International Journal of Health Sciences and Research
Vol.10; Issue: 10; October 2020
Website: www.ijhsr.org
Original Research Article *ISSN: 2249-9571*

Clinical and Etiological Profile of Children with Epileptic Encephalopathy

Arpita Adhikari[1], Payal Shah[2], Mona Gajre[3], Sushma Keshav[4]

[1]Associate Professor, [2]Fellow, [3]Professor, [4]Resident,
Division of Neurology Epilepsy and Developmental Pediatrics, Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai, India.

Corresponding Author: Sushma Keshav

ABSTRACT

Background: Epileptic encephalopathyis a group of electro-clinical syndromes presenting with varied presentation with very few Indian studies. This study aims to describe the aetiology and clinical profile of children with epileptic encephalopathy and classify them into epileptic syndromes.
Methods: History and investigations (electroencephalogram, neuroimaging) of children coming to the paediatric neurology outpatient of a tertiary care hospital in Western India and satisfying the criteria for epileptic encephalopathy were recorded and analysed.
Results: Out of the 34 children studied, 27 had onset of seizures within one year of age and the remaining had seizure onset between 1 to 6 years of age, most common seizure semiology being epileptic spasms (in 22/34) followed by erratic myoclonus, focal tonic clonic and generalized tonic clonic and 8 had multiple seizure types. 27 out of the 34 had microcephaly and developmental delay at presentation. On classification into epileptic syndromes, majority had west syndrome (21/34), followed by early myoclonic encephalopathy (5/34), epileptic encephalopathy with continuous spike and wake during sleep (5/34) and early infantile encephalopathy (1/34). The most common etiology for epileptic encephalopathy in our study was found to be perinatal insult (13/34) in the form of birth asphyxia and neonatal hypoglycemia. Other causes included post infectious sequelae (5/34), structural abnormalities like aicardi syndrome (2/34).
Conclusions: The most common epileptic encephalopathy in our setting was west syndrome with etiology being perinatal asphyxia. Most of the children were infants with microcephaly and developmental delay at presentation.

Keywords: Epileptic encephalopathy, encephalopathy syndromes, modified hypsarrhythmia

INTRODUCTION

The term epileptic encephalopathy refers to a heterogeneous group of conditions in which even in the absence of progressive metabolic and/or structural brain abnormalities, the extremely abnormal brain electrical activity(for instance burst-suppression pattern and hypsarrhythmia) may not only be the cause of seizures, but also interfere with cognitive functions leading to an arrest or regression in intelligence or behaviour.[1] 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 cause of progressive cognitive and neuropsychological deterioration or regression. In other words there is a detrimental effect of continuing seizures and electrographic discharges on the normal function of the developing brain.

In the classification of the International League Against Epilepsy (ILAE)the age-related epileptic encephalopathy syndromes include early myoclonic encephalopathy and Ohtahara syndrome in the neonatal period, West

syndrome, Dravet syndrome and epilepsy of infancy with migrating focal seizures in infancy and epilepsy with myoclonic-atonic seizures, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and epilepsy with continuous spike waves during slow wave sleep in childhood and adolescences.[2] 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, and of symptomatic or idiopathic cause.[3] This age related epileptogenic reaction is peculiar to the immature brain and varies significantly in accordance with the stage of brain maturity at the time that this occurs. Thus, EEG demonstrates primarily burst–suppression patterns in the neonatal period, hypsarrhythmia in infancy and slow generalised spikewave discharges (GSWD) in early childhood.[4]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 in adolescence but often with serious neurocognitive residual effect.

The etiopathology of these syndromes has not been fully elucidated. It may be multiple and not necessarily the same for all. The major determinant is the brain functional and structural immaturity, with a 'cause–effect' interaction between abnormal electrical discharges generated by and modifying/acting upon neuronal circuits in development.

There are very few study in India which have evaluated the clinical profile of epileptic encephalopathy.[5,6] So our aim is to study the etiology & clinical features of patient with epileptic encephalopathies and to classify them under various epileptic syndrome.

MATERIALS AND METHODS

The present study was conducted over a period of 1 year from August 2015 to July 2016 in a tertiary care teaching hospital of a metropolitan city. Cases were selected from the Epilepsy and Neurology Clinic of the Pediatrics department. Children who had recurrent, difficult to control seizures associated with arrest or regression of development in the absence of a progressive brain pathology were considered to be suffering from EE. Data of children with epileptic encephalopathy who had presented during the period was collected.Their clinical features, EEG characteristics, neuroimaging & biochemical marker findings if done and treatment details were studied.

Detailed history with special reference to antenatal, natal and postnatal events, the age at onset of seizures and the type and evolution of seizures were noted. The details of neurodevelopmental assessment were recorded.

EEG and CT/MRI scan done at presentation or if repeated later were documented. Investigations for inborn errors of metabolism had been done where indicated by performing blood gas analysis, serum ammonia, serum and CSF lactate, urinary amino acidogram, muscle and skin biopsy, etc. Details of the same were noted.

On the basis of the clinical profile, EEG and neuroimaging, the patients were categorized under various epileptic syndromes as per the International League against Epilepsy (ILAE) classification.

Data Collection was done with the help of Case Record Forms and was analysed by the investigator.

RESULTS

Over the 1 year study period, 34 children satisfying the inclusion criteria were enrolled in the study. Out of these 34, 23 were males and 11 females. 9/34 were born with a low birth weight and 5/34 were preterm deliveries. Majorities were first by birth order (23/43) (Table 1 and 2).

7/34 were born of third degree consanguineous marriage. Only 4 patients had family history of seizures (Table 3).

21 patients had history suggestive of neonatal encephalopathy meaning failure to

initiate or maintain respiration, seizures and poor feeding (Table 4).

27 patients had onset of seizures within one year of age and the remaining seven patients had seizure onset between 1 to 6 years of age (Table 5)

Seizure spectrum at presentation included epileptic spasms in 22/34 followed erratic myoclonus, focal tonic clonic and generalized tonic clonic. Eight of the total 34 had multiple seizure types (Table 6).

Microcephaly defined as head circumference less than two standard deviations below the mean for age and sex was documented in 27/34.Developmental status was inferred by finding out developmental quotient based on history of milestones and chronological age. 27 and 6 patients had history suggestive of developmental delay and developmental regression respectively at presentation (Table 7).

Comorbidities in the form of visual concerns (23/34), hearing concerns (21/34), tone abnormalities (25/34) and involuntary movements (1/34) were seen in most patients (Table 8).

TABLE 1: SEX DISTRIBUTION

SEX	NUMBER	PERCENTAGE
MALE	23	68
FEMALE	11	32
TOTAL	34	100

TABLE 2: DISTRIBUTION ACCORDING TO BIRTH ORDER

BIRTH ORDER	NUMBER
FIRST	23
SECOND	6
THIRD OR MORE	5
TOTAL	34

TABLE 3: DISTRIBUTION ACCORDING TO CONSANGUNITY

CONSANGUINITY	NUMBER	PERCENTAGE
CONSANGUIENOUS MARRIAGE	7	20%
NON- CONSANGUIENOUS MARRIAGE	27	80%
TOTAL	34	100

TABLE 4: PERINATAL HISTORY

HISTORY OF	YES	NO
NEONATAL ENCEPHALOPATHY	21	13
BIRTH ASPHYXIA	15	19
HYPOGLYCEMIA	3	31
JAUNDICE	6	28

TABLE 5: DISTRIBUTION ACCORDING TO THE AGE OF ONSET

AGE OF ONSET	MALE	FEMALE	TOTAL
0- 1 YEARS	19	8	27
1-6 YEARS	4	3	7
6-12 YEARS	0	0	0
TOTAL	23	11	34

TABLE 6: SEIZURE SEIMIOLOGY

TYPE OF SEIZURE	NUMBER
EPILEPTIC SPASMS	22
ERRATIC MYOCLONUS	2
MULTIPLE	8
FOCAL TONIC	1
GENERALISED TONIC CLONIC	1

TABLE 7: DEVELOPMENTAL HISTORY

HISTORY	NUMBER
DEVELOPMENTAL DELAY	27
DEVELOPMENTAL REGRESSION	6
NORMAL	1

TABLE 8: CO-MORBIDITIES

COMORBIDITIES	NUMBER
VISION	23
HEARING	21
TONE ABNORMALITIES	25
INV MVTS	1

TABLE 9: ELECTROENCEPHALOGRAPHIC FINDINGS

EEG FINDINGS	NUMBER
HYPSARHYTMIA	1
MODIFIED HYPSRYTHMIA	13
SUPPRESSION BURSTS	6
FOCAL IEDS	6
POLYSPIKES	1
CSWS	5
GENERALISED DISCHARGES	1

TABLE 10: NEUROIMAGING

NEUROIMAGING	NUMBER
HYPOXIC ISCHEMIC INSULT	14
NORMAL	9
STRUCTURAL	5
CEREBRAL ATROPHY	2
GLIOTIC LESION	1
OTHERS	2

TABLE 11: CLASSIFIACTION OF EPILEPTIC SYNDROME

FINAL DIAGNOSIS	NUMBER
WEST SYNDROME	22
LENNOX GASTAUT SYNDROME	0
CSWS	5
EARLY MYOCLONIC ENCEPHALOPATHY	5
OHTAHARA	1
LANDAU KLEFNER SYNDROME	0
DRAVET SYNDROME	0
UNCLASSIFIED	1

TABLE 12: ETIOLOGY

ETIOLOGY	NUMBER
NOT KNOWN	11
BIRTH ASPHYXIA	10
STRUCTURAL	5
POST-INFECTIOUS	3
NEONATAL HYPOGYCEMIA	3
OTHERS	2

The most common EEG finding in patients with West syndrome was modified hypsarrhythmia (13/34).Others has hypsarrhythmia, suppression burst, focal inter-ictal discharges and generalized bursts (Table 9).

Neuroimaging (MRI) was done in all patients. 25/34 were abnormal. Abnormal findings included periventricular leucomalacia, cystic encephalomalacia, generalized atrophy, agenesis of corpus callosum, tuberous sclerosis and periventricular nodular heterotopia (Table 10).

Classification into various epileptic syndromes showed majority had west syndrome (21/34), followed by early myoclonic encephalopathy (5/34), epileptic encephalopathy with continuous spike wave during sleep (CSWS) (5/34) and early infantile encephalopathy (1/34) (Table 11).

The most common etiology for epileptic encephalopathy in our study was perinatal insult (13/34) in the form of birth asphyxia and neonatal hypoglycemia. Other causes included post infectious sequelae (5/34), structural abnormalities like aicardi syndrome (2/34), tuberous sclerosis, and neuronal migrational disorder like periventricular nodular heterotopia. One patient had genetic mutation involving the ARX gene. Exact etiology was not known in the remaining 11 patients (Table 12).

DISCUSSION

Epileptic encephalopathy is a group of electro-clinical syndromes presenting with varied presentation which may include new onset seizures, change in semiology of the seizures, developmental arrest or regression, cognitive decline or behavioral issues and EEG showing aggressive abnormal electrical activity with high spike rates.[7] The various syndromes have overlapping features. Besides, they may show evolving changes over a period of time thus making the diagnosis difficult. Very few Indian studies have been done to study the clinical and etiological profile of children with epileptic encephalopathy.

Ours was a prospective observational study conducted in a tertiary care hospital in a metropolitan city. All children coming to childhood neurology and epilepsy OPD with difficult to control seizure with developmental delay were enrolled. Demographic and clinical aspects were studied and grouped epileptic syndromes based on ILAE classification. It was observed that the deleterious effects of epileptic activity are due to the specific brain reaction of excessive neocortical excitability which is age related and peculiar to the immature brain. This could be a reason for most of our study patients (about 80%) belonging to the age group of less than 1 year. Our study showed a male predominance with a male to female ratio of 2.1:1, comparable to previous studies like this similar study involving children with west syndrome from north India, where the mean age of onset was 5.6 months and there was a male predominance.[8]

Etiologically, majority of these children had a history of perinatal encephalopathy and birth asphyxia, while some also had perinatal hypoglycemia and jaundice. This is in agreement with other studies on etiology of intractable seizures conducted across the country and outside.[9,10,11] This is understandable in a developing country like ours. However some studies from the West showed that structural brain anomalies and neuro-metabolic disorders were more common etiologies.[12]

The most common seizure type observed was epileptic spasms followed by erratic myoclonus. About 26% of the children had a normal neuroimaging while 41% had features of hypoxic ischemic insult and some others had structural abnormalities.

On categorization based on ILAE classification, the most common epileptic encephalopathy was west syndrome, constituting 62 % of our study population, similar to previous studies done in India. It constituted to about 77% patients of those presenting in infancy. This is much more

than the other Indian study where 55% of patients with infantile epileptic encephalopathy had west syndrome.[13]One patient could not be classified into any of the electro-clinical syndromes. She had history of epileptic spasms in infancy and had presented with us with drop attacks and generalized tonic seizures. A clinical impression of west syndrome evolving to LGS was kept. But the patient did not have an EEG correlate.

Majority of the patients in the study had psychomotor retardation and microcephaly at presentation pointing towards an early cerebral insult. There are several studies indicating the role of early cerebral insult in development of intractable epilepsy and its sequelae. [14,15,16]

The most common electro-clinical finding was Modified hypsarrhythmia seen in 13 of the 21 patients (62%) with west syndrome. Only one patient had hypsarrhythmia. Similar figures are available in literature, though some showed hypsarrhythmia as commonest EEG finding.[17,18,19] The lower percentage of hypsarrhythmia as compared to modified hypsarrhythmia and other atypical electroencephalographic findings can be a consequence of our brief non-REM records, a time lag between the onset of symptoms and the EEG and the fact that many patients were already on treatment when EEG was done.

In 13 patients (38%) the etiology was related to perinatal insult in the form of birth asphyxia and neonatal hypoglycemia. Structural malformations were seen in 5 patients which included aicardi syndrome and neuronal migration disorders. Only one patient had tuberous sclerosis. A similar pattern of etiology was seen in a study from north India, but the study was confined to children with west syndrome. This was in contrast to a study conducted by Ohtahara et al were the most frequent cause was structural brain anomaly.[20]But this study also was limited to west syndrome patients. A cause could not be found in 11 patients. This could be due to the fact that a detailed metabolic and genetic evaluation was not feasible in all patients.

The main limitations of the study were that the sample size was small and there was no long term follow-up of these patients.

CONCLUSION

In conclusion, the most common epileptic encephalopathy seen in our pediatric epilepsy and neurology OPD during 2015-2016 was west syndrome with modified hypsarrhythmia on EEG. Clinical profile wise, majority were infants (children less than 1 year of age) reiterating the fact that uncontrolled epileptic activity during the developing brain results in deleterious effects. Most common etiology was found to be perinatal insult especially birth asphyxia. Majority of them had microcephaly and developmental delay at presentation and epileptic spasms were the most common form of seizure semiology.

ACKNOWLEDGEMENTS

The authors acknowledge the parents who took part in the study.

Declarations

Funding: None

Conflict of interest: None declared

Ethical approval: The study was conducted after obtaining approval from the Institutional Ethics Committee. Patients and their parents have given informed consent to the research and to the publication of the results.

REFERENCES

1. Fejerman N. Myoclonus and epilepsies. Indian J Pediatr 1997; 64: 583-602.
2. J. Engel Jr., "A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology," Epilepsia, vol. 42, no. 6, pp. 796–803, 2001.
3. Ohtsuka Y, Ogino T, Murakami N, Mimaki N, Kobayashi K, Ohtahara S. Developmental aspects of epilepsy with special reference to age-dependent epileptic encephalopathy. Jpn J Psychiatry Neurol. 1986;40(3):307-13.
4. Wong-kisiel LC, Nickels K. Electroencephalogram of age-dependent

epileptic encephalopathies in infancy and early childhood. Epilepsy Res Treat. 2013; 2013:743203.
5. Seth A, Aneja S, Taluja V. Epileptic encephalopathies of early childhood.Indian Pediatr 2001;38:390–396.
6. Udani VP, Dharnidharka V, Nair A, Oka M. Difficult to control epilepsy in childhood – A long term study of 123 cases. Indian Pediatr 1993; 30: 1199-1206.
7. Parisi P, Spalice A, Nicita F, Papetti L, Ursitti F, Verrotti A, Iannetti P, Villa M. "Epileptic Encephalopathy" of Infancy and Childhood: Electro-ClinicalPictures and Recent Understandings. Current Neuropharmacology, 2010, 8, 409-421.
8. Kaushik JS, Patra B, Sharma S, Yadav D, Aneja S. Clinical spectrum and treatment outcome of West Syndrome in children from Northern India. Seizure. 2013;22(8):617-21.
9. Kalra V, Passi GR. Analysis of childhood epileptic encephalopathies with regard to etiological and prognostic factors. Brain Dev. 1998;20(1):14-7.
10. Chawla S, Aneja S, Kashyap R, Mallika V. Etiology and clinical predictors of intractable epilepsy. Pediatr Neurol. 2002;27(3):186-91.
11. Bellman MH. Infantile spasms. In: Pedley TA, Meldrum BS, editors.Recent advances in epilepsy - I. Edinburgh: Churchill Livingstone, 1983:113–138
12. Beal J C, Cherian K, Moshe S L. Early-Onset Epileptic Encephalopathies: Ohtahara Syndrome and EarlyMyoclonic Encephalopathy. Pediatric Neurology 47 (2012) 317e323.
13. Kalra V, Gulati S, Pandey RM, Menon S. West syndrome and other infantile epileptic encephalopathies – Indian hospital experience. Brain and Development 2001; 23:593–602.
14. Ohtsuka Y, Ogino T, Murakami N, Mimaki N, Kobayashi K, Ohtahara S. Developmental aspects of epilepsy with special reference to age-dependent epileptic encephalopathy. Jpn J Psychiatry Neurol. 1986;40(3):307-313.
15. Donat JF. The age-dependent epileptic encephalopathies. J Child Neurol. 1992; 7(1): 7-21.
16. Yamatogi Y. , Ohtahara S. : Age-dependent epileptic encephalopathy: A longitudinal study. Folia Psychiatr Neurol Jpn 1981; 35:321-332.
17. U. Kramer, W. C. Sue, and M. A. Mikati, "Hypsarrhythmia: frequency of variant patterns and correlation with etiology and outcome," Neurology, vol. 48, no. 1, pp. 197–203, 1997.
18. Halevy A, Kiviti S, Goldberg-Stern H, Shuper A. Harefuah. Infantile spasms and modified hypsarrhythmia. 2011; 150(4): 373-417.
19. R. Calvo-Medina, P. Navas, L. Rodriguez, J. Martinez Anton, M.A. Aviles-Tirado, E. Moreno-Medinilla. Infantile spasm (West syndrome), Electroencephalography (EEG) pattern and developmental outcome, Study of 103 cases. European Journal of pediatric Neurology, 2017:21(1):E107-E108.
20. Ohtahara, S., & Yamatogi, Y. (2003). Epileptic Encephalopathies in Early Infancy With Suppression-Burst. Journal of Clinical Neurophysiology, 20(6), 398–407.

How to cite this article: Adhikari A, Shah P, Gajre Met.al. Clinical and etiological profile of children with epileptic encephalopathy. Int J Health Sci Res. 2020; 10(10):211-216.

******