

Epileptic Encephalopathies in Infants and Children: Study of Clinico-Electroencephalographic Spectrum in a Tertiary Hospital in Bangladesh

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Abstract

Background: The epileptic encephalopathies collectively exact an immense personal, medical, and financial toll on the affected children, their families, and the healthcare system. **Objective:** This study was aimed to delineate the clinical spectrum of patients with Epileptic encephalopathies (EEs) and classify them under various epileptic syndromes. **Methods:** This was a cross-sectional study that was carried out in the department of Neurophysiology of the National Institute of Neurosciences and Hospital, Bangladesh from July 2016 to June 2019. Children with recurrent seizures which were difficult to control and associated with developmental arrest or regression in absence of a progressive brain pathology were considered to be suffering from EE. Children under 12 years of age fulfilling the inclusion criteria were enrolled in the study. These patients were evaluated clinically and Electroencephalography (EEG) was done in all children at presentation. Based on the clinical profile and EEG findings the patients were categorized under various epileptic syndromes according to International League Against Epilepsy (ILAE) classification 2010. **Results:** A total of 1256 children under 12 years of age were referred to the Neurophysiology Department. Among them, 162 (12.90%) fulfilled the inclusion criteria. Most of the patients were male (64.2%) and below 1 year (37.7%) of age. The majority (56.8%) were delivered at the hospital and 40.1% had a history of perinatal asphyxia. Development was age-appropriate before the onset of a seizure in 38.9% of cases. Most (53.7%) of the patients had seizure onset within 3 months of age. Categorization of Epileptic syndromes found that majority had West Syndrome (WS)

(37.65%) followed by Lennox-Gastaut syndrome (LGS) (22.22%), Otahara syndrome (11.73%), Continuous spike-and-wave during sleep (CSWS) (5.66%), Myoclonic astatic epilepsy (MAE) (4.94%), Early myoclonic encephalopathy (EME) (3.7%), Dravet syndrome (3.7%) and Landau-Kleffner syndrome (LKS) (1.23%). 9.26% of syndromes were unclassified. **Conclusion:** EEG was found to be a useful tool in the evaluation of Epileptic encephalopathies. The clinico-electroencephalographic features are age-related. Their recognition and appropriate management are critical.

Keywords

Epileptic Encephalopathy (EE), EEG, Infantile Epileptic Encephalopathy (IEE), Clinico-Electroencephalographic Spectrum, West Syndrome

1. Introduction

Epileptic encephalopathy (EE) refers to a category of conditions in which epileptic activity itself can lead, and can intensify over time, to serious cognitive and behavioral impairments beyond what can be expected from the underlying pathology alone (e.g., cortical malformation). Such impairments can be more selective or global, and they can occur along a severity continuum. Some syndromes are sometimes referred to as epileptic encephalopathies (EEs), with the potential for encephalopathic effects of seizures and epilepsy associated with any type of epilepsy [1]. It may be progressive or it may have a direction that fluctuates. Some syndromes are recognized [Early myoclonic encephalopathy (EME), Ohtahara syndrome or Early Infantile Epileptic Encephalopathy (EIEE), West syndrome (WS), Dravet syndrome, Lennox-Gastaut syndrome (LGS), Landau-Kleffner syndrome (LKS), Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)] while some (Epilepsy of infancy with migrating focal seizures, Atypical benign partial epilepsy of childhood, Hypothalamic epilepsy, Late infantile epileptic encephalopathy, Myoclonic encephalopathy in nonprogressive disorders) have been proposed for inclusion under EEs [2].

The clinical spectrum of EEs is complex and depends on the age of onset, epileptic behavior, environmental and genetic variables [3]. The clinical spectrum varies from severe forms with cognitive and motor deterioration to mild forms with a better course [4]. Clinical and electroencephalographic (EEG) characteristics represent the immature brain's particular age-related epileptogenic reaction. Several studies have shown that better control of seizures leads to an improvement of the developmental outcome in certain children [5] [6]. However, despite aggressive and sometimes off-label use of several medications, the response to anticonvulsants is often poor [7].

In every paediatric neurology clinic, they are major contributors to neuro morbidity-physical, social, intellectual disability, and intractable seizures. Be-

cause of their refractoriness and poor cognitive outcome, even though seizures are controlled, there has been a recent emphasis on their further classification and management [8]. More vigorous use of antiepileptic drugs (AEDs) in the suppression of interictal epileptiform discharges is considered successful. Besides AEDs, immunomodulatory therapies (e.g., corticosteroids, IVIG, plasmapheresis) and the Ketogenic or Adkin's diet are often considered.

In this study, we analyzed and categorized the electro-clinical spectrum of children with EEs into different epileptic syndromes. Their clinical and seizure spectrum, perinatal causes, and EEG results were addressed. However, overlapping clinico-electrical characteristics often make it difficult to classify patients into a particular syndrome.

2. Material and Methods

This was a hospital-based cross-sectional observational study. This study was conducted in the department of Neurophysiology of the National Institute of Neurosciences and Hospital, Dhaka, Bangladesh during the period from July 2016 to June 2019. Children below 12 years of age referred from the epilepsy clinic of the pediatric neurology department were screened.

Children who had a recurrent seizure, not controlled by two or more antiepileptic drugs with adequate dose and duration having severe cognitive and behavioral impairments not explained by the underlying pathology alone were considered to have EEs and enrolled. These children usually had multiple seizure types and seizures could directly worsen their cognition and behavior. Patients with subacute sclerosing panencephalitis were excluded. A convenient consecutive sampling method was applied and data were collected in a pre-designed questionnaire. These children were evaluated by history and physical findings. The neurodevelopmental assessment was done by a Developmental therapist using Rapid neurodevelopmental assessment [9] [10] tools. EEG was done in all children at the presentation where surface electrodes were distributed according to the 10 - 20 International System where impedances were kept at or below 5000 ohms. EEG and EKG were recorded simultaneously. EEG recordings were taken during spontaneous sleep and awake state for about 60 mins.

Age of presentation and seizure onset, seizure spectrum, developmental profile, perinatal events including mode of delivery, perinatal asphyxia, Central nervous system infection, neonatal jaundice, family history of seizure, microcephaly, EEG abnormalities, brain imaging (CT, MRI) findings were evaluated. Name of the antiepileptic drugs (AEDs), response to ACTH or other drugs were also noted.

Considering the age of onset of the seizure, its semiology and evolution, interictal condition, and EEG findings, the patients were categorized under various epileptic syndromes according to International League Against Epilepsy (ILAE) classification 2010. Despite the evolution from one form of EE to another, the categorization which was done on enrolment was retained for the study. Child-

ren with EEs were classified into WS, LGS, EME, EIEE, Dravet syndrome, LKS, MAE, and CSWS. When electro-clinical classification could not possible, it remained unclassified.

The criteria for various EEs in this study were [4] [11]:

Ohtahara syndrome (EIEE): Age of onset ranging from birth to 3 months of age, high-frequency tonic spasms are the defining seizure type, other seizure types also occur; burst suppression pattern without sleep-wake differentiation on interictal EEG.

Early myoclonic encephalopathy (EME): Seizure onset in neonatal period, erratic, fragmentary, or massive myoclonus, focal seizures, and late tonic spasms; EEG pattern is bursts-suppression with long suppression periods; more distinct during sleep.

West syndrome (WS): Cluster of spasms started within 3 to 12 months of age, psychomotor deterioration, and hypsarrhythmia on EEG.

Lennox-Gastaut syndrome (LGS): Age of onset ranging from 1 to 8 years of age, refractory polymorphic seizures (≥ 2 seizure types, the tonic seizure must be one seizure type), on EEG-bilateral synchronous slow spike-and-wave discharges (1.5 - 2.5 Hz) with abnormal slow background and/or paroxysmal fast activity.

Dravet syndrome: Age of onset between 5 and 8 months, history of febrile seizure followed by afebrile multiple seizure types in a previously normal child, psychomotor regression; rhythmic theta (4 - 5 Hz) activity and generalized photoparoxysmal responses, slow background, multifocal epileptiform discharges or asymmetric paroxysms of generalized poly-spike/spike-slow waves on EEG.

Landau-Kleffner syndrome (LKS): Age of onset ranging from 5 to 8 years, developmentally age-appropriate children presented with verbal auditory agnosia, language regression, behavioral abnormalities; tonic-clonic, focal motor, atypical absences, head drop, and subtle seizures; posterior temporal (vertical dipole) epileptiform discharges markedly activated by NREM sleep on EEG.

Myoclonic astatic epilepsy (MAE): Seizure onset between 2 and 5 years of age, multiple seizure types (myoclonic-astatic, tonic-clonic, tonic, and atypical absences; apraxia, dysarthria, and cognitive deterioration; poly-spike waves or spike-wave complexes at a frequency of 2 - 4 Hz on ictal EEG, spike-waves of 3 Hz may appear later and non-convulsive status may be seen on EEG.

Continuous spike-and-wave during sleep (CSWS): Age of ranging from 4 to 7 years; multiple seizure types; psychomotor and speech regression, behavioral abnormality and motor involvement (ataxia, dystonia, dyspraxia) are often present; continuous spike-wave complexes exclusively during non-REM sleep, with a spike-wave index for at least 80-85% of slow sleep on EEG.

All data were entered in SPSS 16 for Windows statistical software. Continuous data were presented as means and standard deviations whereas categorical data were presented as proportions. Written informed consent for enrollment was taken from every parent. Ethical clearance from the ethical review committee (ERC) of the hospital was taken before starting the study.

3. Results

A total of 1256 patients under 12 years were referred to Neurophysiology Department for EEG from July 2016 to June 2019. Among them, 162 (12.90%) fulfilled the inclusion criteria. Their mean age was 32.43 (1 - 120) days. Most of the patients were male (64.2%) and below 1 year (37.7%) of age (**Table 1**).

Most (56.8%) were delivered at term (82.7%) at the hospital (56.8%) and cesarean section was done only in 39.51% of cases. 40.1% had a history of perinatal asphyxia. Development was age-appropriate before the onset of a seizure in 38.9% of cases. In 13.3% of cases, there was a family history of seizures (**Table 2**).

Most (53.7%) of patients had seizure onset within 3 months of age (**Figure 1**) and on neurodevelopmental assessment, the majority (96.9%) had a developmental

Table 1. Age and sex distribution of patients (n = 162).

Sex	Male: 104 (64.2%) Female: 58 (35.8%)
Mean age (month)	32.43 (1 - 120)
Age at presentation (month)	1 - 3: 11 (6.8%) 4 - 12: 50 (30.9%) 13 - 36: 48 (29.6%) 37 - 60: 24 (14.8%) >60: 29 (17.9%)

Table 2. Perinatal and developmental profile of the studied population (n = 162).

Variables	Number	Percentage (%)
Gestational age		
Term	135	82.7
Preterm	19	11.7
Place of delivery		
Hospital	92	56.8
Home	70	43.2
Mode of delivery		
Normal vaginal delivery	98	60.49
Cesarean section	64	39.51
Etiology		
History of perinatal asphyxia	65	40.1
CNS infection	36	22.22
Septicemia	27	16.67
Bilirubin encephalopathy	10	6.17
Development age-appropriate before the onset of seizure	63	38.9
Family history of seizure	22	13.3

delay either global or at specific domains. 23.4% of patients had microcephaly (**Table 3**).

Infantile spasm (45.1%) and myoclonic seizures (40.1%) were the commonest types of seizures (**Table 4**). EEG was found to be abnormal in 93.2% of patients on enrollment. The most common EEG abnormality was multifocal epileptiform discharges (31.9%) and generalized epileptiform discharges (27.5%) (**Table 5**).

Electroclinical diagnosis established WS (37.65%) to be the most common followed by LGS (22.22%), EIEE (11.73%), CSWS (5.56%), MAE (4.94%), EME (3.7%), Dravet (3.7%) and LKS (1.23%). 9.26% of children having EE remained unclassified (**Figure 2**). Sodium valproate was the most commonly prescribed drug and 18.02% of patients were on monotherapy.

Table 3. Physical findings of the studied population on enrollment (n = 162).

Variables	Number	Percent (%)
Developmental delay	157	96.9
Tone abnormalities	66	40.7
Quadriplegia	42	25.9
Microcephaly	38	23.4
Visual deficit	22	13.5
Hemiplegia	9	5.5
Hearing deficit	7	4.3

Table 4. Seizure spectrum of the studied population (n = 162).

Seizure semiology	Number	Percent (%)	Percent (%) of cases
Epileptic spasm	73	23.9	45.1
Myoclonic seizure	65	21.3	40.1
Tonic	37	12.1	22.8
Atonic	31	10.2	19.1
Generalized tonic clonic	30	9.8	18.5
Clonic	24	7.9	14.8
Focal onset	22	7.2	13.6
Absence	16	5.2	9.9
Focal followed by secondary generalization	7	2.3	4.3

Table 5. EEG findings in the studied population (n = 162).

EEG findings	Number	Percent (%)	Percent (%) of cases
Multifocal epileptiform discharge	44	27.7	31.9
Generalized epileptiform discharge	38	23.9	27.5
Hypsarrhythmia	20	12.6	14.5
Focal epileptiform discharge	15	9.4	10.9
Burst suppression in both awake & sleep	14	8.8	10.1
Modified hypsarrhythmia	13	8.2	9.4
Generalized paroxysmal fast activity	10	6.3	7.2
Burst suppression predominantly in sleep	5	3.1	3.6

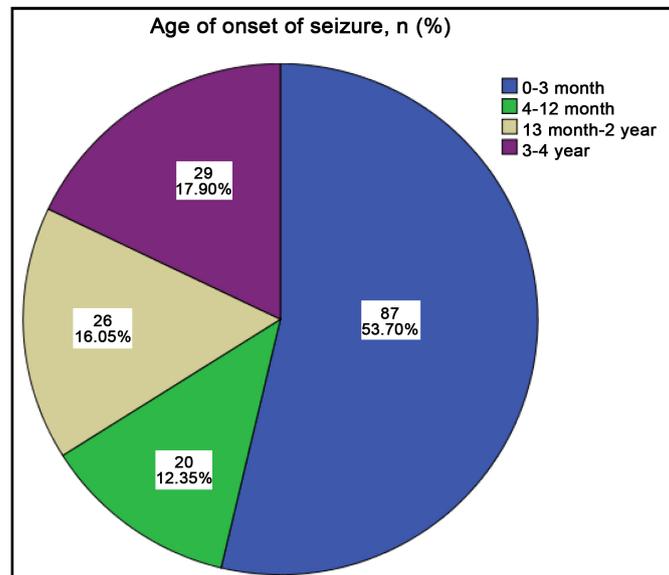


Figure 1. Age of onset of seizure (n = 162).

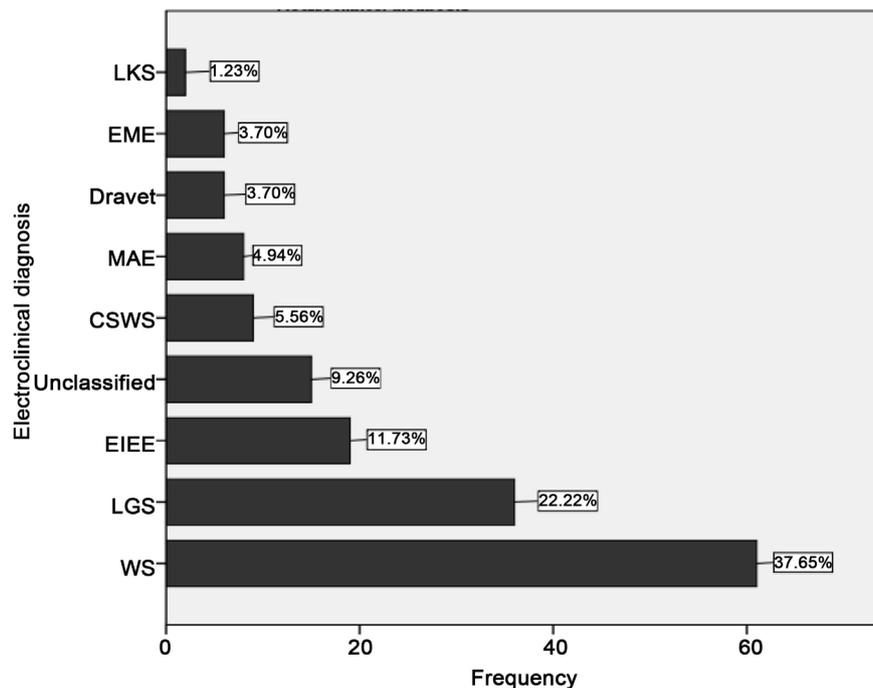


Figure 2. Electroclinical diagnosis among the studied population (n = 162). WS—West syndrome, LGS—Lennox-Gastaut syndrome, EIEE—Early Infantile Epileptic Encephalopathy, CSWS—Continuous spike wave of slow sleep, MAE—Myoclonic-astatic epilepsy, Dravet—Dravet syndrome, EME—Early myoclonic encephalopathy, LKS—Landau-Kleffner syndrome.

4. Discussion

EEs are an age-related diverse group of disorders where seizure control becomes very difficult and there is either developmental arrest or regression. It has a distinctive seizure pattern and specific EEG abnormalities. It may be progressive or

may have a waxing-waning course. However, syndromic classification is often difficult. These conditions can overlap and develop into other clinical and electroencephalographic characteristics. In the literature [12] [13] [14], this is well known. These kids also switch from one doctor to another without a correct diagnosis and receiving several medications. For better results, these patients need early diagnosis and intensive care. The task of electroclinical classification is therefore extremely important for the proper management of EEs in these patients.

This study included 162 (12.90%) patients with suspected epileptic encephalopathy. Males were almost twice the number of female patients. This finding is similar to the findings in other studies [11] [15]. Although only 6.8% of patients presented at 1 to 3 months of age, half of the enrolled children had onset of seizure within 3 months of age. Therefore, there was a delay between the onset of symptoms and disease recognition. Earlier the onset of seizures more is the damage [14]. A history of perinatal asphyxia was present in around 40% of patients. Perinatal asphyxia emerged as an important etiological factor in many of the EEs in different studies [11] [16]-[23]. In this study, there was a history of central nervous system infection in early infancy in 22.22% of cases. This finding differs from the data of developed countries where most of the cases are due to prenatal causes [24] [25].

In all EEs, developmental delay or arrest is a prime concern. In our study, it was observed at initial presentation in 96.9% of cases which is comparable to literature (90%) [13] and another study [11]. In this study, 38.9% of children with EEs were developmentally age-appropriate before the onset of a seizure and many of them became retarded at the time of enrollment in the study. Microcephaly was found in 23.3% of patients which is less than other previous studies [11] [17] [26] and to a figure mentioned in literature [27]. An earlier cerebral insult like intrauterine infections, asphyxia, metabolic, genetic, or developmental malformation of the brain may cause microcephaly [11].

In a previous study, WS and EIEE were found to be the most common and constitute almost half of all EEs [11]. Most of the patients of EIEE and WS presents in the first three months of their life with seizures. In this case series, seizures started within the first 3 months of age among most patients and the WS was the most frequent EE. Infantile spasms and myoclonic seizures were the commonest type of seizures followed by tonic and atonic seizures. As WS and LGS constitute the majority of cases in this series, these seizures are expected to be the most frequent seizure types. Most of the EEGs were abnormal; multifocal and generalized epileptiform discharges were the commonest abnormality. Multiple independent epileptiform discharges have been considered important EEG findings in many of the EEs [28] [29]. EEG recordings allow early detection of EEs thereby facilitating immediate aggressive treatment.

In a national household survey in Bangladesh, it is shown that the prevalence of epilepsy among children aged <18 years is 8.2 per 1000 [30]. So it is a huge burden for a developing country like us. A study conducted in Dhaka Shishu

(Children's) Hospital among children with epilepsy aged 2 months to 15 years found "Severe epilepsy syndrome" in 31% of cases. Where WS (66%) was the commonest followed by Myoclonic encephalopathy (24%), LGS (9%), and LKS (1%) [16]. Kalra *et al.* [11] in a study in the All India Institute of Medical Sciences observed that Infantile epileptic encephalopathies (IEE) comprised 3.5% of Paediatric Neurology Clinic registrations. WS was the commonest IEE and comprised 55.3%. EIEE, LGS, and EME were found in 26.6%, 16%, and 2.1% cases respectively. In our study, we found 12.90% of children (>12 years of age) had EEs. WS was the commonest electroclinical syndrome followed by LGS in this study. These findings are similar to other studies [22] [31] [32]. Our study also observed that majority of children with WS had a history of perinatal asphyxia.

Classification under specific epileptic syndromes was difficult in 9.26% of cases and remained unclassified. Among them, the majority have a history of perinatal asphyxia, CNS infection, or septicemia. Most of them had predominantly generalized tonic-clonic and myoclonic seizures along with other seizure types and faced developmental regression after the onset of the seizure. EEG did not reveal any specific pattern. The majority showed multifocal, focal, and generalized epileptiform discharges.

The progression of EEs in children is variable and the prognosis does not depend on a specific factor. However, the electro-clinical syndrome gives some clues about the cause and outcome of the disease. It is useful to set up a treatment strategy as most of EEs are pharmacoresistant. Early, aggressive and multidisciplinary treatment approaches are needed for these children.

Therefore, the burden of EEs is huge in a country with limited resources like Bangladesh. It collectively exerts a profound financial toll on the families of affected children, healthcare providers, and the whole healthcare system. A high index of suspicion, proper EEG recordings, and appropriate analysis of EEG are mandatory for the early diagnosis of these patients. The knowledge of specific electro-clinical syndrome will help to treat these children early and appropriately which may improve the long-term outcome of these children with EEs.

This study was conducted in a single-center tertiary hospital and did not represent the actual situation of the country.

5. Conclusion

The frequency of EEs in infants and children is quite high. Perinatal asphyxia is an important cause. Most starts at an early age with a deleterious effect on the developing brain. Infantile spasms, myoclonic seizures are among the commonest seizure types. EEG in most cases shows multifocal epileptiform discharges in addition to other type-specific findings. WS and LGS constitute the major bulk of the EEs in children.

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Authors' Contributions

Bithi Debnath designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Mohammad Enayet Husain reported all the EEG and managed the literature searches. RajibNayan Chowdhury and Narayan Saha managed the analyses of the study. All authors read and approved the final manuscript.

Consent

Written informed consent was taken from the parents or guardians before inclusion in the study.

Ethical Approval

Ethical clearance from the ethical review committee (ERC) of the hospital was taken before starting the study.

Conflicts of Interest

There is no conflict of interest with any of the authors of this article.

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