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Can Neonatal EEG act as Predictor of Neurodevelopmental Outcome in Preterm Infants?

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Abstract

Background: Preterm infants are at high risk of neurodevelopmental delay including cognitive, motor impairment etc. Accurate recognition of infants at increased risk of abnormal neurodevelopmental outcome is challenging during the neonatal period. By predicting neuro-developmental outcome infants may benefit from early intervention, influencing positive outcomes. Electroencephalography (EEG) is used to evaluate brain function. Previous studies have shown that the EEG provides valuable information regarding brain function & possible neurodevelopmental outcome in preterm infants.

Methodology: To evaluate the role of EEG in predicting the neurodevelopmental outcome of preterm infants. This prospective observational study was conducted in NICU of Bangabandhu Sheikh Mujib Medical University & Institute of Pediatric Neuro-disorder and Autism (IPNA) over a period of one year. Neonates having gestation < 37 completed weeks admitted in NICU of BSMMU were being enrolled in the study. EEG of the enrolled babies was done during hospital admission in neurophysiology laboratory, IPNA, BSMMU. Assessment of neurodevelopmental status was performed at 6 months & 12 months of corrected age using the Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III). If score <70, it was considered as neurodevelopmental impairment. Hearing screen was done by Transient auto acoustic emission test with Hearing screener. Vision was assessed clinically as field of vision, visual equity and also by ophthalmoscope.

Results: During the study period, 123 neonates having gestational age <37 weeks were assessed for eligibility and 92 were enrolled in the study. EEG was done in all of the 92 neonates. Among them 12 were lost to follow up and 80 infants completed 12 months follow up and were included in the final analysis. Among the 80 neonates 51 (64%) had normal EEG and 29 (36%) had abnormal EEG. Total 23 (28.7%) had abnormal neurodevelopmental outcome at 12 months of age. Among them 20 (86.95%) were in the abnormal EEG group and 3 (13.04%) were in the normal EEG group. Abnormal neurodevelopmental outcome was significantly higher among the abnormal EEG group (p=<0.001). In the study population, neonates having abnormal EEG had significantly higher rate of perinatal asphyxia and neonatal seizure. Other morbidities didn't show any significant difference. Both 6 months and 12 months neurodevelopmental assessment showed adverse outcomes in all domain are significantly higher among the abnormal EEG group. Logistic regression analysis also showed that abnormal neurodevelopmental outcome is significantly associated with abnormal EEG in preterm infants.

Conclusion: Preterm neonates having abnormal EEG findings during hospital stay had adverse neurodevelopmental outcome at 6 months and 12 months of age. Perinatal asphyxia and neonatal seizure were higher among abnormal EEG group.

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Introduction

With the improvement of modern perinatal medicine and intensive care, the survival rate of preterm infants, especially those with low birth weight, have been increasing [1]. Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation) with a rate ranging from 5% to 18%, and this number is rising [2]. However, prematurity may negatively affect the normal maturational processes without overt brain damage or medical complications that could affect the neurocognitive outcome [3]. Following birth, a preterm infant is exposed to many unexpected multifactorial stimuli and inputs, and to an environment that is different from the in-utero condition. Extrauterine life in preterm infants has been shown to influence brain maturation as measured by electroencephalography (EEG). Less mature EEG patterns and sleep architecture have been reported in preterm infants when compared with term infants at matched postconceptional term ages. It has been suggested that this adaptation in brain function might be a "physiological" dysmaturity as a result of biological and environmental stress [4]. There are two main types of brain injury in premature infants, namely, intracranial hemorrhage and periventricular white matter softening [1]. Severe brain damage in premature infants can lead to death or moderate-to-severe neurodevelopmental disorders, including cerebral palsy, intellectual disability, vision and hearing impairment, and seriously affect the quality of life of preterm infants. Therefore, the early evaluation and its adverse neurological prognosis in preterm infants become the focus of medical research in preterm infants. Early recognition of at-risk infants may allow early intervention to improve the outcome. Since systematic surveillance programs are hard to sustain on a large scale, it is useful to identify low-risk and high-risk infants in order to provide a more efficient follow-up [5]. Predicting neurodevelopmental outcome is a challenge for physicians, and it is also a pronounced parental concern. Cerebral imaging, neurophysiological methods and clinical examination are used in neonatal intensive care units (NICUs), but none is sufficient by itself [6]. The role of EEG in neonatal seizure detection is well-established, being the multichannel video-EEG the gold standard [7]. Electrographic seizures (ESz) without clinical correlates are common in neurologically abnormal neonates and have been associated with subsequent neurodevelopmental deficits [1,3,8]. Previous studies in preterm infants have shown that neonatal EEG was predictive of neurodevelopmental outcomes [4]. EEG can provide second-by-second information about the health of the neonatal brain, the impact of conditions such as brain hemorrhage, sepsis, low blood pressure, and the effect of drugs. The baseline EEG activity may suggest underlying etiologies, e.g., inborn errors of metabolism or epileptic encephalopathy [9]. Specific EEG patterns have been associated with structural abnormalities on neuroimaging, such as positive rolandic sharp waves (PRSWs) and white matter injury. Furthermore, the spatial and temporal organization of the EEG reflects brain development, and when these patterns are disrupted, impaired development may result. EEG is therefore useful for real-time monitoring of the brain, providing information on possible structural brain injury, transient brain dysfunction and systemic disorders [4]. This study was done to determine the predictive value of conventional EEG for early neurodevelopmental outcomes in the current perinatal care, with a particular focus on EEG within the first month of life.

Methodology

This prospective observational study was conducted in Neonatal Intensive Care Unit (NICU) of Bangabandhu Sheikh Mujib Medical University, a tertiary care hospital of Dhaka city & Institute of Pediatric Neuro-disorder and Autism (IPNA) after approval by Institutional Review Board. The duration was one year. Neonates having gestation <37 completed weeks admitted in NICU of BSMMU are being enrolled in the study after getting informed consent from the parents. Neonates with major congenital anomalies were excluded. Proper maternal history like diabetes, hypertension, antenatal corticosteroid, APGAR score at first and fifth minute were recorded in data collection form. Gestational age was calculated from the first day of last menstrual period (LMP) in a mother with previous regular menstrual cycle. In cases where LMP was not known, early obstetrical ultrasonography was used to assess the gestational age. In cases where both were missing, gestational age assessment was made by using the New Ballard Score. Birth weight was recorded for each baby as soon as possible after delivery using an electronic scale having a sensitivity of 10 grams. Infant's sex was determined through observing phenotype of genitalia.

EEG of the enrolled babies was done in all babies during hospital admission. The eligible infant who met the inclusion criteria were divided into two strata: normal EEG group and abnormal EEG group. Assessment of neurodevelopmental status was performed at 6 months & 12 months of corrected age using the Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III).

EEGs was performed in neurophysiology laboratory, IPNA, BSMMU. Electrodes were placed according to Modified International 10-20 system of electrode placement. Both referential and bipolar montages were used for EEG recordings. In addition to EEG, EKG, lateral eye movements, nasal airflow and abdominal respiration were monitored.

All EEGs were interpreted by a certified neurophysiologist who were not be aware of the patients' history and were counter checked by one of the pediatric neurologists. Background rhythms and epileptiform activity were evaluated

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independently. Inter ictal activity was also recorded; whether discharges were focal or generalized, morphology or propagation of discharges was also be noted. The presence or absence of sleep spindles were recorded. Different patterns of EEG were classified as normal, focal, multi focal and generalized epileptic discharge, burst suppression.

In every patient follow up was done at 6 and 12 months. At every follow up EEG, developmental assessment was done.

Neurological impairment was assessed by Bayley Scales of Infant Development, Third Edition. If cognitive or motor score <70, it was considered as neurodevelopmental impairment. Hearing screen was done by Transient auto acoustic emission test with Hearing screener. Hearing impairment was considered if hearing aids in both ears is required. Vision was assessed clinically as field of vision, visual equity and also by ophthalmoscope. Blindness was considered if there is some or no useful vision in either eye.

The study was conducted under good clinical practice of Bangladesh guideline. Reference, Directorate General of Drug Administration, Ministry of Health and Family Welfare, Govt. of the people's Republic of Bangladesh.

Statistical analysis: After collecting the data, it was entered in a personal computer. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version25. Continuous variables were presented as mean ± SD for normally distributed data and as median (interquartile range) for skewed data. Categorical variables were presented as frequencies and percentages. The unpaired Student t test was used for quantitative variables with a normal distribution and the Mann-Whitney U test was used for variables with a skewed distribution. The chi square test was performed for qualitative variables. Results were considered statistically significant if values of- P<0.05.

Results

During the study period, 123 neonates having gestational age <37 weeks were assessed for eligibility and 92 were enrolled in the study. EEG was done in all of the 92 neonates. Among them 12 were lost to follow up and 80 infants completed 12 months follow up and were included in the final analysis.

Among the 80 neonates 51 (64%) had normal EEG and 29 (36%) had abnormal EEG. Total 23 (28.7%) had abnormal neurodevelopmental outcome at 12 months of age. Among them 20 (86.95%) had abnormal EEG and 3 (13.04%) had normal EEG. Abnormal neurodevelopmental outcome was significantly higher among the patients with abnormal EEG (p=<0.001) (Table-1).

There is no significant difference in between two groups in gestational age, birth weight, sex, place and mode of delivery. Frequency of maternal antenatal corticosteroid, PROM, hypertension and diabetes mellitus also showed no significant difference in between two groups (Table-2).

Table 1: Neurodevelopmental outcome at 12 months of age, N=80.

Variable	Normal EEG group, n = 57	Anormal EEG group, n = 23	P-value
Neurodevelopmental outcome			
Normal, n (%)	54 (94.7)	3 (13.0)	<0.001
Abnormal, n (%)	3 (5.3)	20 (87)	

In the study population, neonates having abnormal EEG had significantly higher rate of perinatal asphyxia and neonatal seizure. Other morbidities like sepsis, RDS, shock, IVH and PDA didn't show any significant difference (Table-3).

Table 4 and Table 5 showed the comparison of neurodevelopmental outcome among the two groups at 6 months and 12 months of age. Both 6 months and 12 months neurodevelopmental assessment showed adverse outcome in all domain is significantly higher among the abnormal EEG group.

Table 2: Baseline characteristics of the study population, N=80.

Variable	Normal EEG group, n = 57	Abnormal EEG group, n = 23	P-value
Gestational age categories: 34-<37 weeks (%) 32-34 weeks (%) 28-<32 weeks (%) ≤28 weeks (%)	1 (1.8) 36 (63.2) 20 (35.1) 0	1 (4.3) 14 (60.9) 6 (26.1) 2 (8.7)	0.121
Birth weight categories: Low Birth Weight Very Low Birth Weight Extremely Low Birth Weight	16 (28.1%) 38 (66.7%) 3 (5.3 %)	5 (21.7 %) 13 (56.5%) 5 (21.7%)	0.084
Mean birth weight (gram) ±SD	1363.68 ± 281.822	1277.173 ±386.158	0.269
Mean gestational age, (weeks) ±SD	31.91 ± 2.06	31.61 ± 2.52	0.534
Male: female Male Female	 31 (54.4%) 26 (45.6%)	 11 (47.8%) 12 (52.2%)	0.595
Inborn	55 (96.5%)	21 (91.3%)	0.335
Mode of delivery Vaginal Caesarean	 5 (8.8%) 52 (91.2%)	 5 (21.7 %) 18 (78.3 %)	0.112
Antenatal corticosteroid	55 (96.5%)	20 (87%)	0.111
Maternal PROM	17 (29.8%)	2 (8.7%)	0.085
Maternal hypertension	26 (45.6%)	10 (43.6%)	0.862
Maternal diabetes mellitus	17 (29.8%0	3 (13%)	0.095

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Binary logistic regression analysis also showed abnormal neurodevelopmental outcome was significantly associated with abnormal EEG in preterm infants (Table 6).

Table 3: Neonatal morbidities among normal and abnormal EEG group, N=80.

Morbidities	Normal EEG group, n = 57	Abnormal EEG group, n = 23	P-value
Perinatal Asphyxia	3 (5.3%)	5 (21.7%)	**0.026**
Neonatal seizure	2 (3.5%)	5 (21.7%)	**0.009**
Neonatal Sepsis	24 (42.1%)	11 (47.8%)	0.641
Respiratory distress syndrome (RDS)	19 (33.3%)	9 (39.1%)	0.623
Shock	11 (19.3%)	7 (30.4%)	0.28
Intraventricular hemorrhage	10 (17.5%)	6 (26.1%)	0.318
PDA	2 (3.5%)	3 (13%)	0.111
Need for CPAP support	23 (40.4%)	12 (52.2%)	0.335
Need for mechanical ventilator support	5 (8.8%)	5 (21.7%)	0.112

Table 4: Neurodevelopmental outcome at 6 month corrected age.

Outcome	Normal EEG group, n = 57	Abnormal EEG group, n = 23	P-value
Cognitive impairment	4 (7%)	21 (91.3%)	**<0.001**
Motor impairment	4 (7%)	21 (91.3%)	**<0.001**
Speech impairment	4 (7%)	21 (91.3%)	**<0.001**
Hearing impairment	4 (7%)	21 (91.3%)	**<0.001**
Visual impairment	5 (8.8%)	10 (43.5%)	**<0.001**
Global development delay	4 (7%)	21 (91.3%)	**<0.001**

Table 5: Neurodevelopmental outcome at 12 month corrected age.

Outcome	Normal EEG group, n = 57	Abnormal EEG group, n = 23	p-value
Cognitive impairment	3 (5.3%)	20 (87%)	**<0.001**
Motor impairment	3 (5.3%)	20 (87%)	**<0.001**
Speech impairment	3 (5.3%)	20 (87%)	**<0.001**
Hearing impairment	3 (5.3%)	20 (87%)	**<0.001**
Visual impairment	5 (8.8%)	10 (43.5%)	<0.001
Global development delay	3 (5.3%)	20 (87%)	**<0.001**

Table 6: Binary Logistic regression analysis of global development delay at 12 months of age with EEG findings and co-morbidities.

Variables	Odds ratio	95% confidence interval		P-value
		Lower	Upper	
Abnormal EEG	162.708	23.534	112.4896	0
Perinatal asphyxia	0.845	0.038	18.813	0.915
Neonatal seizure	2.695	0.403	18.013	0.306

Discussion

Despite being a well-established technique used for monitoring the brain over many years, the contribution of EEG to understanding brain development in preterm infants is an evolving field. The increasing survival rates of very and extremely preterm infants continually update our knowledge of brain function in this specific population. This prospective observational study demonstrated that abnormal neonatal EEG was significantly associated with adverse neurodevelopmental outcomes at 1 years of age. In this study, we found that the worse the EEG abnormalities, the higher the rate of non-optimal developmental outcome and the stronger the association. This finding is similar to study conducted by Périvier et al. [5] in which neonatal EEG surveillance exhibited a good specificity and a good positive likelihood ratio for neurodevelopmental outcomes in very preterm infants assessed at 2 years of corrected age. In this regard, Pisani and Spagnoli [10] reviewed neurophysiologic and neuroimaging tools to be used in evaluating newborns at high risk of neurological sequelae. They also recommend integration of EEG, ultrasound, MRI and, when available, evoked potentials data in order to achieve accurate prognostication [10]. In this study, a neonate having abnormal EEG was significantly associated with higher rate of perinatal asphyxia and neonatal seizure. Multichannel video-EEG is still a gold standard for seizure detection. Furthermore, video-EEG monitoring is not limited to the only seizure detection, but it also provides information for a more accurate assessment of the background activity and some specific waves/pattern and features indicative of the brain development [7]. Jan et al. [11] recommend that use of continuous video-EEG be considered whenever possible, both to treat seizures more specifically and to avoid overtreatment. Abnormal EEG patterns, such as burst suppression or abnormal background activity, have been correlated with an increased risk of adverse neurodevelopmental outcomes, including cognitive impairments, motor deficits, and behavioral disorders. Early identification of these abnormal EEG patterns can inform clinical decision-making and facilitate targeted interventions to optimize developmental trajectories in preterm neonates [1]. The integration of additional physiological data and complementary tools with EEG now allows for a more comprehensive assessment of neonatal brain health [12,13]. Despite these advancements, continuous monitoring of brain maturation in preterm infants and the prediction of long-term neurodevelopmental outcomes remain challenging. Various aspects, such as establishing reliable preclinical models of encephalopathy in premature infants, require careful study [13]. It is our strong belief that EEG will persist in providing unique insights into the functioning of the premature brain. When combined with advanced data-modelling techniques, EEG holds the potential to unveil robust biomarkers of brain function in both healthy and pathological conditions.

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Limitations

1. Neurodevelopmental outcome was seen only up to 12 months of age.
2. EEG was performed only single time among the study neonates.

Conclusion

Preterm neonates having abnormal EEG findings had adverse neurodevelopmental outcome at 6 months and 12 months of age. Perinatal asphyxia and neonatal seizure were associated with abnormal EEG.

Recommendations

1. All preterm neonates should undergo EEG evaluation to predict neurodevelopmental outcome.
2. Further multicenter prospective studies using multiple sequential or continuous EEG monitoring with longer duration of follow up should be conducted.

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