

Interictal EEG findings in Neonatal Seizures and their role on Prediction of Neurodevelopmental Outcome

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Abstract:

Background: Seizure is a common symptom of many serious neurological disorders in newborn. There are several neurodevelopmental consequences after neonatal seizures. Electroencephalogram (EEG) is one of the tools to assess the brain status. Different EEG changes are found in neonatal seizure, like burst suppression, focal discharge, discontinued pattern, electrical inactivity etc. Burst suppression, low voltage, trace discontinue, trace alternance are common background abnormalities. Knowledge about the relation of abnormal EEG and neurodevelopmental outcomes may be helpful for early identification & proper intervention as well to prevent poor neurodevelopmental outcome.

Objective: The aim of the study was to observe the relation of EEG changes and short term neurodevelopmental outcome of neonates with seizure.

Method: This longitudinal cohort study was done in a tertiary care center in Bangladesh. Neonates who had at least one episode of seizure and an EEG in the neonatal period were enrolled in the study. EEG was interpreted by a neurophysiologist and a Pediatric neurologist independently. EEG findings along with clinical and laboratory data were recorded. All infants were followed up at 3 months clinically

and developmental assessment was done with Rapid Neurodevelopmental Assessment tools. All data were recorded in a structured questionnaire.

Result: Total 76 infants were enrolled, among them 16 were excluded. Among the study subject, 52% were male. The commonest seizure type was clonic seizure; About 40% of the neonates had perinatal asphyxia. Overall, 68% of EEG were abnormal; background abnormality was present in 42% of cases. At 3 months follow up, 68% of infants were found with at least one form of developmental impairment and seizure persisted in 42% subjects. Abnormal EEG background was significantly related to developmental impairment and subsequent epilepsy.

Conclusion: In this study, infants who had at least one abnormal EEG had adverse neurodevelopmental outcome. Burst suppression pattern in EEG was mostly associated with poor outcome. Moreover, about one third of the infants with abnormal EEG had epilepsy at 3 month follow up.

Key words: Neonatal seizure, EEG, Neurodevelopment outcome

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Introduction:

Neonatal seizure is a common manifestation of many neurological dysfunctions in newborn period.¹ Seizure is found as high as 10-25% of new born admission in any neonatal intensive care unit. Almost half of neonatal seizure cases developed serious neurological morbidity.² Developmental outcome following neonatal seizure depends upon etiology and extent of damage of brain;

Regardless of the etiology, neonatal seizures itself may cause injury to the brain and lead to developmental delay as well epilepsy³.

Recognition of infants who are at risk of adverse neurodevelopment outcome is challenging at early neonatal period. Here, EEG gives important information regarding the underlying status of the neonatal brain. Common EEG abnormalities in neonates are background

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disturbance; focal epileptiform discharges, burst suppression, diffuse encephalopathy etc.^{4,5} This study was designed to estimate the neurodevelopmental outcome based upon the EEG findings over other known perinatal factors related to development.

Study population and methodology

This was longitudinal cohort study was conducted from February 2020 to July 2021 in the Department of Paediatric Neurology, Institute of Pediatric Neurodisorder and Autism, Bangladesh Medical University (BMU) and Department of Neonatology, BMU. Approval from Institutional Review Board was taken before commencement of study. Consent from guardian was taken before enrolment of subject. Any newborn in the Neonatal Intensive Care Unit who developed seizures during hospital stay was a potential study candidate. Neonates who had multiple congenital anomalies and required ventilator support were excluded. In all cases the seizures were witnessed by a physician, usually a neonatologist. In selected cases, video recording was done to review whether it was seizure or not.

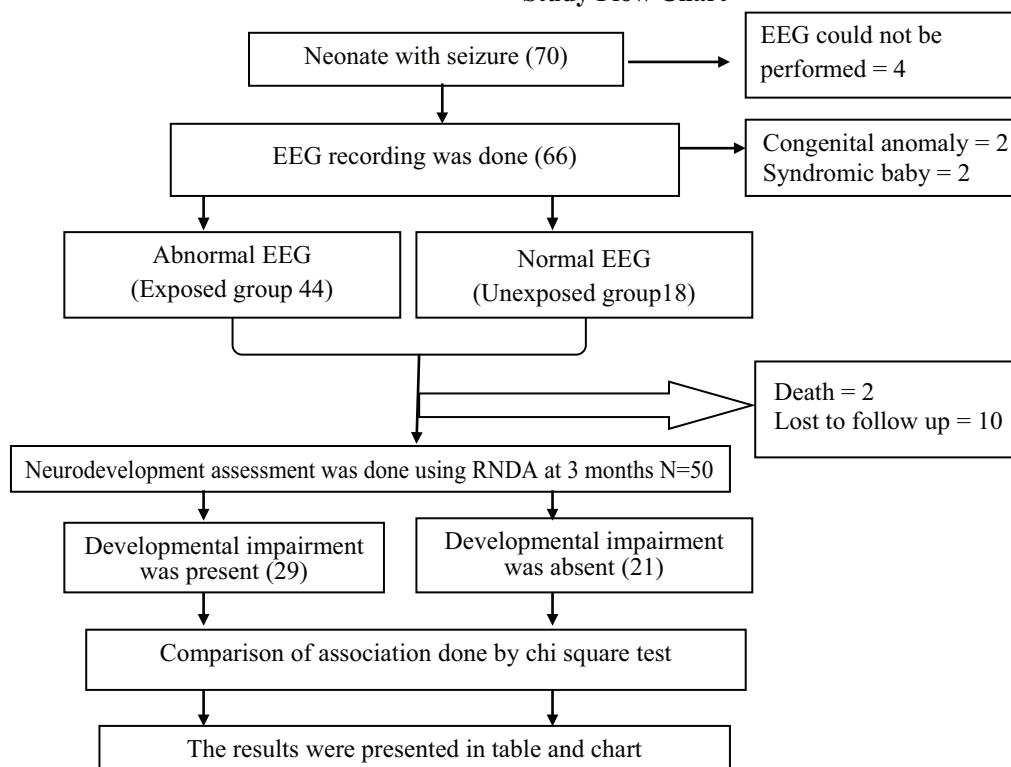
Detailed antenatal, natal, postnatal history and through physical examination was done; Data including gestational age, birth weight, gender, mode of delivery,

perinatal clinical factor, and Apgar score were recorded. In all cases, serum calcium, glucose, magnesium, electrolytes were measured in the immediate post-seizure period. Examination of spinal fluid, computerized axial tomography (CT scans)/MRI of brain and/or ultrasound examinations of the brain according to clinical suspicion was done. Information on electroencephalography (EEG) findings, head ultrasonography (HUS) or brain magnetic resonance imaging (MRI) findings, and clinical course after admission including responsiveness to antiepileptic drugs (AEDs), were also recorded. The day of onset of seizures, clinical type of seizures was noted. Those babies having more than one type of seizures were defined as having mixed type of seizures. Neurodevelopment assessment was done by Rapid Neurodevelopmental assessment tools⁵. EEG was done in all infants as early as the seizure was subsided. EEGs was performed in neurophysiology laboratory, IPNA, BMU. Electrode were placed according to modified International 10-20 system of electrode placement.

Follow up

A thorough assessment was done during discharge of the baby, counseling about further newborn care was done. Schedule for next visit was ensured, a contact

Study Flow Chart



number was given to share minor medical issues in between discharge and schedule visit. If any new problem arises they were allowed to visit and share their problem. Every infant was asked to revisit at 3 months of age (Corrected age was calculated in preterm babies). A complete neurodevelopmental assessment was done with RNDAs tools. Main emphasis was given whether there was any seizure or infants had delay in achieving appropriate mile stone.

Statistical Analysis:

Statistical analyses were performed using MedCalc and IBM SPSS Statistics V.21 (SPSS). For comparisons between the outcome groups (normal and abnormal), the Mann-Whitney U test was used for continuous variables and Chi square test for categorical variables. Fisher's exact test also assessed the associations between outcome and EEG grading at each of the time points. All tests were two sided and a p value <0.05 was considered statistically significant.

Result:

In this study percentage of male female ratio was nearly same. Most of the child were term (68%) and out born (70%). In 60% cases the mode of delivery was vaginal. Forty percent neonate had history of perinatal asphyxia. Birth weight was within normal limit in 62% cases. Among the various seizure type – clonic seizure was most common (64%) followed by multiple seizure (22%) and 64% had multiple episodes of seizure. (Table No I)

More than half (66%) of the study subjects developed seizure within 3 days of life. Septic screening was positive in 32% cases, brain malformation in 18% and IVH in 14% cases. Multiple risk factors were present in 24% cases. Regarding immediate outcome eighty eight percent of study subjects were discharged, but 12% newborn died. (Table No I)

Overall EEG abnormality was present in 68% cases, and 82% had moderate to severe abnormality among those 42 % EEG had background abnormality. Regarding background abnormalities, electrical inactivity was found in 14% cases and burst suppression in 12% cases. Forty eight percent epileptiform discharges were sharp waves and 18% were sharp and slow waves. Focal epileptiform discharge was found in 48% neonate, while 24% had temporal discharges and 14% had frontal discharges. (Table No VI)

At 3 month follow up, 42% cases had epilepsy and 56% had some sort of developmental impairment. Motor development and cognitive impairment were most frequent impairment (42% each) (Table II)

Among the infants who had epilepsy at 3 months, 62% had abnormal EEG background and 38% had initially normal background. Morphology and propagation of discharge did not show any relation of development of post natal epilepsy but discharges in temporal lobe showed significant relation of development of epilepsy at 3 months. Sixty seven percent infant was found at least one form of developmental impairment at 3 months who had initial EEG abnormality (Fig.1). In patients with developmental impairment at 3 months, 76% had EEG background abnormality. (Table No IV)

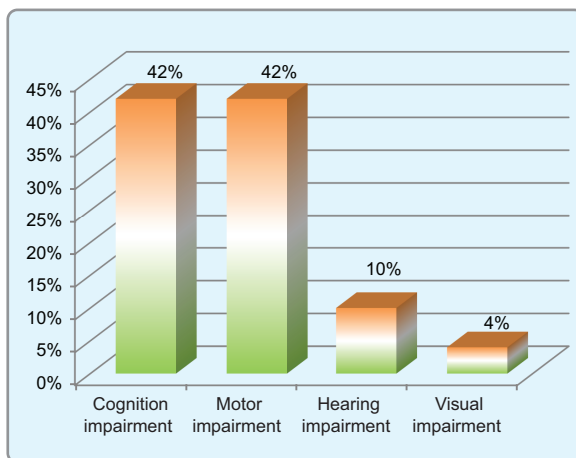
Table I

Clinical characteristics of the study subjects (N=50)

	Frequency (f)	Percentage (%)
Place of delivery		
Inborn	15	30.0
Out born	35	70.0
Gestational age		
Term	34	68.0
Preterm	16	32.0
Mode of delivery		
LUCS	20	40.0
NVD	30	60.0
Perinatal asphyxia (present)	20	40.0
Birth weight		
Normal	31	62.0
LBW	19	38.0
Consanguinity (present)	2	4.0
Family history of seizure (present)	2	4.0
Seizure type		
Clonic	32	64.0
Myoclonic	5	10.0
Subtle	2	4.0
Multiple	11	22.0
Seizure recurrence		
Single episode	18	36.0
Multiple episode	32	64.0

Table II*EEG findings of the study subjects (N=50)*

	Frequency (f)	Percentage (%)
Overall EEG finding (n=50)		
Normal	16	32.0
Abnormal	34	68.0
EEG background (n=50)		
Normal	29	58.0
Abnormal	21	42.0
Background abnormality (n=21)		
Burst suppression	6	29
Electrical Inactivity	6	29
Abnormal Trace Alternant	3	14
Abnormal Trace <i>discontinue</i>	2	10
Asymmetry	4	19
Morphology of abnormal discharge (n=31)		
Spike	1	3
Sharp	22	71
Sharp & slow wave	7	23
Spike & slow wave	1	3
Propagation (n=31)		
Focal	21	68
Regional	5	16
Unilateral	2	6
Bilateral	3	10
Site of focal discharge (n=21)		
Temporal	12	57
Frontal	8	38
Parietal	1	5
EEG abnormality (n=31)		
Mild	6	18
Mod/Severe	28	82

**Figure 4:** *Distribution of developmental impairment according to domain***Table III***Epilepsy outcome at 3 months follow up according to EEG findings (N=50)*

Epilepsy at 3 months	EEG findings Abnormal (f=34)	Normal (f=16)	p-value
Yes	21 (61.8)	0 (0.0)	<0.001
No	13 (38.2)	16 (100.0)	
Development Impairment			
Yes	23 (67.6)	6 (37.5)	0.044
No	11 (32.4)	10 (62.5)	

Chi-Square test was done

Table IV*Distribution of epilepsy cases at 3 months follow up according to EEG background abnormality (N=50)*

Epilepsy	EEG background Normal (f=29)	Abnormal (f=21)	p-value
Yes	8 (27.6)	13 (61.9)	0.015
No	21 (72.4)	8 (38.1)	

Chi-Square test was done

Table V*Distribution of developmental impairment cases at 3 months follow up among according to EEG background abnormality (N=50)*

Development Impairment	EEG background Normal (f=29)	Abnormal (f=21)	p-value
Yes	13 (44.8)	16 (76.2)	0.027
No	16 (55.2)	5 (23.8)	

Chi-Square test was done

Table VI

Epilepsy outcome according to morphology, propagation and site of focal discharge (N=50)

	Epilepsy		p-value
	Yes (f=21)	No (f=14)	
Morphology			
Spike	0 (0.0)	1 (7.1)	0.318
Sharp	16 (76.2)	8 (57.1)	
Sharp & slow	4 (19.0)	5 (35.7)	
Spike & slow	1 (4.8)	0 (0.0)	
Propagation			
Focal	15 (71.4)	6 (42.9)	0.367
Regional	3 (14.3)	6 (42.9)	
Unilateral	1 (4.8)	1 (7.1)	
Bilateral	2 (9.5)	1 (7.1)	
Site of focal discharge			Temporal
11 (73.3)	1 (16.7)	0.035	
Frontal	4 (26.7)	4 (66.7)	
Parietal	0 (0.0)	1 (16.7)	

Chi-Square test was done

Discussion:

In this study majority of study subjects had EEG abnormality. Over all neurodevelopmental impairment were present in 56% subjects; other consequence were epilepsy (42%), cognitive impairment (42%), motor deficit (42%), vision (4%) and hearing impairment (10%). Most post natal epilepsy cases had initial abnormal EEG. In most cases infants with developmental impairment also had an initial abnormal EEG. In a study by Holmes et al out of 42 cases, 20 (48%) cases had abnormal patterns in EEG^{6,7}. Among them 13 had abnormal neurodevelopmental outcome.⁸ In another study done by Nagarajan et al infants with neonatal seizures had significant neurodevelopmental consequences: i.e. neurodevelopmental impairment in 63%; cerebral palsy in 30%, vision and hearing impairment in 23%, and epilepsy in 33%.⁹ Legido et al reported cerebral palsy and developmental delays in about two thirds of the survivor babies in who had EEG documented seizures¹⁰. While Anand et al found severe neurological impairment in 18.5% infants who had initial abnormal EEG.¹¹ Thus, EEG has great predictability of neurodevelopmental outcome particularly for epilepsy.

In this study, 62% cases with EEG background abnormality eventually developed epilepsy at 3 month

of age; whereas 76% cases with background abnormality showed some form of developmental impairment. Background abnormality was commonest abnormal findings; the background abnormalities found here were burst suppression, electrical inactivity, trace alternant, trace discontinua. In a related study by Rowe et al who followed up 74 term and preterm neonates for 33 months; they found poor developmental outcome with abnormal background rhythms and epileptiform activity on EEG and they concluded that EEG is highly sensitive tool for predicting outcome.¹²

The incidence of postnatal epilepsy increases when more abnormality is seen in EEG backgrounds.^{13,14} In this study electrical inactivity was found in 14% cases and burst suppression in 12% cases. Among abnormal discharges, 48% had sharp waves and 18% had sharp and slow waves. Focal epileptic discharges was found in 42% cases and regional epileptic discharges in 18% cases.

Here, focal discharges were found mostly (24% cases) in temporal region followed by frontal region (16%). In our study, sharp wave was the commonest form of discharges; morphology had no clinical significance. Patrizi, S al found delta and sharp waves remained the most common ictal discharge throughout the ictus in the preterm infants while sharp waves and delta activity were the two most common patterns in the full term infants.¹⁵

Sinclair et al compared the patterns of burst suppression on EEG with long term neurological outcome in term infants with hypoxic ischemic encephalopathy (HIE) and they found better outcome for infants with neonatal HIE and modified burst suppression compared to burst suppression.¹⁶ Douglass et al and Holmes et al., studied burst suppression pattern on EEG among neonates with seizures in two separate studies and found that it is highly predictive for severe deficit on follow up.¹⁷ In this study, sharp wave was the most common epileptiform discharge; among them 42% were localized discharge. Similar findings were found in a study done by Parvin et al.¹⁸; they did not show any significance with neurodevelopmental outcome and type of epileptiform discharge.¹⁸

In this study, discharges from temporal lobe showed significant relation with post natal epilepsy. C Pizzani et al also found that EEG patterns like burst suppression,

isoelectric patterns and marked voltage suppression , an inactive or isoelectric pattern predict epilepsy .¹⁹

Limitations:

1. Study subjects were enrolled in a purposive sampling
2. Short term follow up was given
3. Study carried out in a single tertiary care center
4. Sample size was small

Conclusion:

This longitudinal cohort study showed EEG abnormality was significantly associated with adverse neuro-developmental outcome; around two third subjects with initial abnormal EEG showed poor outcome. Moreover, EEG background abnormality was mostly associated with developmental impairment and epilepsy in follow up. Epileptiform discharges in temporal lobe were significantly associated with development of epilepsy.

Recommendations:

1. Long term follow up multicenter study and consecutive sampling will give better information about DI and EEG findings
2. Neonate who had have an abnormal EEG should closely monitor about early development

Conflict of interest: None

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