Original article:

The prognostic significance of eeg pattern in neonatal seizure in tertiary care hospital

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Abstract:

Introduction: The occurrence of seizure due to various etiologies, may be the first and perhaps the only clinical sign of a central nervous system disorder in newborn infant. EEG may be used to prognosticate the neonates who inherently display a narrow behavioural and clinical profile .The aim of this study is to study the prognostic significance of neonatal EEG pattern.

Material and methods: The study was conducted in a tertiary care hospital in central India and included full term neonates with clinical seizures. Two consecutive recordings of EEG were performed(first during the NICU stay and second at three months of age) along with neurodevelopmental assessment.

Results: total 60 enrolled cases, 7 cases (11.67%) were lost during the study. At the age of six months 52 (86.66%) cases completed the follow up for neuro-developmetal assessment. Rate of developing epilepsy and delayed development was significantly higher in children with abnormal first and second EEg patterns.

Conclusion: When used selectively, the neonatal EEG may be a good tool for prediction of short & long term outcome in neonates with seizures.

INTRODUCTION:

The occurrence of seizure may be the first and perhaps the only clinical sign of a central nervous system disorder in newborn infant as such the occurrence of seizure in neonates may be due to very wide range of etiologies like asphyxia, metabolic disturbances, infection or IVH etc. These seizures may indicate the presence of potentially treatable etiology and should prompt an immediate evaluation to determine cause and also to institute etiologic specific therapy.[1] Some types of seizure are associated with relatively high incidence of early death and in survivors, a higher incidence of neurological impairment, development delay and post neonatal epilepsy.[2]

The neonatal Electroencephalography may be a good tool for prediction of short & long term outcome in neonates with seizures. EEG for short, is a non-invasive way to monitor brain activities. A normal interictal EEG indicates good chance of favorable outcome, EEG may be used to prognosticate the neonates who inherently displays a narrow behavioral and clinical profile. It is considered the gold standard for distinguishing epileptic seizures from non-epileptic paroxysmal events and for detecting subclinical seizure activity in high-risk babies.The abnormal background activity in even 1 EEG of the sequential recordings was more significantto determine neurological outcome than abnormal ictal activityor abnormalities in the organization of sleep

state.[3] The aim of this study is to study the prognostic significance of neonatal EEG pattern.

METHODOLOGY:

This was a prospective type of observational study, conducted in Department of Pediatrics, Kamla Raja Hospital, G.R Medical College, Gwalior (MP) for 1 year. 60 Term babies having clinical seizures and age less than 28 days who were admitted in SNCU of a tertiary care hospital in central India, were included in the study. All low birth weight, very low birth weight ,extremely low birth weight and having congenital anomalies were excluded from the study. Ethical clearance was taken from the ethical committee of Gajra Raja Medical College Gwalior.Informed written consent of parents or guardian was taken prior to enroll the baby in study. Non-stretchable tape, electronic weighing machine, infantometer, CDC growth charts to plot the anthropometric data like length, weight and head circumference, EEG facility and C. AmeilTison Development Assessment tool were required for the study.Information was recorded in a preformed proforma like name of mother and father, age and sex of the baby, address telephone number and socioeconomic status of the parents.The day of onset of seizures, clinical type of seizures were recorded. Those babies having more than one type of seizures were recorded in proforma as having mixed type of seizures. Detailed antenatal and natal history was taken.Possible investigations like septic screening, random blood glucose, serum calcium, trans fontanelle ultrasonography and cerebrospinal fluid for routine, microscopy and culture were done in order to know the cause of the seizures. Few other etiologies like intraventricular hemorrhage or the seizures for which the cause could not be identified were placed under the heading other. Electroencephalography (inter ictal) was done in the Department of Neurology Gajra Raja Medical College Gwalior during the course of stay in the SNCU and the pattern was recorded. Second EEG was done at the age of 3 months and the pattern was recorded in the proforma.We used the epidemiological definition of epilepsy by which occurrence of more than 2 unprovoked seizures episode by >24 hours apart.We used the term 1st EEG for the neonatal EEG and the term 2nd EEG for the EEG done at the age of 3 months.We assigned an arbitrary code 0,1,2,3,4,5,6,7,8,9 to the individual EEG pattern so that we may have ease in collection, processing and tabulation of the data.

The codes were as follows

0 -	Normal
1 –	Focal/ multifocal lateralization
2 –	Positive sharp rolandic waves
3 –	Excessive sharp waves activity
4 –	Periodic low voltage activity
5 –	Multiple poly spike pattern
6 –	Gross asynchronacy/high voltage delta activity
7-	Persistent marked voltage suppression
8-	Burst suppression pattern
9 –	Isoelectric background pattern

Neurodevelopment assessment of these babies was done at the age of 6 months using C AmielTison neurodevelopmental assessment tool. This tool and scoring system was included in our proforma. A score of '0' was given to the baby who was found to be having normal neurodevelopmental outcome, while score of '1' and '2' were given to babies who were having moderate and severe neurodevelopmental delay respectively.All the data were collected and then processed and analysed. Epical 2000 info software was used for calculation of χ^2 value, and P value. Fishers exact test for Risk ratio, Odds ratio were applied using 2 X 2 table. Kappa values were calculated for significance of association.

Observations and Result :

Out of 60 enrolled cases, 7 cases (11.67%) were lost during the study. At the age of six months 52 (86.66%) cases completed the follow up for neuro-developmetal assessment. Rate of developing epilepsy and delayed development was significantly higher in children with abnormal first and second EEG patterns.

Table No. 1 Distribution of pattern of 1st EEG with etiology of seizures

S. No.	EEG pattern	Birth asyphyxia	Hypocalcemia	Hypoglycemia	Meningitis	Others	Total
		No.	No.	No.	No.	No	No.
1.	0	28	10	06	04	00	48
2.	1	08	2	00	00	00	10
3.	2	04	00	00	00	00	04
4.	3	00	00	02	02	00	04
5.	4	04	2	00	00	00	06
6.	5	20	00	00	04	2	26
7.	6	02	00	00	00	0	02
8.	7	08	00	00	00	00	08
9.	8	08	00	00	02	00	10
10.	9	02	00	00	00	00	02
Total		**84**	**14**	**08**	**12**	**02**	**120**

48 cases who had normal pattern neonatal EEG, out of them 28 cases were of birth asphyxia. 72 cases had abnormal pattern EEG and most of the abnormal pattern EEG were found in birth asphyxia. Most of the cases of hypocalcemia and hypoglycemia were having normal pattern EEG.

Table No. 2 Distribution of EEG pattern with post neonatal epilepsy

S.No.	EEG pattern	Total	Post neonatal epilepsy (%)
		No.	No.
1.	0	48	02
2.	1	04	00
3.	2	02	00
4.	3	02	00
5.	4	04	02
6.	5	26	06
7.	6	00	00
8.	7	08	06
9.	8	010	08
10.	9	00	00
Total		**104**	**24**

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Total104 cases completed the follow up, out of them 24 developed epilepsy. Eighty percent of those cases who had burst suppression pattern and 75% cases of those who had voltage suppression pattern in 1st EEG showed epilepsy. Those cases who had normal pattern 1st EEG, only 4.2% developed epilepsy.

Table No. 3 Distribution of cases and their neurodevelopmental outcome

S.No.	Development	No. of cases
1.	Normal development	60
2.	Moderate delay	28
3.	Severe delay	16
Total		**104**

At the age of six months, after application of C. Amiel Tison method of neuro-developmental assessment it was found that out of 104 cases, 60 were normal, 28 were having moderate developmental delay and 16 were having severe neurodevelopmental delay.

Table No. 4Distribution of outcome in normal and abnormal 1st EEG

S. No.	EEG	Neurodevelopmental outcome		Total	P value/ χ^2 value
		Neurodevep. delay	Normal		
1	**Abnormal EEG**	38	18	56	P<0.01 and χ^2 =14.04
2	**Normal EEG**	06	42	48	
Total		**44**	**60**	**104**	

Total 56 cases had abnormal neonatal EEG and out of them 38 were found to be having neurodevelopmental delay. Total 48 cases had normal neonatal EEG and out of them only 6 were found to be having neurodevelopmental delay. This distribution is significant (p<0.01 and χ^2 =14.04).

RR = 5.428 (95% confidence interval 0.83, 16.13)

Odds ratio = 14.8 (95% CI 3.48, 62.78)

Kappa value (κ) = 0.544 .Here the sensitivity of the 1st EEG is 0.86 (86.4%) for predicting neurodevelopmental delay and the specificity is 0.7 (70%) .Positive predictive value is 0.68 (67.8%) which means that with each abnormal EEG there are 67.8% chances of neurodevelopmental delay. Negative predictive value is 87.5%.

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Table No. 5 Distribution of outcome in normal and abnormal 2nd EEG

S. No.	EEG	Neurodevelopmental outcome		Total	P value/ χ^2 value
		Neurodevep. delay	Normal		
1	**Abnormal EEG**	38	04	42	p<0.01 and χ^2= 30.26
2	**Normal EEG**	06	56	62	
Total		**44**	**60**	**104**	

Twenty one cases had abnormal EEG at 3 months of age and out of them 38 were having neurodevelopmental delay. Total 62 cases had normal EEG at 3 months of age and out of them only 6 were having neurodevelopmental delay.

P<0.01 and $\chi^2 = 30.256$

RR = 9.35 (95% CI 3.16, 27.65)

Odds ratio = 88.67 (95% CI 13.51, 582.05)

Kappa value (κ) = 0.80

Here the sensitivity of the 2nd EEG is 0.86 (86.4%) for predicting neurodevelopmental delay and the specificity is 0.93 (93.3%)

Positive predictive value is 0.90 (90.5%) which means that with each abnormal EEG there are 90.5% chances of neurodevelopmental delay. Negative predictive value is 90.3%. These statistics show the strong relation between abnormal EEG at 3 months of age and neurodevelopmental delay at the age of 6 months.

DISCUSSION:

EEG is one of the oldest, yet valuable, diagnostic and prognostic test in neonates. It has been used for decades to objectively assess the neurological status of critically ill neonates and may provide objective evidence for abnormal cerebral functioning following perinatal depression. Compared to other methods such as the CT scan or MRI, which provide a snap shot of the brain structure, EEG gives a continuous stream of data that indicates the neurological state of the patient. This makes EEG more suitable for long term monitoring of subjects and for viewing changes in neurological state during the time of recording. It is much helpful in seizures detection and quantification and for assessment of cortical activity. In critically ill newborns, EEG is even preferable to neurological examination, as their clinical repertoire is narrow, making the neurodevelopmental examination of rather limited value.The prognostic value of neonatal EEG has been long recognized in term as well as in preterm infants. The value of EEG and evoked potentials in predicting later outcome of NICU discharged babies is not questioned.

In this study 68 were male while 52 were female, making a male: female ratio 1.3:1. In the study of neonatal seizures by **LakraMahaveeret al**[4] where male to female ratio was 2:1. In this study when the socioeconomic status of the parents of the enrolled cases were tabulated we found that 40% belong to grade III and 30% belong to grade IV of Kuppuswami Scale of Socioeconomic status. It shows that most of the cases were from middle and lower classes.We found that out of total enrolled cases, 92 were vaginally delivered while 28 were delivered by cesarean section. It indicate that significant proportion of cases were delivered vaginally. Similarly **Lakhra Mahaveeret al**[5] found that 68% were born by normal vaginal delivery, 28.1% by LSCS and 3.1% by forceps delivery. It was

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observed that 62 had seizures within 24 hours of life ($p<0.01$ and χ^2 =34.32), 30 cases has seizures between 24hours -72 hrs. of life. 16 had onset of seizures between 72 hours – 7 days. 12 cases had seizures onset after 7 days of life. This clearly shows that the occurrence of seizures during <24 hours is most common and is highly significant ($p<0.01$ and χ^2=34.32).

92 cases had onset of seizure within 72 hours of life which is highly significant for onset in <72 hours of life ($p<0.01$ and χ^2 =76.21). Similarly in a study of neonatal seizures by **Ronen Gabriel et al**[6] onset of seizures on first day of life was 36%, 64% had onset of seizures within first 48 hours, and 83% within first week of life.

Clonic seizures in 48 cases were found most common type of seizures in the present study, followed by subtle 38 ,tonic 24, myoclonic 4 and mixed seizures 6. Those cases who had more than 1 type of seizures were considered as having mixed seizures. Similarly **Ajay kumaret al**[7] and **Tekgul et al**[8] also found that the clonic seizure to be the most common type of seizures.**Brunquell et al**[9]and**LakraMahaveer et al**[4] showed that subtle seizures are the most common type of neonatal seizures but in the present study clonic seizures were found to be most common, it may be due to the fact that Subtle seizures are difficult to recognize and also difficult to interpret, as they may be normal neonatal activity. This study included only the term babies while the subtle seizures are primarily seen in preterms babies. The diagnosis of seizures in this study was based on clinical description. The variability inherent to the capacity of clinically identifying neonatal seizures has been evaluated previously; showing reliability in recognizing seizures based on the analysis of medical records. It is widely known that the gold standard to recognize neonatal seizures is video-EEG.A systematic review of literature of previous cohort study by **Nunes ML et al**[10]on neonatal seizures, was performed they found that from the 36 selected studies, 24 (67%) studies were based only on clinical diagnosis of seizures, 7 used confirmed EEG seizures and only 2 of them were based on video-EEG. The interesting finding of this study is that the clinical profile of the newborns, risk factors and outcome were similar, independently of the methodology used to diagnose the seizures. In a study by **RushdaAftabet al**[11] most common seizures noted were multifocal clonic constituting 50% of all cases, while tonic seizures were present in 25.26% and subtle seizures were present in 12.63% cases.

Birth asphyxia 84was the most common etiology observed in the study followed by hypocalcemia 14, CNS infection 12, hypoglycemia 8 and then other causes 2 . The other cases include intraventricular hemorrhage or for which the etiology could not be found. Birth asphyxia ($p<0.01$, χ^2 =119.38) was significantly associated as the cause of seizures in the study. Birth asphyxia as the commonest cause of neonatal seizures in studies by **SoniArunet al**[12]seen in 76.9% of cases and **Ronen Gabriel et al**[6] seen in 40% of cases according to most of the studies birth asphyxia is the commonest cause of neonatal seizures followed by metabolic or infectious causes. Intracranial hemorrhage constitutes small percentage of seizures. In this study the cases having seizures within 24 hours of age were due to birth asphyxia 56 .Most of the seizures due to hypocalcemia and hypoglycemia were found to be of onset between > 24 hours to < 7 days of age. 8 cases of meningitis had onset of convulsion at the age >7 days. In a study of neonatal seizures by **Rose Arthur L et al**[13], majority of babies with perinatal anoxia convulsed on

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first day of life (5/10 – 50%), hypoglycemic neonates convulsed on second and third day (5/7 – 71%), majority of neonates with CNS infection convulsed at the end of first week and early second week (9/13 – 69%) and babies with hypocalcemia present with convulsions during first and second day of life (6/28) and again during late first week and second week (19/28). In this study only one case was having isoelectric background pattern and it was died at home after discharged from the hospital. In a study conducted by **Chen Yang et al**[14] the infants whose EEG showed isoelectric tracings or isoelectric tracings accompanied with much abnormal discharge had very poor prognosis. In the present study 24 developed epilepsy. Epidemiologically more than 2 unprovoked seizures in more than 24 hours were taken as epilepsy. It is mainly seen in those cases who had burst suppression and voltage suppression pattern in neonatal EEG. Similar result were found by **Magda et al**[15] that the group of newborns that had seizures presented an increased risk of developing epilepsy compared to newborns from the same cohort without seizures (19.3/100 vs. 1.8/100, p<0.001). Their incidence of epilepsy at a mean age of 33 months was 30% and developmental delay was observed in 35 (101) patients, among them 11 also had epilepsy.

When C. AmielTison method of neuro developmental assessment at the age of 6 months was applied, it was found that out of 52 cases, 30 (57.70%) were normal, 14 (26.92%) were having moderate developmental delay and 8 (15.38%) were having severe neurodevelopmental delay. Similarly **Linda GM et al**[16] found that 57% of the survivors had a normal outcome. Their most important finding was that the back ground pattern on which the status epilepticus arises was the best predictor of subsequent neurodevelopmental outcome. All of the survivors had a follow-up and 4 infants (19% of survivors) developed post neonatal epilepsy.

The background pattern was correlated with neurodevelopmental outcome. In 50% of the infants with a poor outcome, the background pattern was abnormal before the status epilepticus and in 71% after the status epilepticus. The background pattern at the onset of status epilepticus was the main predictor of neurodevelopmental outcome.

We had 42 cases of birth asphyxia but only 36 cases completed the follow up for developmental assessment at the age of 6 months. Twenty cases (55.5%) were found to be having developmental delay and 16 (44.5%) were without delay. This shows that more than half of the cases of birth asphyxia developed delay. Out of the 36 cases of birth asphyxia, 14 (38.9%) had normal pattern 1st EEG. Out of these 14 cases, 11 cases (78.6%) were with no delay while 3(21.4%) were with developmental delay. Ten cases had multiple poly spike pattern, out of these 9 (90%) cases had developmental delay and 1 (10%) case was with no delay. This shows that most of the abnormal patterns when associated with birth asphyxia are indicative of poor outcome or delay.

Similarly **Magda et al**[15] found a significant association between abnormal EEG and developmental delay (p=0.014).**C Pizzani**[17] also found that EEG patterns like burst suppression, isoelectric patterns and marked voltage suppression are so severely abnormal that they are considered sufficient for the formulation of the prognosis, without the need for serial tests. Some authors feel that predictions can be accurately be advanced when the initial EEG shows a burst-suppression pattern or

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an inactive or isoelectric pattern even if the test is obtained shortly after birth.

These statistics show the strong relation between abnormal EEG at 3 months (2nd EEG) of age and neurodevelopmental delay at the age of 6 months.Similar results were also found by **Rose AL and Lombroso CT[13]** as they stated that neonates with seizures and normal EEG had 86% chance of normal neurodevelopment regardless of other clinical data, also neonates with seizures with abnormal EEG have only 93% chance of developmental delay.

These observations show that normal EEG patterns are associated with normal outcome; patterns like positive sharp rolandic waves, excessive sharp wave activity, multiple poly spike pattern and asynchronacy are associated with moderate neurodevelopmental delay while patterns like persistent marked voltage suppression, burst suppression pattern and isoelectric background pattern are associated with severe neurodevelopmental delay. Also when compared, the EEG done at the age of 3 months (2nd EEG) is more predictive of neurodevelopmental delay as compared to the neonatal EEG (1st EEG).

CONCLUSION:

When used selectively, the sequential neonatal EEG may be a good tool for prediction of short & long term outcome in neonates with seizures due to multiple aetiologies.

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