficient data about the adult form is not available [12, 29]. MRI findings are normal in most of the cases. Adult form of Dravet's syndrome may present with cerebral-cerebellar atrophy or cerebellar atrophy only [29].

Between ages of 1–5, myoclonic seizures may manifest with massive, generalized myoclonic jerks, and sudden falling attacks. Myoclonic jerks increase throughout the day and with emotional lability and disappear in sleep. Focal seizures may develop in 45–80% of the cases between 4 months and 4 years in simple partial motor or complex partial form, persisting as unilateral seizure or may develop into generalized seizure [11, 15, 30].

EEG is generally normal within the first 12 months. Generalized spike, spike and wave (5-6 sec) complexes may be observed in multiple foci localized in central regions and vertex photosensitivity is reported in 50% of the cases. Unexpected EEG findings have recently been reported [11, 28, 30].

Treatment is resistant to several medications. Carbamazepine and lamotrigine are shown to exacerbate the seizures. Effects of other anticonvulsants vary. VAP, TPM, and LEV are the most promising agents used in USA. In Europe, more successful results are achieved by combining stiripentol, a cytochrome P450 inhibitor, with clobazam (CLB) and VPA, especially in prevention of status epilepticus [12, 31]. Recent studies indicate that addition of a voltage-gated calcium channel blocker, such as verapamil, to anticonvulsant therapy is beneficial. Ketogenic diet is another method for management or minimizing seizure frequency [31–37].

3. Myoclonic-Astatic Epilepsy or Doose Syndrome

Myoclonic-astatic epilepsy or Doose syndrome is a form of generalized epilepsy developing between 7 months and 6 years of life with myoclonic attacks, absence and tonic seizures [1, 38, 39]. Peak age is 1–5 and males are more prone than females. One-third of cases have history of febrile convulsion [1, 15]. EEG may show spike-wave, wave-multiple spike complexes in ictal period with 2–4 Hz frequency. It is initially normal in interictal period, 3 Hz wave-spike discharges may be observed in sleep in later periods [40–42]. Fifty-eight percent of the cases have normal intelligence, while 20% and 22% show mild and severe mental retardation, respectively. Cases with mental deterioration are usually resistant to treatment. Seizures may be managed after 3 years in a certain percentage of patients [22, 42, 43]. Neuroradiological findings are generally normal [41]. Genetical basis is not clear [22, 38, 39]. VPA and ethosuximide (ESM) are still the commonly preferred medications for management of myoclonic seizures [40, 42]. Although BDZ and clonazepam (CZP) are beneficial for management of generalized seizures, they are not preferred since they cause behavior changes [41]. Lamotrigine (LTG) can be used for generalized seizures [44, 45]. CBZ and vigabatrin (GVB) are not recommended [41].

Topiramate (TPM), levetiracetam (LEV), acetazolamide (AZD) and sulthiame (SLT) are common; however, the number of cases and studies is not sufficient [22, 41, 46–48]. Ketogenic diets are effective but difficult to maintain for long periods [40, 49]. Progressive myoclonic epilepsies, that is, MERRF syndrome (myoclonus epilepsy with ragged-red fibers) can be mistaken for with Unverricht-Lundborg disease, and late-infantile neuronal ceroid lipofuscinosis; however, neurological development in later stage, continuity and persistence of the disease facilitate differential diagnosis.

4. ESES or CSWSS

First defined in 1971 as a juvenile form of epileptic syndrome named subclinical status epilepticus, ESES (or CSWS) is characterized with neuropsychologic and behaviour changes and develops during sleep [3, 10, 50]. ESES and CSWS are synonyms; however, ESES indicates EEG findings while CSWS refers to electroclinical findings [10, 51]. Prevalence is not known, but incidence is reported to be 0.5%. Equal male-female incidence is defined in early studies; extended studies indicate higher incidence in males. Generalized tonic-clonic seizures, atypical absence, myoclonic and atonic seizures may be observed. Mental retardation, lower IQ secondary to deterioration, and motor loss such as aphasia, behaviour disorder, ataxia, and dyspraxia accompany the seizures. Clinical course is composed of 3 stages: (1) initial period with seizures and no mental retardation; (2) intermediate period composed of neuropsychologic regression, seizures and ESES, and (3) final period composed solely of neuropsychological deficit. Cases solely presenting with mental retardation or behaviour disorder with no seizures are also noted [10, 52–56]. In these cases, diagnosis is confirmed with night video-polysomnography (V-NPSG). In most cases, EEG anomalies and neuropsychologic losses continue in puberty meanwhile there may be regression in seizures, improvement in behaviour and motor findings, and normal EEG pattern may return. Although genetic factors are unknown, a study reported relation with familial seizures and monozygotic state, and 15% of cases is associated with febrile convulsions [56, 57]. MRI and CT studies indicated 33% anomaly with significant diffuse or unilateral cerebral atrophy [58]. LTG, LEV, VPA, steroids, and BDZ are among treatments, the best outcomes are observed with diazepam (DZP) [6, 59]. Corticosteroids are beneficial in some resistant cases [60–62].

5. Landau-Kleffner Syndrome

William Landau and Frank Kleffner reported epileptic encephalopathy for the first time in 1957 in six children who underwent various types of seizures and developed acquired aphasia [6, 63]. LKS first appears between ages of 3 and 7 in children with normal motor-mental-linguistic development [64]. Range may be 2–14 in rare cases. Male-female ratio is 2 : 1. Family history is incidentally (+). The main criterion is determined as normal development in premorbid period; however, preexisting language anomaly is reported in 13% of

the cases. Aphasia is progressive and usually develops gradually. Total speech loss develops approximately in 1 year and acute-onset aphasia is rare. Various types of aphasia may be observed during the whole course. Hearing is usually normal, but patients may develop mutism and unresponsiveness to all verbal and nonverbal stimuli. Hyperactivity, aggressiveness, impulsiveness and attention deficit are extremely common [65–69]. EEG shows spikes or spike-waves prominent in temporal or centrotemporal sleep. Methohexital suppression test, intraoperative electrocorticography, and magnetoencephalography results are localized in superior temporal gyrus, intra- and peri-Sylvian cortex. EEG is rarely normal in sleep. ESES can be observed rarely. In pathogenesis, frequent EEG discharges are estimated to interrupt central pathways of speech development. This relation is explained for similar syndromes like Benign childhood epilepsy with centrotemporal spikes (BECTS) [59, 70–74]. MRI findings are normal. SPECT studies reveal temporal hypo- or hypermetabolism. Hypermetabolism are associated with active epileptic discharges [68].

LKS prognosis is poor depending on the earlier date of onset (prelinguistic). However, some cases show significant improvement in communication in second and third decades of life [75]. Seizure management is usually successful with appropriate drug choice. CBZ may deteriorate the seizures, monotherapy with VPA or its combination with BDZ seem to be the best choice. Higher and long-term use of adrenocorticotropic hormone (ACTH) and steroids is strongly recommended due to beneficial results. CLB, nitrazepam (NZP), VPA, ESM, and flunitrazepam are used, and PB, CBZ, and PHT are not used. IV immunoglobulins are as successful as steroids [60–62, 74–76].

6. Lennox-Gastaut Syndrome

LGS is a rare form of epileptic encephalopathy, first described in 1969 by Lennox and Gastaut [77]. Classical triad includes early onset with multiple and various types of seizures, mental deterioration, and generalized slow spikes waves in EEG [76–79]. First seizure occurs at 1–8 years, peaking between 3 and 4, and is etiologically divided into symptomatic and cryptogenic. Major division includes cryptogenic cases. Symptomatic cases are secondary to hypoxic-ischemic encephalopathy, vascular damage, tuberous sclerosis, Down's syndrome, trauma, brain tumor, and perinatal meningoencephalitis. WS is reported in history of 10–25% of the cases [44, 80–82] (Figure 1).

Tonic seizures are the most common seizures of LGS (74–90%) and occurrence in the initial period is not mandatory for diagnosis. The second most frequent symptom is atypical absences, followed by atonic seizures and myoclonic seizures. Nonconvulsive status epilepticus is observed in 54–97% of the cases [81, 82]. EEG findings are characteristic: generalized slow spike-waves (2–2.5 c/s) and burst in awake state, burst or fast wave and slow polyspikes and generalized fast activity at about 10 c/s during sleep [80].

Antiepileptic drugs, ketogenic diet, hormonal therapies, and surgical and rehabilitation methods are used in

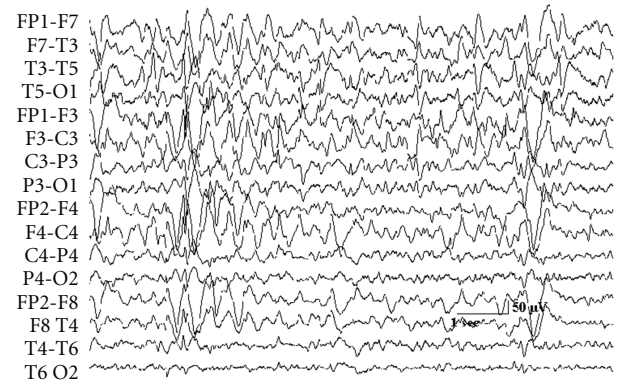

Figure 1: Slow electroencephalographic spike and wave discharges in Lennox-Gastaut syndrome.

treatment. Monotherapy or combined therapy with old-generation antiepileptic medications did not give significant benefit; however, benzodiazepines are still utilized. The most promising choices seem to be LTG and rufinamide (RUF). Carisbamate (CBM), fluorofelbamate (FFBM), ganaxolone (GNX), and remacemide (RMC) are among the antiepileptic medications of the future. Ketogenic diet is as effective as in all types of intractable epilepsies. Difficulty in continuation and complications of some medications (kidney stones) are of concern. Initiation of ACTH and corticosteroids short time after disease onset, especially in cryptogenic cases, is known to be effective, but they are not used frequently due to increased rate of relapse. Other choices are amantadine, imipramine, IV immunoglobulin, and TRH analogs. Surgical treatment options include callosotomy and VNS (vagal nerve stimulation). Nonmedical treatment methods are composed of specific education and rehabilitation [45, 83–90] (Figure 2).

Prognosis is extremely poor. Most of the cases continue to live dependently [80].

7. Ohtahara Syndrome or Early-Infantile Epileptic Encephalopathy

Ohtahara Syndrome, first described in 1976 by Ohtahara et al., characterized with tonic seizures and burst suppression pattern in EEG, develops earlier than other forms of epileptic encephalopathies, is resistant to treatment, and has one of the poorest prognosis among other types [6, 91–93]. Cause is unknown but it generally accompanied structural brain anomalies such as Aicardi syndrome, migrational disorders, porencephaly, and hemimegalencephaly; male-female prevalence is equal. First seizure may occur in the first day of life, but general onset is within 1–3 months [7, 94–101].

Single or clusters of tonic spasms occur in awake state or during sleep. Other seizure types are rare. It accounts for 0.2–4% of all juvenile epilepsies. Seventy-five percent of cases turn into West Syndrome within 3 to 6 months, and some of these turn into Lennox-Gastaut syndrome.

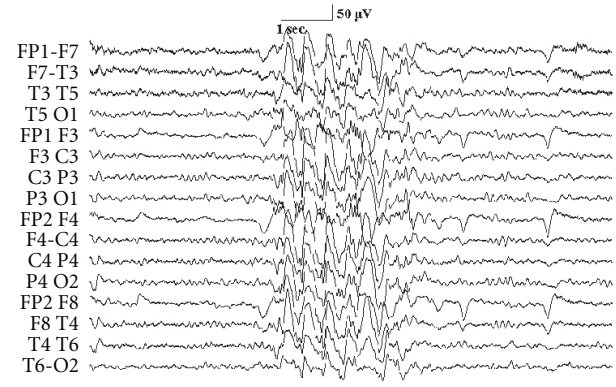

Figure 2: Polyspike and wave discharged been recorded in atypical absence seizures (Lennox-Gastaut syndrome).

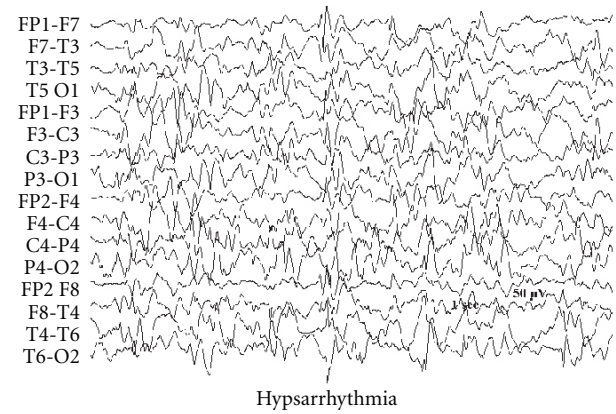

Figure 3: Hypsarrhythmia electroencephalogram in infantile spasms shows chaotic high-amplitude background (West syndrome).

ARX gene mutation, Stxbp 1 (MUNC 18-1) mutations are reported in some cases [102–104].

ACTH, VGB, and zonisamide offer some benefits; however, no treatment showed significant improvement in long-term. Severe morbidity and high mortality are inevitable [105–112].

8. West Syndrome or Infantile Spasms or Salaam Spasms/Tics

West Syndrome, a well-known form of epileptic encephalopathy first described in 1841 by James West, has a 0.16–0.42 incidence in thousand births [6]. Triad includes epileptic seizures, hypsarrhythmia in EEG and psychomotor retardation [113]. It usually starts within the first year of life peaking at 5 months. Seizures appear in various types and are usually in the form of sudden, bilateral, and symmetrical flexor, extensor or mixed-type spasms of the neck, body, and extremities. These spasms usually have 20–100 clusters [64, 114–117].

Early diagnosis and treatment prevent poorer prognosis and development of Lennox-Gastaut syndrome. There are three forms: symptomatic, idiopathic, and cryptogenic [118] (Figure 3).

EEG shows random high-amplitude slow wave and spike complexes and is first described by Gastaut in 1950, and named hypsarrhythmia by Gibbs. It may gain multifocal character in time or may rarely turn into generalized spike discharges [112–116] (Figure 4).

Preferred agents are ACTH and VGB [115–130].

9. Severe Epilepsy with Multiple Independent Spike Foci (SE-MISF)

Ohtahara et al. described the clinical symptoms, also previously described by Noriega-Sanchez and Markand, characterized by high-frequency seizures and MISF in EEG, which generally involves both hemispheres and develops secondary to cerebral pathologies in children between 4–7 years [41, 101].

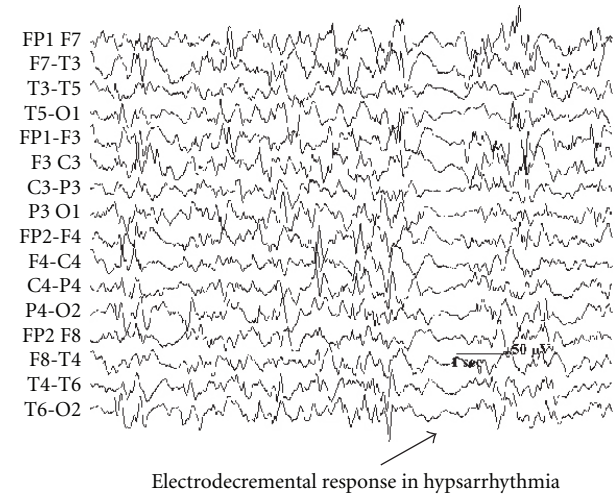

Figure 4: Electroencephalogram response in hypsarrhythmia was associated and recorded in infantile spasms (West syndrome).

Various types of frequent generalized minor seizures usually manifest along with mental retardation. Condition develops secondary to pre-, peri-, and post-natal factors (degenerative disorders, neurocutaneous diseases, infections, hypoxic-ischemic encephalopathy, hydrocephaly, and cerebral malformations), and patients develop WS and LGS, continuing their lives with severe seizures and mental retardation [59, 131–133].

VPA, BDZ, VGB, PTH, and ZNS combinations are used for treatment. Neurosurgical intervention is not an option [59, 133, 134].

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Review Article

Cognitive Outcome of Status Epilepticus in Children

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Epileptic encephalopathy encompasses conditions in which cognitive, motor, or sensory deficits result as a consequence of epileptic activity defining certain syndromes. It therefore represents a more severe subset of epilepsy, which can be generally characterized as frequent or severe seizures leading to cerebral dysfunction. This disturbance in cerebral functioning can in turn hinder, somewhat dramatically, cognitive development and further impact the future lives of patients. In this paper, we describe the cognitive consequences of status epilepticus in children and in adults in the context of plasticity theories. Recent studies maintain that consequences of SE may be severe cognitive sequelae, especially in early life. Since the residual consequences of SE in adulthood seem less detrimental and long-lasting, we argue that early life insults, such as those created by SE, during a rapid period of development and functional specialization, result in specific cognitive deficits dependent on the sensitive period at which SE occurred.

1. Introduction

Epileptic encephalopathy encompasses conditions in which cognitive, motor, or sensory deficits result as a consequence of epileptic activity defining certain syndromes [1]. It therefore represents a more severe subset of epilepsy, which can be generally characterized as frequent or severe seizures leading to cerebral dysfunction. This disturbance in cerebral functioning can in turn hinder, somewhat dramatically, cognitive development and further impact the future lives of patients. In this paper, we consider status epilepticus as an epileptic encephalopathy owing to its impact on cognitive development in early life.

2. Status Epilepticus (SE)

Status Epilepticus (SE) is a medical epileptic emergency characterized by either rapidly repeating seizures without recovery or regain of consciousness between episodes, or prolonged continuous epileptic activity, both creating a fixed or lasting condition [2, 3]. It is an event rather than a syndrome. It is accepted that the duration of an episode of SE is 30 minutes or more, period after which cerebral functioning is highly probable of being affected and immediate medical attention is needed [4]. Recently, the notions of impending SE and established SE have been introduced [5] in order to provide the best possible care for patients presenting with SE. In adults, patients presenting a seizure lasting more than five minutes can be designated as impending SE. In children, impending seizures are considered when seizures last between 5 and 10 minutes [5].

The prevalence of SE varies. Three epidemiologic studies suggest 17 to 108/100000 as being the prevalence of SE [6–8]. Although SE can occur at any age, it is most often encountered in infancy and childhood, 40% of all cases occurring prior to 2 years of age, a period in which the brain is in rapid development [9]. Such prevalence is argued to be present in early life owing to the exceeding amount of neurons and excitatory connections prior to functional specialization while undergoing neuronal pruning, which increases the vulnerability of the developing brain to SE [10]. In affected children, an imbalance between inhibitory and excitatory neurotransmissions is argued to lead to anomalies in neuronal impulses leading to prolonged seizures [11]. In fact, the pathophysiology of SE seems to involve a loss of inhibitory mechanisms, which result in a deficiency of the neuronal metabolism, which is unable to keep up with the demands of the continuous epileptic activity [12]. The seizures are most

frequently generalized, but may also be partial and either convulsive or nonconvulsive [13]. SE is further classified in accordance with its respective etiology [14]. Idiopathic SE occurs in otherwise healthy individuals without metabolic dysfunction nor an acute insult to the Central Nervous System (CNS). Furthermore, remote symptomatic SE occurs in patients with a history of insult to the CNS without acute provocation such as in mental retardation. Febrile SE, the most common etiology in children [15], occurs when the only provocation of the CNS is a high fever, usually higher than 38,4 degrees Celsius. In this population, 86% of children demonstrate normal prior development [16]. Acute symptomatic SE occurs during an acute illness with a known insult to the CNS such as in meningitis. Although there has been debate on the long-term effects of SE on cerebral functioning, recent research investigating more accurately the cognitive sequelae related to SE demonstrate that cognitive functions under development are exposed to being altered and damaged in children presenting with SE, owing to its high incidence in infancy, a period of marked and rapid cognitive development.

3. Plasticity versus Vulnerability in the Developing Brain

In considering the impact of an early insult on cerebral and cognitive development, two opposing theories are contradictory in their predictions. The plasticity theory posits that the young brain is flexible and therefore capable of recovery after insult. As such, since there is less functional specialization in early life, functions that would depend on a damaged area would simply reorganize to functionally cope with the insult [17, 18]. As such, this theory predicts that early brain damage is the most biologically manageable, resulting in less vulnerability to the impact of damage as opposed to an older brain. In contrast, the vulnerability theory posits that the young brain is the most fragile and therefore vulnerable to early insult. It argues that owing to the lack of functional specialization, the brain will attempt to recover endangered functions, but will do so aberrantly creating faulty connections in early life [19]. As such, a crowding effect will take place such that healthy tissue will take over the damaged tissue in attempt to recover the cognitive function at hand, but consequently limiting the tissue's quantitative and qualitative resources [20]. This effect was first demonstrated in the context of hemispheric dominance following left hemisphere damage in early life such that an insult to the left hemisphere prior to one year of age resulted in the proper development of language but faulty development of nonverbal skills; owing to brain plasticity, the emerging language functions took over neurons dedicated to nonverbal skills. The reverse effect was observed when the insult occurred after one year of age [20, 21]. As such, healthy tissue, although already specialized for a certain function will forgo that specialization for the proper development of the function underlying the insult, creating a "crowding" of cognitive functions for that particular tissue. Therefore, the vulnerability perspective of the developing brain predicts that early life insults are the most difficult to recover from.

In further investigating the opposing predictions of both theories of the impact of early insult on the developing brain, the vulnerability theory has been the most supported [22–25]. It has been found that young neurons more readily grow to make new connections, which following an insult, may facilitate aberrant connections [26]. As such, the developing brain is the most vulnerable to insult resulting in subsequent damage post-SE potentially persisting in later life. Furthermore, findings demonstrate that not only is the severity of the sequelae following SE predicted by the extent and location of the insult, but the nature of the sequelae itself is determined by the timing of the SE episode [27]. As such, the developmental period at which the insult occurs is argued to predict which cognitive functions will be most affected and therefore predict the general outcome of the patient.

4. A Model of Human Development

In concordance with the vulnerability theory, early insults to the brain have the most detrimental impact on cerebral and cognitive development persisting in later life. As such, faulty neuronal connections following an early life insult during a critical period of development will hinder the normal development of brain functions, for which the sequelae will persist in later life [28]. However, already developed functions at the time of the insult will be spared. The notion of critical periods during infancy through adolescence is widespread and generally accepted [29]. Critical periods allow for a logical hierarchy in development such that windows of opportunity allow for the specialization of functions. Furthermore, certain structures and their underlying function must be well specialized prior to others. As such, sensing pathways such as those involved in vision and hearing must develop prior to language pathways, which in turn must develop prior to higher cognitive functioning, including executive functions [29]. Critical periods, consequently, expose certain functions as more vulnerable than others in particular and specific periods during development. The vulnerability of different cognitive functions therefore varies with the developmental process itself. In the presence of an early insult to the brain, the function under development will be hindered, affecting not only that particular function, but also the development of subsequent functions dependent on the hindered one. Healthy development of cognitive functions depends on the integrity of the structure the function underlies. As such, following an early life insult, the integrity of a particular structure is compromised, further compromising the cognitive function that structure is responsible for.

5. Physiological Alterations Resulting from SE

Prolonged and frequent seizures, such as those involved in SE consistently show physiological brain damage. In fact, the physiological properties of cells have been shown to be altered following an SE event [30, 31]. The most vulnerable structure to the seizures is the hippocampus, which is involved in learning and memory. Hippocampal edema, cell loss particularly in the Sommer sector, and abnormalities

have consistently been detected within this structure following SE [10, 32]. Also in human, other structures have been demonstrated to show necrosis following events of epileptic attacks such as the amygdala, dorsomedial thalamic nucleus, medial layers of the neocortex, cerebellum, the piriforme and entorhinal cortices [30–33]. Neuronal degeneration and loss in these areas have been shown to occur rapidly after a SE event [30, 34]. Cerebral atrophy has also been demonstrated following SE [35]. Animal studies have further supported these physiological alterations. The work of Meldrum involving induced SE in baboons has demonstrated similar neuronal necrosis involving the neocortex, hippocampus, amygdala, thalamus, and cerebellum [35]. In a long-term followup, different SE animal models have found structural changes [36–38]. For example, smaller volumes of the hippocampus, thalamus, putamen, and perirhinal cortex have been found [38]. Interestingly, severity of hippocampal volume loss correlated with severity in spatial learning impairments. Of note, animal data describing the consequences of an induced single episode of SE tend to show greater deleterious consequences in immature rat brains in comparison to adult rat brains [39]. Although physiological alterations following SE have been shown specifically and consistently, the cognitive sequelae resulting from these abnormalities is not as clear and widespread.

6. Cognitive Sequelae of Status Epilepticus in Animal Models

Cognitive sequelae following SE were first studied using animal models in which animals showed a normal development until seizure onset. Following induced SE in rat pups, impairment in emotional behavior was observed, characterized by an increase in anxiety and fear [40, 41]. Furthermore, increased hyperactivity and spontaneous exploratory behavior was shown with a similar experimental design [40, 42]. Also, owing to the vulnerability of certain structures involved in the limbic system such as the hippocampus and amygdala, learning and memory impairments are consistently marked. Learning deficits, usually demonstrated by decreased habituation and reduced adaptations to novelty, are observed following SE, and these deficits persist into later life in rodents [40, 41, 43]. Also owing to acquired anomalies in these limbic structures, spatial and emotional learning and memory are impaired shortly after SE [41, 42, 44]. Memory impairments were thus marked in these models [44]. Whether these findings can generalize to the impact of early SE on the development of these cognitive functions to humans is a matter of debate. However, recent research has argued for cognitive sequelae resulting from SE in early life.

7. Cognitive Sequelae of Status Epilepticus in Humans

7.1. Children. Cognitive sequelae resulting from SE in early life have been demonstrated. In general, studies demonstrate progressive structural and functional alterations following SE, generally reporting broad cognitive consequences of SE. Even so, deficits in verbal and nonverbal intellectual ability have been identified following SE [45–47]. Furthermore, global IQ deficits are demonstrated in early onset seizures [26, 46]. Several landmark studies have well demonstrated the presence of cognitive deficits following SE in early life. Aicardi & Chevrie [48] retrospectively studied 239 children having undergone one episode of SE lasting one hour or more, under the age of 15. Fifty-seven percent (57%) of the cohort presented with mental or neurological sequelae. More specifically, 20% of the cohort developed motor delays and 33% presented IQs lower than 80, all in children whose development was unremarkable prior to the SE event. Furthermore, 48% presented with mental retardation following the episode, the majority of affected children again demonstrating normal development prior to SE. Furthermore, Yager et al. [49] followed 52 children over 18 months following an episode of SE. Twenty-eight percent (28%) of otherwise healthy children developed neurological sequelae following SE, and 25% of children who were predisposed to pathologies including previous epileptic activity deteriorated further following SE. Lacroix et al. [50] also longitudinally followed 147 children following an episode of SE. Thirty percent (30%) showed a neurological deficit following SE at discharge, and 68% of these children still demonstrated these deficits one year after. Taken together, these data demonstrate marked cognitive and neurological dysfunction following SE, supporting the vulnerability theory of insult to the developing brain. However, even though dysfunctions are shown, the specific nature of the deficit remains unclear. The lack of appropriate and specific methods in evaluating the deficits makes conclusions general and nonspecific. Neuropsychological testing is however a good tool in evaluating the specific cognitive functions potentially affected as opposed to the assessment of level of functioning as a whole. Neuropsychological testing is advantageous since it can easily be adaptable to the hospital setting, however it should be noted that in infants, the age at testing poses a certain constraint on the sophistication of the assessment.

In taking these limitations into consideration, a recent study by Roy et al. [51] further assessed the vulnerability theory by studying the effect of a single episode of febrile SE on the developing brain in otherwise healthy children. They specifically examined psychomotor function as well as executive functions in these children. Executive functions, mainly involved in regulation of behavior, begin rapid development in early life, continuing through to adolescence [52–54] and are the underlying functions of the frontal lobes. Since executive skills are developed in different trajectories over a longer timeframe during development, comparing the impact of an insult at different times during this development can shed light onto its potential differing consequences. Following the hierarchy in the development of the brain, the frontal lobes depend on the structural and functional integrity of other structures as they encompass higher cognitive functions. An early insult to the brain would therefore hinder executive functions. Roy et al. [51] compared younger and older children in differing critical periods using neuropsychological testing to evaluate the prediction that the function under development would be the most vulnerable

to an insult. This is precisely what they found. In younger children (prior to 11 months of age) presenting with a febrile SE, hand-eye coordination and motor ability were most affected but were spared in older children. In contrast, older children presenting a febrile SE demonstrated personal and social deficits. Similarly, Anderson et al. [27] had previously demonstrated, with a larger age range of children and of insults, that consequence of early brain insult on executive functions was dependent on which critical period the episode occurred. As such, an insult prior to 2 years of age demonstrated deficits in goal-setting, a skill spared in children whose onset was in middle or late childhood. Furthermore, an insult prior to 3 years of age was associated with deficits in cognitive flexibility and working memory, these skills being spared in those for which SE episode occurred after the age of 10. It is important to note however that Anderson et al. [27] did not investigate the impact of an episode of SE per se, but rather the impact of early brain insult in general and as such, did not take the underlying etiologies into consideration. Indeed, studies in school age children presenting with SE are lacking. Roy et al. [51] however, investigated children affected precisely by Febrile SE and not only used healthy matched controls, but also included a control group composed of children affected by a simple Febrile Seizure (FS). Simple FS are brief (less than 15 minutes) and are argued to be unremarkable in their effects on the developing brain. As such, prolonged (SE) seizures were compared to brief (FS) seizures allowing to isolate the impact of fever and brief seizures themselves. Taken together, this particular study alone gives important insight into the presence and specific cognitive impairments observed following a single febrile SE episode in otherwise healthy children.

7.2. Adults. Patterns of cognitive sequelae following SE in adulthood seem to differ than those seen in infancy and childhood. In a prospective study of SE occurring in adults (mean age was 40) with no underlying pathology, Adachi et al. [55] did not demonstrate intellectual deficits following the episode as evaluated by neuropsychological testing (WAIS-R), but rather both the experimental and control group of matched healthy individuals could not be differentiated. This finding was also previously demonstrated [56]. In fact, resolution of long-lasting SE cognitive sequelae in adults have been demonstrated 6 to 24 months post-SE episode, and resolution of acute sequelae have been shown to resolve within 1 to 4 weeks, suggesting a reversible effect of the residual consequences of SE. Also demonstrating this effect was a case report of a 25-year-old woman with a history of epilepsy starting at age 14, hospitalized after an SE episode [57]. Neuropsychological testing demonstrated severe memory and executive function deficits at the time of the insult. However, one year after the insult and following unremarkable antiepileptic treatment, the cognitive deficits were reversed, and the woman returned to her Master's studies. These data of the impact of SE in adulthood suggest that it's effects are less severe than in childhood, such that not only do studies show unremarkable intellectual deficits following SE, but also show reversible effects of the deficits. It should be noted however that the SE described above were idiopathic. Symptomatic epilepsies in contrast involve greater presence and severity of cognitive impairments. However, even though the case study presented was symptomatic and still demonstrated reversible effects, etiology, and potentially other aspects underlying the SE episode, must be taken into account when considering its impact on cognition.

8. Other Aspects Potentially Underlying Cognitive Decline in SE

Whether an episode of SE results in cognitive deficits seems to not only rely on the onset of SE (infant versus adult) but rather on a web of interweaving aspects related to epilepsy and SE. Certain risk factors have been shown to affect prognosis following such an episode.

8.1. Etiology. The origin of the SE is an important risk factor. As there are several possible etiologies, the cause of SE can interplay with the actual seizures with regards to outcome. Idiopathic SE tends to have a more favorable prognosis than symptomatic SE [46, 49, 58]. Furthermore, a typical pattern of development prior to the episode is related to better outcome [50]. In contrast, the risk of developing epilepsy increases to more than 50% in convulsive symptomatic SE. In addition, more than 20% of children with acute symptomatic SE show new cognitive impairments compared to less than 10% in other types of SE [59]. The risk for SE is increased in neurologically deficient children [48] and children with a history of seizures are at higher risk for neurological sequelae [60]. Additionally, younger children tend to have more severe etiologies, as a decrease of acute symptomatic cases is observed after the first year of life [9]. However, 75% of children under 2 years of age demonstrated normal development until the insult [9]. In general, the presence of an organic etiology is related to poorer prognosis [46]. It should be noted however, that cognitive effects of the seizure itself without an underlying pathology have been reported [61, 62]. Taking etiology into account, if not cautious with the methodology used, the cause of the potential observed deficiency (etiology versus SE) can be confounded [4].

8.2. Duration and Frequency of Seizures. Longer durations of an SE episode are related to increased risk for deficits [58, 63]. In fact, it has been demonstrated that episodes lasting less than one hour result in neuronal injury, and episodes lasting more than one hour result in neuronal death [64], supporting the previous argument. Duration of SE is also related to etiology such that prolonged episodes typically accompany more severe etiologies [65].

Recurrent seizures are more persistent in individuals with prior neurological abnormalities [66]. Controversies exist as to the impact of recurrent seizures on cognition. It has been proposed that recurrent seizures lead to cognitive impairment, specifically, intellectual and memory deficits [44, 66]. Also, it has been shown that a long history of seizures is associated with mental deficits [67]. Furthermore, it has been demonstrated that early life seizures result in long-term

deficits [68], further supported by an animal model demonstrating deficits in learning and memory following recurrent SE [68]. In contrast, it has also been proposed that recurrence of seizures itself does not pose a risk for cognitive development [66, 69]. As demonstrated in SE, some epileptic models do not always demonstrate aggravated consequences of recurrence of seizures [70]. Following this perspective, in epileptic patients, it is suggested that the predisposed brain develops somewhat of a tolerance to the impact of seizures therefore producing less damage, whereas the naive brain is more vulnerable to one insult [71]. This perspective is however very delicate and must be debated.

8.3. Age of Onset. The risk involved in the age of onset of SE has been covered in this review such that, thus far it has been shown that SE onset in early life, a period at which individuals are more prone to SE, has a greater impact on cognitive functioning than in later life, in which even reversible effects are observed. As discussed under the related effects of etiology, SE presents greater severity in children as they more often show a symptomatic etiology than in adults [9, 48]. Furthermore, adults presenting with SE tend to have a history of seizures [9]. As such, consideration must be taken of the underlying etiology in the younger SE population on interference with development. In adults however, age of onset and duration of the SE episode has not been related to prognosis [53].

8.4. SE as Cause of Injury. In animal models, brain injuries following SE have been repetitively revealed. In children, SE can cause hippocampal lesions, at least in the acute phase [34]. Further studies are needed to investigate if long-term hippocampal MRI volume loss are due to reduced edema or to a loss of neuronal tissue. Furthermore, more human studies are needed to establish the link between hippocampal lesions following SE and cognitive impairments. This could be facilitated with the recommended use of MRI in cases of SE [72]. Investigating the link between these lesions in the limbic system and behavioral impairments could also be interesting and perhaps shed even more light on patient outcome following SE.

8.5. Other. With respect to gender, males have a higher propensity of developing symptomatic SE in contrast to females, which demonstrate a higher propensity of developing idiopathic SE [48]. However, gender itself does not have an impact on prognosis following an SE episode. It has also been suggested that an enriched environment can aid in memory decline such that enriched environments facilitate hippocampal plasticity, which in turn leads to bettered formation of long-term potentiation [73]. In contrast, race does not influence this prognosis [47, 74].

Taken together, several marked risk factors must be taken into consideration in evaluating the impact of SE on cognition such that several confounding variables are possible. However, awareness and caution in the methodologies and analyses used can shield from the confounding effect of these risk factors.

9. Impact of Antiepileptic Treatment (AED) on Cognition

Antiepileptic drugs (AED) have various effects between patients as well as between seizures and epilepsy types. The success of AED is usually measured as a reduction in the number of seizures, not necessarily as its impact on cognition following epilepsy [75]. As such, evaluation of cognitive ability following treatment poses more difficulty. In fact, some AED themselves have been shown to induce cognitive deficits such as mild memory, attention, and psychomotor problems [76]. Even though no comparative studies have been performed to investigate the side effects of more recent AED, it has been argued that Topiramate is involved in attention, concentration, and memory problems [77]. Taken together however, it is suggested that use of AED is not the major factor causing cognitive comorbidity in epileptic encephalopathies [78]. In SE, it has been demonstrated that cognitive outcome following SE depends on the time between the episode and the initiation of treatment [48, 58]. AED administered during an SE episode, in contrast to those administered in most epileptic conditions, are usually termed "aggressive treatment" since they are meant to be administered very rapidly and withdrawn within the following 24 hours [79]. Its purpose is to shorten the episode in hopes to protect against neuronal damage and therefore to potentially protect against the cognitive sequelae related to prolonged episodes [58, 79]. As such, AED have been shown to reduce cognitive sequelae following an episode [48, 58]. This was also observed in animal models [80]. More speci-fically, the use of AED in children presenting with SE has demonstrated a control of the seizures that resulted in a prevention of further cognitive deterioration [79]. Although AED stopped further cognitive sequelae, they did not allow recovering maladapted functions. Since AED did not allow recovering of anomalies in cognitive functions since SE onset, our argument that an insult to the developing brain at particular sensitive periods is detrimental to cognitive development is further supported.

10. Controversies

Even though we are arguing that SE has an unforgiving impact on cognitive development, as in any body of literature, results can be controversial. Firstly, a poor prognosis in early life SE has not always been reported [65, 81]. Also, it has been reported that the underlying causal factor of SE is related to outcome as opposed to age of onset [59, 82]. However, there are certain methodological considerations in these and other studies. Lack of standard categorization of underlying etiologies, as well as lack of consideration for type and frequency of seizures between testing could impact results. Furthermore, heterogeneous groups are often compared relative to age of onset, duration and frequency of seizures, etiology, treatment, and genetic factors also creating potential confounds [83]. Furthermore, it has been observed that retrospective studies tend to show greater intellectual deficit following SE than prospective studies [55].

In addition, measures of cognitive ability are often lacking accuracy and specificity such that deficits in specific skills are overlooked when simply assessing global IQ. IQ itself is not an appropriate measure for cognitive dysfunction. As such, more specific tests should be used in attempt to measure the cognitive skills of interest, such as would allow neuropsychological assessments. Again, this type of assessment is advantageous such that tests can be selectively chosen for each patient or each group of patients, categorized by site of lesion for example, in order to better comprehend the precise pervading deficits as opposed to a simple level of intelligence.

11. Discussion

In spite of these controversies and methodological issues, we maintain that consequences of SE may be severe cognitive sequelae, especially in early life. More recent studies more readily take these methodological issues into account creating a better experimental design. Also, they use more specific tests and aim and specific cognitive functions. As such, these recent results better demonstrate the presence and severity of the cognitive sequelae resulting from SE in infancy. Since the residual consequences of SE in adulthood seem less detrimental and long-lasting, we argue that early life insults, such as those created by SE, during a rapid period of development and functional specialization, result in specific cognitive deficits dependent of the sensitive period at which occurred SE. These deficits can potentially lead to deficits in later childhood expressed as such as learning disabilities, the residua of which may persist into later life. Further investigations involving the long-term effects and impacts of early life SE on later development and later life functioning are needed. Although adult-onset SE seems to spare the cognitive integrity of affected patients, it is still unknown whether early-onset SE has detrimental impacts in later life.

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Review Article

Epileptic Encephalopathies with Status Epilepticus during Sleep: New Techniques for Understanding Pathophysiology and Therapeutic Options

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Encephalopathy with status epilepticus during sleep (ESES) is an epileptic encephalopathy, as defined by the International League Against Epilepsy (ILAE) Task Force on Classification and Terminology, that is, a condition in which the epileptic processes themselves are believed to contribute to the disturbance in cerebral function. Clinical manifestations of ESES are heterogeneous: apart from different seizure types, they consist in combinations of cognitive, motor, and behavioural disturbances associated with a peculiar electroencephalographic pattern of paroxysmal activity significantly activated during slow sleep, which culminates in a picture of continuous spikes and waves during sleep (CSWS). The pathophysiological mechanisms underlying this condition are still incompletely understood. Establishing a clear-cut correlation between EEG abnormalities and clinical data, though interesting, is very complex. Computer-assisted EEG analyses especially if combined with functional magnetic resonance imaging (EEG-fMRI) and metabolic neuroimaging have recently emerged as useful approaches to better understand the pathophysiological processes underlying ESES. Treatment of ESES is not just limited to seizures control but it should be focused on controlling neuropsychological outcome through an improvement of the continuous epileptiform activity. General agreement on treatment guidelines is still lacking. Implementation of new techniques might allow a better understanding of the pathophysiology of ESES and could enhance therapeutics options.

1. Introduction

Encephalopathy with status epilepticus during sleep (ESES), is an epileptic encephalopathy, "a condition in which the epileptic processes themselves are believed to contribute to the disturbance in cerebral function" (ILAE Task Force on Classification and Terminology). It is characterised by heterogeneous clinical manifestations and a specific electroencephalographic (EEG) pattern of continuous spikes and waves during slow sleep (CSWS).

"Subclinical electrical status epilepticus induced by sleep in children" was firstly described by Patry et al. in 1971 [1]; 6 children showed continuous activation of epileptic discharges in sleep without any specific abnormalities when awake. In this first description no association with clinical symptoms was hypothesised.

In 1977, Tassinari et al. proposed the term "SES" or "ESES" and suggested a connection between electroencephalographic pattern and cognitive impairment [2]. Subsequently, in 1989 the Commission of Classification and Terminology (CCT) of ILAE introduced the more descriptive term of continuous spikes and waves during slow sleep (CSWS) [3]. Currently, the two terms ESES and CSWS are often used interchangeably. Clinical variants associated with an EEG pattern of ESES/CSWS are (1) encephalopathy with CSWS/ESES, (2) Landau Kleffner syndrome (LKS), (3) acquired opercular syndrome, and (4) atypical benign childhood epilepsy with centrotemporal spikes (BECTS).

(1) Encephalopathy with CSWS/ESES is an epileptic encephalopathy, characterized by different seizure types, combinations of cognitive, motor, and behavioural disturbances, and the peculiar electroen-

cephalographic pattern of paroxysmal activity significantly activated during slow sleep.

(2) LKS is a rare epileptic syndrome (incidence of 0, 2% in epileptic population) with a clinical onset between 3 and 8 years of age, characterised by acquired aphasia, ESES/CSWS, seizures, neuropsychological deficit, and behavioural disturbances. Awake EEG may contain multifocal or generalised discharges, often posterotemporal; during sleep there is a marked activation as in ESES/CSWS [4]. Hallmark of the syndrome is the acquired aphasia [5]. Language impairment, which could be antecedent to seizure's onset, manifests itself after a period of normal speech development firstly through an auditory agnosia followed by an expressive language deficit.

(3) Acquired epileptiform opercular syndrome is a rare epileptic syndrome whose onsets are around 4–8 years of age. Clinically it is characterised by oro-facio-lingual deficits, such as severe motor dysfunction, drooling, dysarthria, speech arrest, or weakness of the face and tongue. Seizures are usually focal motor seizures involving the face and occasionally rolandic, partial complex, or atypical absences. The EEG pattern presents centrotemporal bilateral or temporal spikes; sleep is characterised by spike and waves complex with secondary bilateral synchrony and up to a picture of ESES/CSWS [6].

(4) Atypical BECTS: BECTS is the most frequent benign childhood epilepsy with an onset between 3 and 8 years. It is characterised electroclinically by infrequent nocturnal partial seizures and interictal sharp waves and spike-waves in the centrotemporal regions, significantly activated during slow sleep up to a pattern of ESES/CSWS. Clinically, presents simple partial seizures sometimes generalised which consist of brief hemi facial twitches followed by arrest of speech, drooling with preservation of consciousness. Pharmacological treatment is usually effective and a spontaneous remission often occurs at the end of childhood. Despite being defined as "benign," long-lasting consequences such as neuropsychological deficits, behavioural problems, and learning disabilities are increasingly recognized in the course of the epilepsy and should not be considered as atypical features. Atypical features are instead early age at onset and frequent spikes or spike-wave discharges which seem to be risk factors for neuropsychological deficits but also for an atypical evolution which can lead to the appearance of severe neuropsychological impairments and continuous spikes and waves during slow sleep [7]. In the presence of these features the term Atypical BECTS is used.

2. EEG Pattern, Clinical Manifestations, and Aetiology

An increase in epileptiform discharges during sleep is described in many epileptic syndromes; the prototype of which is encephalopathy with CSWS/ESES. Since the hallmark of this condition is its electroencephalographic features, a clear definition of EEG pattern is compulsory to define the syndrome. In wakefulness, EEG is usually abnormal and shows epileptiform discharges that are focal, multifocal, or diffuse, often with frontotemporal or fronto-central predominance [8, 9].

The quantification of anomalies during sleep has played a central role in the diagnostic criteria of ESES/CSWS. Percentage of epileptiform activity during sleep can be expressed as spike-wave index (SWI), which is obtained as the total number of minutes of all spike and slow-wave abnormalities divided by the total number of minutes of nonrapid eye movement sleep (NREM) and multiplied by 100. In the first report by Patry et al. [1] "continuous" referred to a SWI of 85%–100% in 3 or more recordings over a period of 1 month. Although threshold values of this parameter were set as 90% [10], >85% [8], 60% [11], 50% [12], and 25% [13], currently a huge increase in EEG abnormalities during sleep associated with clinical symptoms of gradual cognitive and behavioural deterioration is sufficient and considered a hallmark of ESES/CSWS [14]. Recently, a disruption in the downscaling process of slow wave during NREM sleep across the night has been suggested as being involved in the psychomotor regression [15].

Clinical manifestations of ESES/CSWS include various seizure types (partial simple or complex, generalised tonic clonic, and typical and atypical absences seizures) [16] associated with cognitive, motor, and behavioural disturbances. Main clinical feature is the global regression in a wide spectrum of general cognitive impairment which includes deficit in language [17–19],temporospatial skills, [10], and short-term memory [20, 21]. Hyperactivity, instability, disorientation, and aggressiveness have been described [22]. In addition, motor deficits such as ataxia, dystonia, dyspraxia bilateral, or unilateral have also been reported [23].

Longer duration of ESES/CSWS and presence of frontal anomalies superimposed to the typical EEG pattern plus frontal neuropsychological deficit [24] are considered the main predictors for a poor outcome.

Although the majority of the cases have unknown aetiology-cryptogenic cases [25], ESES/CSWS has been sometimes associated with identifiable brain pathology such as migrational disorders [26], shunted hydrocephalus [27], polymicrogyria [28], porencephaly [9], and thalamic lesions [29]. Recently, it has been found that particular types of chromosome aberration, such as 8p deletion, 9p duplication [30, 31], and dup X (p11.22-p11.23), may have propensity to develop a neurological phenotype characterised by ESES/CSWS [32].

3. ESES/CSWS New Techniques: Understanding Pathophysiology

The typical presentation of ESES/CSWS, which shows an acute phase with specific EEG pattern, variable seizures types, and psychomotor delay, followed by a recovery phase

with neuropsychological and electrical improvement, seems to suggest the role of continuous interictal activity in determining the psychomotor delay. However, some authors still consider ESES/CSWS activity as an epiphenomenon mirroring the underlying brain pathology, rather than the direct cause of the psychomotor regression [33]. Although the most plausible hypothesis establishes a correlation between interictal EEG activity and neuropsychological impairment, a direct relationship has yet to be defined. This is partly due to intrinsic characteristics of epileptiform discharges, which appear with considerable variability (in terms of topography, amplitude, spatial, and temporal distribution) both during their evolution in the same subject, and across different subjects. Moreover, in the literature large prospective studies are lacking, while there is a prevalence of small series and case reports in which clinical syndromes, EEG criteria, and assessment methods are extremely inconsistent. In the literature, there is only one paper on a large series, just recently published. The authors studied the correlation between clinical features of patients with ESES/CSWS and focal or generalized increase of epileptiform activity (50% or more during nonrapid eye movement sleep compared with wakefulness). They concluded that focal or generalized activation of epileptiform activity in sleep is not related to any significant difference in the clinical features of patients [34].

Improvement of new techniques of investigations and large perspective studies are needed to better understand pathophysiological processes underlying ESES/CSWS. Among neuroimaging techniques, recently emerging useful approaches seem to be the computer-assisted EEG analyses especially if combined with functional magnetic resonance imaging (EEG-fMRI) and metabolic investigations such as positron emission tomography (PET) and single-photon emission-computed tomography (SPECT). Modern methods of EEG source localization (EEG source localization (ESL)) are able to provide information, with temporal resolution in the order of milliseconds, regarding the power source at the onset and during the propagation of epileptic discharges [35]. Valuable tools to analyse the multifocal nature of the EEG signal are the so-called "Blind Source Separation" methods such as independent component analysis (ICA). This technique allows separating in time series, the statistically independent components of an EEG signal using an information-maximization approach [36, 37]. By using this method, it becomes possible to obtain and to separate space-temporal components with a constant topographic pattern over time, but with temporal patterns maximally unrelated to each other. In the literature, there are several studies showing that ICA, despite being "blind" to the waveform of input data, is able to provide more information on the nature of the temporal evolution of bioelectric phenomena than expected. Moreover, ICA has been largely applied to EEG data since it is able to reflect the evolution of space-temporal EEG field [38, 39]. It has also been used to remove ballistocardiogram and ocular artefact which are the two mainly artefacts contaminating EEG data recorded during MRI scan. In LKS and ESES/CSWS EEG, source analysis applied to magneto-encephalographic data has shown a bilateral spikes generator in or propagate to the perisylvian cortex [40, 41].

Functional magnetic resonance imaging (fMRI) has obtained recognition for being a useful research tool able to map cortical activity in a noninvasive manner. A multimodal approach combining EEG and fMRI (EEG-fMRI) is also a promising technique which may be applied to patients with epilepsy for investigating hemodynamic changes associated with interictal epileptiform discharges (IED). This technique has been already applied to identify neuronal network in primary and secondary generalised epileptiform activity [42] and focal epilepsy [43]. EEG source analyses can contribute to the comprehension of the complex relationships between bioelectric and hemodynamic changes related to interictal spikes. By combining the two techniques—EEG source analysis and EEG-fMRI—it is possible to obtain new information on the dynamics of epileptic networks. EEG source analysis in fact provides high temporal resolution which can improve the localising value of EEG-fMRI, while the spatial definition of the BOLD activity may increase the power of source localization [44].

Furthermore, metabolic investigations such as SPECT as well as PET allow underpinning seizure-related changes of cerebral perfusion, glucose metabolism, and neuroreceptor status. The application of such new techniques in LKS and ESES/CSWS has already suggested, with interesting findings. In LKS, an EEG-fMRI study has shown that spike-wave discharges involve more complex networks than Heschl's gyrus alone, as suggested in previous literature, and are associated with increased blood-oxygenation level-dependent (BOLD) response in primary and associative auditory cortex, as well as temporoparietal junction [45]. More recently, activation in the perisylvian/prefrontal network associated with both activation and deactivation in the thalamocortical network has also been reported [46].

Similar results have also been demonstrated with metabolic studies. De Tiege et al. performed a PET study using 18F-fluorodeoxyglucose (FDG) in 9 children during acute and recovery phases of ESES/CSWS. They showed an increased metabolism at the site of epileptic focus and hypometabolism in connected area, in particular prefrontal cortex. Interestingly during the recovery phase a complete or almost complete regression of both hypermetabolic and hypometabolic abnormalities observed during the acute phase was observed. These findings together with the natural history of the disease led the authors to hypothesize the mechanism of remote inhibition to describe the psychomotor regression in ESES/CSWS [47, 48].

A better understanding of the complex pathophysiological mechanisms of ESES/CSWS gained with the assistance of these new techniques can shed light on the possible therapeutic approaches for the treatment of ESES/CSWS. Knowing the epileptic networks likely to be involved in generating the typical EEG pattern of ESES/CSWS and possibly responsible for the psychomotor regression and deficit in language, cognition, and behavior can be a starting point for considering therapeutics options from a different perspective. This might be the case of nonconventional pharmacological options such as vagus nerve stimulation, surgery, and

corticosteroids therapy which are part of the comprehensive therapeutic approach for ESES/CSWS. The hypothesis that seizures but mainly epileptic activity are responsible for cognitive, behavioural, and language deterioration seems to be demonstrated by the recent findings acquired using new techniques. It is getting more evident that EEG abnormalities lead to dysfunctions in different domains and therefore the treatment of encephalopathy with ESES/CSWS requires the reversal of the ESES/CSWS pattern on EEG.

4. Therapy

There is little evidence to guide treatment since only uncontrolled studies and case reports on the efficacy of different antiepileptic drugs (AEDs) are present in literature.

Treatment options for ESES include some "old" AEDs (Valproate [49], Ethosuximide [50], and Benzodiazepines [51, 52]) and "new" AEDs (Levetiracetam [53, 54]). However, evidence to guide therapeutic decisions about these AEDs remains on class IV studies (case reports or expert opinions) and open-label uncontrolled trials (class III). Despite the interesting results, it appears difficult to infer general conclusions from single cases: the number of patients included in these trials in fact is too small to suggest the use of a specific therapy in the whole population. Due to the poor response to a single antiepileptic drug, epileptic syndromes with ESES/CSWS are since the beginning treated with a polytherapy of antiepileptic drugs, such as valproate (VPA) or ethosuximide (ESM) with benzodiazepines [55].

Nonconventional pharmacologic treatment options such as intravenous immunoglobulins [56], ketogenic diet [57], vagus nerve stimulation [58], and epilepsy surgery with multiple subpial transaction [59] have shown efficacy in small case series and are part of the comprehensive treatment plan for children with ESES. Several studies have demonstrated that some AEDs such as phenobarbital (PB) and carbamazepine (CBZ) can worsen ESES/CSWS. Although they may reduce seizures, they are usually not indicated for patients with ESES/CSWS due to the negative effects on neuropsychological outcome and EEG pattern [60–62].

Efficacy and tolerability of steroids in epileptic syndromes with ESES/CSWS have been demonstrated as well [63, 64]. Children who received corticosteroids for cognitive and/or behavioural deterioration associated with ESES/CSWS were retrospectively reviewed. Positive response was found in terms of normalization of the EEG and improvement of neuropsychological function. Urbain et al. [65] reported a normalization of EEG together with the normalization of overnight memory performance in one patient with ESES/CSWS who was treated with corticosteroids therapy. Although in one single case, the hydrocortisone effectiveness in obtaining a normalization of EEG and in positively influencing neuropsychological performances is confirmed. The use of corticosteroids in the treatment of ESES/CSWS seems to be the most effective approach; however, some questions arise. First of all, which is the best option between ACTH and Hydrocortisone? Second, when is it appropriate to start? Third, which dose is the correct one? And finally, for how long the therapy should last?

In the lack of shared protocols the oral therapy (Hydrocortisone) appears to be the most utilized; however, dose and duration are extremely variable. From the literature [66], it is clear that extending the range of AEDs to a large number of drugs does not lead to any results in terms of disappearance of EEG pattern and that the early use of hydrocortisone is crucial as in other epileptic encephalopathies [67]. Studies of long-term followup in ESES/CSWS [68] have shown that the permanent cognitive impairment which most patients experience can be predicted by the absence of response to drug treatment and relapse and longer duration of ESES/CSWS appears to be the major predictor factor of poor outcome. Therefore, it is important to use an appropriate dose of medication to normalize the EEG pattern and repeat a cycle of therapy whenever the EEG pattern should return.

In consideration of the side effects related to high and/or prolonged use of corticosteroid therapy, a possible alternative approach is represented by the use of pulse therapy for short cycles (high e.v. dose for three–five days repeated every three-four weeks) which could be undertaken for long time in relation to the EEG pattern. This approach has been used for other neurological conditions and its effectiveness has been also reported in ESES/CSWS [69, 70]. The aim of this procedure is to prevent the side effects associated to prolonged corticosteroids therapy using high dose for a short time and repeat it several times if the EEG pattern does not disappear or comes back.

Controlled trials and new studies taking into account a variety of clinical variables trying to answer the previous questions should be performed in order to provide an improved evidence for a rational approach to the treatment of ESES.

Conflict of Interests

None of the authors of this study has any conflict of interests in relation to this work.

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Clinical Study

Epileptic Encephalopathy in Children with Risk Factors for Brain Damage

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In the study of 887 new born infants with prenatal and perinatal risk factors for brain damage, 11 children with West syndrome that progressed into Lennox-Gastaut syndrome and another 4 children with Lennox-Gastaut syndrome that had not been preceded by West syndrome were found. In this study we present the main findings of these 15 subjects. In all infants multifactor antecedents were detected. The most frequent risk factors were prematurity and severe asphyxia; however placenta disorders, sepsis, and hyperbilirubinemia were also frequent. In all infants MRI direct or secondary features of periventricular leukomalacia were observed. Followup of all infants showed moderate to severe neurodevelopmental delay as well as cerebral palsy. It is concluded that prenatal and perinatal risk factors for brain damage are very important antecedents that should be taken into account to follow up those infants from an early age in order to detect and treat as early as possible an epileptic encephalopathy.

1. Introduction

The concept of epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time [1]. Although the encephalopathic effects of seizures and epilepsy may potentially occur in association with any form of epilepsy, the West and the Lennox-Gastaut (LG) syndromes are clear examples of this concept. West syndrome is an intractable epileptic syndrome characterized by epileptic spasms and hypsarrhythmia that is frequently associated with developmental arrest. This syndrome may evolve to the LG syndrome. The LG syndrome is characterized by severe, intractable, mixed type of seizures, mental retardation, and a slow spike and wave pattern (1.5 to 2.5 Hz) on the EEG [2].

In this study we were interested to present the incidence of the LG syndrome from our cohort of children that were specifically involved because they present prenatal and perinatal antecedents of risk factors for brain damage and report the clinical, electroencephalographic, and magnetic resonance images (MRI) findings.

2. Material and Methods

The protocol was approved by the Research Ethics Committee of the Instituto de Neurobiología of the Universidad Nacional Autónoma de Mexico, and complies with the ethical principles for medical research involving human subjects established by the Declaration of Helsinki.

2.1. Patients. In the period between 2003 and 2011 we have studied 887 infants. From our records we found 11 children with West syndrome that progressed to the LG Syndrome. Also another 4 children with LG Syndrome that had not been preceded by West Syndrome were found. The total sample was of 15 children, 8 were male. The mean gestational age

was of 35.46 + 4.17 weeks in a range between 28 to 40 weeks. All children came from different hospitals at the city of Querétaro referred to our Unit because they had risk factors for perinatal brain damage.

2.2. Clinical Examination by an Expert Pediatric Neurologist. Neurological assessment of the first study was done according to Amiel-Tison's neurological criteria [3, 4]. Children were followed every month during the first year, every 4 months during the second year, and later every 6 months.

2.3. Psychological Assessment

2.3.1. Bayley II Developmental Assessment. This test is for the developmental assessment for ages 1–42 months. It has 3 scores: mental, psychomotor, and behavioral scales. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months) [5, 6].

Other tests were used after 42 months: Wechsler Preschool and Primary Scale of Intelligence (WPPSI) that is adequate up to 7 years [7].

2.3.2. EEG Recordings. The study was performed in a dimly lit soundproof room. While recording each child remained on its mother's lap and wore a polyester cap with surface electrodes distributed according to the 10–20 International System (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz). Impedances were at or below 5000 ohms. EKG and EMG were recorded simultaneously. Referential EEG recordings were taken during spontaneous sleep for a 20 min interval using linked ear lobes as reference. A digital electroencephalograph (Medicid 4) was used with gain of 20,000, amplifier bandwidth was set between 0.5 to 100 Hz, and the sample rate was 200 Hz. Four EEG recordings were obtained in the first year of life, two at the second year and one at three, four, and five years old.

2.3.3. MRIs Studies. Scans were obtained using a 1.0-T Philips Intera in axial planes to obtain T1W, T2W, PDW, T2 FLAIR and T2-EPI sequences. T1W, T2W, and PDW data were also obtained in axial, coronal, and sagittal slices. A licensed pediatric radiologist reviewed all MRI scans and made the radiological diagnosis. Measurements of the volumes of the corpus callosum and the lateral ventricles were made. These values were compared against the normative values of our database. This normative data base was obtained from the MRI of 313 normal infants with an age range between 0 and 38 months (unpublished results).

3. Results

From the 887 infants with antecedents of risk factors for brain damage, 15 met criteria for West syndrome and later on 11 of these 15 presented the LG syndrome, therefore 15/887 (1.69%) was the prevalence of the West syndrome. Another group was composed of 4 children who had their debut with the LG syndrome without being preceded by the West syndrome. Thus, 15 children (15/887 = 1.69%) presented the LG syndrome.

Table 1: Number of children that present specific risk factors.

Factor	Number of children
Prenatal risk factors	
Abortion threat	1
Oligohydramnios	1
Vesicoureteral infections	1
Aged mother	1
Tobacco use	2
Addiction to solvents	1
Perinatal risk factors	
Prematurity	7
Severe asphyxia (3 with cardio respiratory arrest)	6
Underweight	4
Neonatal sepsis (1 with septic shock)	4
Neonatal seizures	4
Hyperbilirubinemia multifactorial	4
Respiratory distress	4
Acute fetal distress	2
Meconium aspiration	2
Congenital malformations	2
Anemia	2
Dystocic delivery	1
Placental abruption	1

3.1. Risk Factors. All children had prenatal and perinatal history of risk factors for brain damage. All children had more than one risk factor. Table 1 shows the number of children that present each factor. Prematurity and severe asphyxia (with 3 newborn infants that showed cardiorespiratory arrest) were the most frequent factors.

3.2. Clinical Features. Hypoxic ischemic encephalopathy was observed in 3 infants (20%), microcephaly in 4 (27%), and hydrocephaly in 4 (27%). Two infants presented bilirubin encephalopathy (13%) and one had pulmonary hypertension (7%). Cerebral palsy was observed later on in all children.

Types of Epileptic Seizures. Table 2 shows the number of subjects that had different types of seizures. In children with West syndrome many different types were observed, with epileptic spasms being the most frequent, while in the LG group myoclonic seizures were observed.

3.3. Psychological Evaluations. Ten children showed severe retarded psychomotor development and 5 showed moderate retarded psychomotor development.

3.4. EEG Findings. The average number of EEG recordings was 9 in both groups. Every child with West syndrome had

Table 2: Types of epileptic seizures found in children with West and Lennox-Gastaut syndromes.

	n	%
Epileptic spasms	8	53.3
Tonic seizures	3	20.0
Myoclonic seizures	2	13.3
Atonic seizures	2	13.3
Tonic-clonic seizures	1	6.7
Clonic seizures	5	33.3
Focal seizures with observable motor components	5	33.3
Dyscognitive seizures	2	13.3

hypsarrythmia and two of them had also abnormal focal slow waves. The hypsarrhythmia onset average age was 8.18 months (SD = 2.7, range of age = 4–12 months), while EEG features of the LG Syndrome began close to the 3 years old (Mean = 2.95 years, SD = 0.87, interval of age 2–5 years). Considering all the EEGs obtained in each child of both groups, it was observed that all showed single spikes, multiple spike complex, spike-wave complexes, slow spike-wave complexes, and polyspikes-wave complexes. The frequency of the spike-wave and sharp-wave complexes was between 1.0 and 2.5 Hz. Sharp waves were observed in 11 children. Three of the 15 children presented recruiting rhythm, and the discharges with burst suppression as well as initial focal discharges with secondary generalization were relatively frequent in both groups. Sleep organization of the slow phase was progressively deteriorated with age.

Figure 1 shows the EEGs recorded in one infant with West syndrome that evolved to LG syndrome on which it is possible to observe hypsarrhythmia at 6 months and later on, at 4 years, generalized discharges of slow spike-and sharp-wave complexes (around 1.0 Hz) and recruiting rhythm.

3.5. MRI. In all children MRI was abnormal. The most frequent abnormality was the presence of periventricular leukomalacia (PVL). Primary signs of PVL (presence of diffuse extensive intensities in the territory of the white matter and/or presence of macroscopic cysts [8, 9], were observed in 6 infants (3 cystic). Furthermore, the secondary radiological sequels of the PVL, irregularly dilated ventricles, and atrophy of the corpus callosum [8, 9] were found in 9 infants, thus all children showed MRI features compatible with PVL.

Other MRI observations were: 3 infants with intraventricular hemorrhages and 2 with periventricular hemorrhages, 3 with crossed cerebellar diaschisis, one with cerebellar hemorrhages, and one with a left parietal infarction. Cerebral atrophy was observed in 6 infants and hydrocephaly in 2 patients.

Volumes of the corpus callosum and the lateral ventricles were measured and compared with the normative values obtained in 313 normal infants with an age range between 0 and 38 months. These norms were computed in our institution allowing the comparison of the values of a particular subject with them. Deviations greater or lower than one standard deviation (SD) from the mean value according to age have a probability of belonging to the normal group equal or lower than 0.10, and deviations greater or lower than 2 SD of the mean have a probability of belonging to the normal group equal or lower than 0.05.

Values greater than 1 or 2 standard deviations (SD) from the mean value according to age of the lateral ventricles are considered moderate or severely abnormal. In the case of the Corpus Callosum, values lower than 1 or 2 SD are considered moderate or severely abnormal.

Table 3 shows the results of this analysis in all children made at one year of life and at 2 years old. First of all it is possible to observe that the volume of the Corpus Callosum was thin in 14 children at one year old and in all at 2 years old (only in one infant was moderately abnormal). The right lateral ventricle was severely enlarged in 12 children and in one moderately enlarged at one year old. However, at 2 years old, 14 children showed severely enlarged right ventricle. The left ventricle at one year old was severely abnormal in 12 children at one year old and in 13 at 2 years old. There was only one child with normal values of both lateral ventricles at one and 2 years old.

An example of the evolution of the different MRI features in a newborn with PVL is shown in Figure 2. This figure shows the MRI of a male infant born at 36 gestational weeks with PVL. He presented cardio-respiratory arrest, neonatal seizures, hypoxic-ischemic encephalopathy, and sepsis in the neonatal period. Later on he showed a severe retarded psychomotor development. At 2 months of corrected age it was possible to observe in the MRI the presence of diffuse leucomalacia in the occipital regions; the corpus callosum and the lateral ventricles had normal volumes. At 14 months of age the volume of the corpus callosum was very small (less than 2 SD) and the volumes of the lateral ventricles were greater than 2 SD from the norm, and at 32 months the corpus callosum maintains the small volume and the lateral ventricles maintain the great volumes.

4. Discussion

The aim of this study was to describe the incidence of the LG syndrome in a cohort of children that get into our research project in relation to the study of newborns with pre- and perinatal risk factors for brain damage, which was 1.69%. According to Gastaut et al. [10] the prevalence of the Lennox-Gastaut syndrome in a major epilepsy center (5.1% with 10.2% of patients below age 15 and 0.6% of patients above this age) is greater than the West syndrome, although Kurokawa et al. [11] observed the contrary in the Japanese population.

It has been described that in many infants with the West syndrome, mainly those with preexisting brain damage, a transition to Lennox Gastaut syndrome is common. This transition has been documented by Olmos-Garcia de Alba et al. [12].

In our population, 11 infants accomplished the criteria for West syndrome that evolved to the LG syndrome. Various authors have reported different percentages for this: 20% of the cases [13], 49% [14], 58.7% [15] and even 70% [16]. In our population of 887 infants, 15 children presented the West

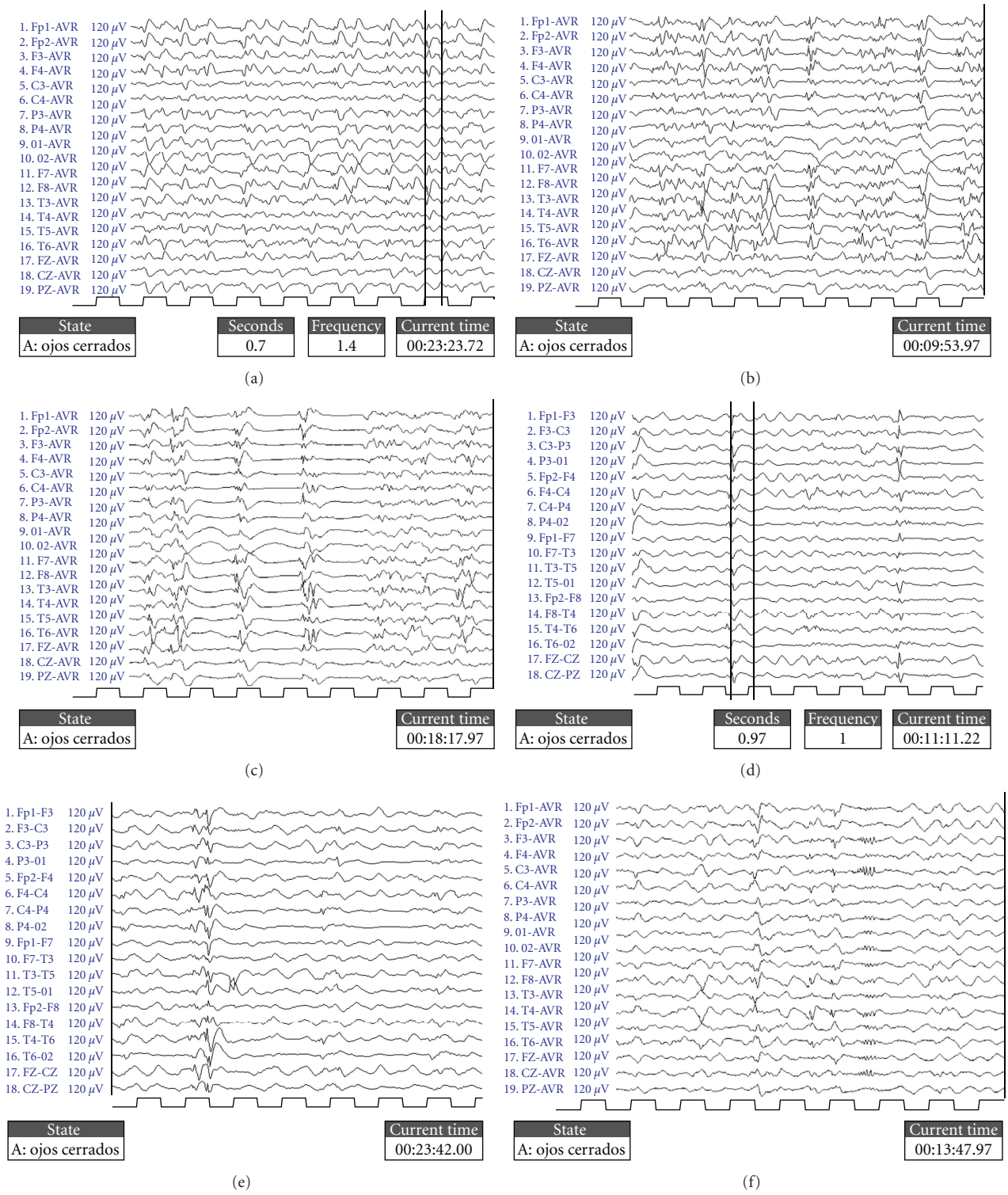

Figure 1: In the first and second rows of the figure appear three EEG segments from the recording obtained at 9 months (a, b, c). It can be noted the presence of hypsarrhythmia (a–c), slow spike and sharp-wave complexes (around 1.4 Hz), particularly in frontal regions (a), and also discharges of burst-suppression (b, c). In the second and third rows of the figure there are another three EEG segments (d, e, f) but now recorded at 4 years old. It can be observed (d, e) generalized discharges of slow spike and sharp-wave complexes (around 1.0 Hz) and recruiting rhythm (f).

Table 3: Individual volumes of the corpus callosum, right and left lateral ventricles obtained from MRI of the children at 1 and 2 years old[1].

Child	Corpus callosum volume (mL)		Right lateral ventricle volume (mL)		Left lateral ventricle volume (mL)	
	1 year	2 years	1 year	2 years	1 year	2 years
1	4.2	3.8**	9.9**	15.2**	6.2*	11.0**
2	0.7**	0.5**	8.6**	9.8**	12.2**	15.7**
3	0.5**	1.2**	71.6**	90.3**	242.0**	306.2**
4	0.3**	0.2**	147.2**	310.2**	220.8**	281.0**
5	0.3**	0.2**	36.3**	33.8**	235.6**	240.3**
6	2.3**	2.3**	3.7	7.3**	5.8*	8.7**
7	0.8**	0.7**	151.3**	172.8**	21.3**	27.9**
8	2.7**	3.47**	9.6**	9.7**	11.0**	11.2**
9	2.5**	1.9**	2.8	5.0	3.0	4.5
10	0.9**	2.0**	16.0**	19.0**	18.0**	21.0**
11	1.6**	1.8**	19.1**	18.5**	24.7**	23.5**
12	1.9**	2.0**	13.2**	19.8**	12.9**	18.9**
13	0.3**	1.6**	33.1**	98.9**	49.6**	143.4**
14	3.0*	4.8*	9.3**	8.7**	7.2**	6.9*
15	0.5**	0.7**	5.3*	8.0**	6.2*	10.3**

[1] Children numbers 12–15 belong to the group of Lennox-Gastaut syndrome that had not been preceded by West syndrome.
*One and **two standard deviations from the mean of the normative volumetric values corrected by age from normal children of 0–26 months (unpublished data from our research group).

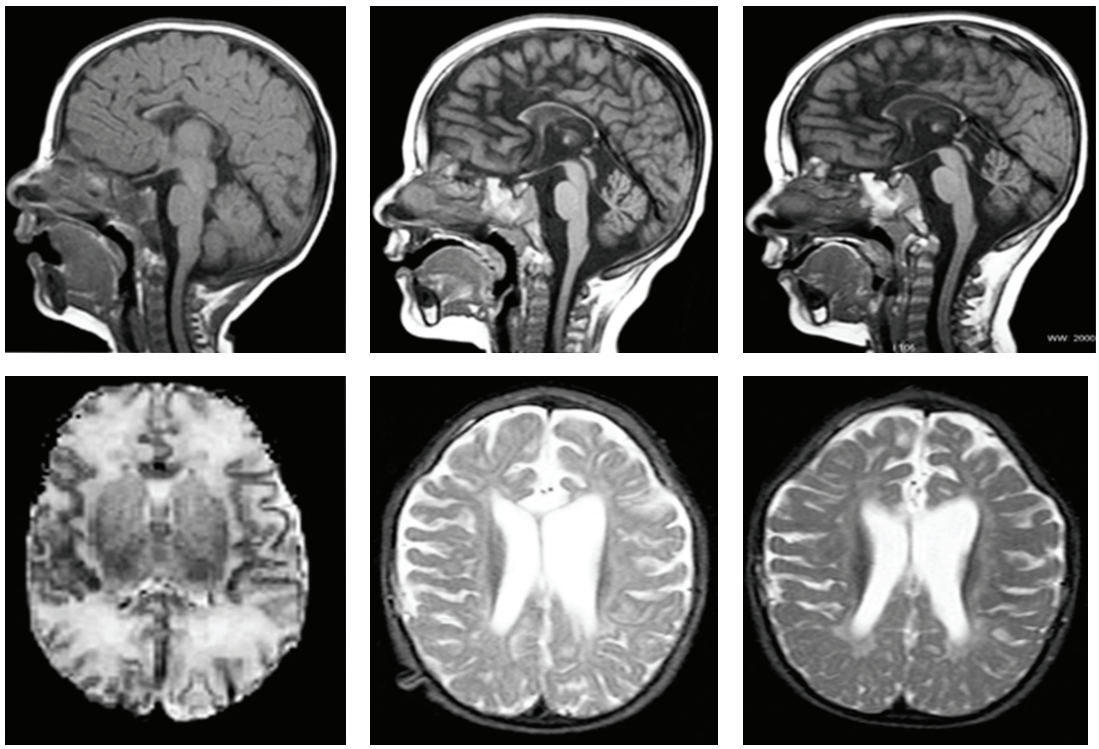

Figure 2: This figure shows the MRIs of a male infant born at 36 gestational weeks with PVL. At 2 months of corrected age it was possible to observe in the MRI the presence of diffuse leukomalacia in the occipital regions; the corpus callosum and the lateral ventricles had normal volumes. At 14 months of age the volume of the corpus callosum was very small (less than 2 SD) and the volumes of the lateral ventricles were greater than 2 SD from the norm, and at 32 months the corpus callosum maintains the small volume and the lateral ventricles maintain the great volumes.

syndrome, and from this, 11 (73%) showed this transition. Taking into consideration that all the children had severe brain lesions, the prevalence observed of this transition, although high, is not exceptional.

The most frequent risk factors were prematurity and severe asphyxia, which may explain the presence of PVL in all children. From the 887 infants studied in our institution, although 40% were lost in the followup, all of them had MRI scans and the primary diagnosis of PVL was made in 479 (54%), 9 of them present giant cysts almost without brain. The most frequent abnormality was the presence of diffuse excessive intensities in the territory of the white matter. Larger volumes of the lateral ventricles and delay myelination were very frequently observed as has been referred [17, 18]. The diagnosis of PVL in our study was confirmed by MRI in all subjects, 3 with abnormally increased signal intensity on T2-weighted images and 3 with macroscopic cysts in the white matter. In the remaining infants, sequels from PVL, as large volumes of the lateral ventricles and thin corpus callosum were observed. The statistical analysis of the volumes of the Corpus Callosum and the lateral ventricles also gave important information, since almost all the children showed values of their volumes that were out of the limits of the normal population according to our normative data. It is important to note that the values of the volumes were more abnormal at 2 years old than at one year old, indicating the structural severity that relates with more clinical and neuropsychological abnormal evaluations with age.

The West syndrome is a common complication (26%) of severe PVL [17]. Kuzmanic-Samija et al. [19] described 37 infants with West syndrome caused by PVL. However, in our population, from 479 infants with PVL only 15 developed the West or the LG syndrome (3.13%).

From the clinical point of view all children showed seizures of different types, severe to moderate retarded psychomotor development, cerebral palsy, and abnormal EEGs. Every child presenting the West syndrome had hypsarrythmia, and those with the LG syndrome show the characteristic slow spike and wave discharges. These clinical findings correspond to the concept of epileptic encephalopathy, according to the last ILAE classification [1].

5. Conclusions

Prenatal and perinatal risk factors for brain damage are very important antecedents that should be taken into account for the followup of the infant from an early age. Presence of PVL in premature newborns increases the risk for motor and cognitive sequelae and sequential, EEG recordings allow early detection of an epileptic encephalopathy to prescribe immediate treatment.

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