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Research Article

EVALUATION OF CLINICAL, ETIOLOGICAL AND EEG PROFILE OF NEONATAL SEIZURE

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ABSTRACT

Objective: Neonatal seizure is a paroxysmal behavior caused by hyper-synchronous discharge of a group of neurons. Neonatal seizures are the most common overt manifestation of neurological dysfunction in the newborn. The electroencephalography (EEG) is an important tool in the evaluation of an infant with symptoms referable to the central nervous system. It provides an excellent and non-invasive method of assessing at risk newborns and of formulating a prognosis for long-term neurological outcome. Hence, this study was planned to evaluate clinical, etiological, and EEG profile of neonatal seizure and its corelation with developmental outcome.

Methods: Prospective observational study was done among 71 cases of neonatal seizures patients admitted in Netaji Subhash Chandra Bose Medical College hospital from November 2014 to October 2015. All consecutive term and preterm neonates with documented seizure who were discharge from neonatal intensive care unit (NICU) with proper consent and counseling of parents were included in this study.

Results: Total 71 newborns were enrolled, out of them 21% (n=15) were admitted within 24 h of birth, 42% (n=30) were admitted within 24–72 h, and 37% (n=26) newborn admitted at >72 h of birth. Total number of male included were 56% (n=40), while female were 44% (n=31). Out of 71 newborn, 60 newborn (84%) had subtle seizure, 4 (6%) had tonic seizures, 2 (3%) clonic seizure, and 5 (7%) had subtle with clonic seizure. In our study, most common causes of seizure were birth asphyxia 50% (n=36), meningitis 15% (n=11), and hypoglycemia 13% (n=9). Other common cause are hypocalcemia 8.5% (n=6), kernicterus 2.8% (n=2), and intraventricular hemorrhage 1.5% (n=1).

Conclusion: In our study, we have found that preterm babies appear to have adverse neurodevelopmental outcome due to any brain insult occurred during neonatal period. Onset of seizure was found to be important predicting factor for developmental outcome. Frequency of seizure also has impact on developmental outcome, newborns who have single episode of seizure had good developmental outcome.

Keywords: Neonatal seizure, Electroencephalography profile, Electroencephalography, Term and preterm neonates.

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INTRODUCTION

Neonatal seizure is a paroxysmal behavior caused by hyper-synchronous discharge of a group of neurons [1]. Neonatal seizures are the most common overt manifestation of neurological dysfunction in the newborn. It may be the first and the only manifestation of neurological dysfunction after a variety of insults. Neonatal seizures are clinically significant, because very few are idiopathic. The prevalence is approximately 1.5% and overall incidence approximately 0.7–2.7/1000 live births. The incidence in pre-term infants is very high (57–132/1000 live births). Most (80%) neonatal seizures occur in the first 1–2 days to the 1st week of life. Continuous electroencephalography (EEG) monitoring of infants after one clinical seizure showed that 79% of subsequent EEG seizures were clinically silent. Such phenomenon seems to be more common in preterm infants. The immature brain seems more prone to seizures; these are more common in the neonatal period than during any other time throughout life [1]. This may reflect the earlier development of excitatory synapses, predominating over inhibitory influences at the early stages of maturation. A seizure may arise from varying foci at different times. Not all clinical seizures are correlated with EEG changes and not all seizures shown on EEG recordings are clinically apparent. Seizures may interfere with cardiorespiratory function and with nutrition and may have detrimental long-term effects on cerebral development. The EEG is an important tool in the evaluation of an infant with symptoms referable to the central nervous system. It provides an excellent and non-invasive method of assessing at risk newborns and of formulating a prognosis for long-term neurological outcome. The major areas in which EEG can provide unique information in the assessment of newborn full term and preterm infants are: [2]. Evaluation of infants with compromised cerebral function caused by primary neurological disorders (e.g., hypoxic ischemic encephalopathy and cerebral infarction), and those with significant systemic disease (e.g., severe respiratory distress syndrome or sepsis) who are at risk of secondary encephalopathies.

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The prospective observational study was conducted in 71 term and preterm neonates admitted at tertiary care center, Department of Pediatrics, Netaji Subhash Chandra Bose Medical College, Jabalpur, MP. Ethical clearance was taken from the Ethical Committee of University and Medical College. Before conducting study, all the procedure were fully explained to mother and written consent was taken. All consecutive term and preterm neonates with documented seizure who were discharge from NICU with proper consent and counseling of parents were included in study during November 2014–October 2015. The following neonates were excluded from study.

1. Babies of mother on anti-epileptics
2. Neonates with documented seizure due to congenital malformation, fro example, congenital hydrocephalus, anencephaly, and mylomeningocele
3. Refusal by mother to participate in the study
4. Neonatal death.

A predesigned pro forma was used for data collection. The face to face interview was taken from mother, followed by clinical examination of newborn and investigations.

Table 1: Age-wise (at admission) distribution of newborns

Age at admission	Frequency (n=71)	%
24≤h	15	21.13
25–72 h	30	42.25
>72 h	26	36.62
Total	71	100.00

Table 2: Gender-wise distribution of newborns

Gender-wise distribution of newborns	Frequency (n=71)	%
Male	40	56.34
Female	31	43.66
Total	71	100

Table 3: Distribution of cases according to birth weight

Birth weight	Frequency (n=71)	%
<1500 g	12	16.90
1500–2500 g	39	54.9
>2500 g	20	28.1
Total	71	100

Table 4: Distribution of cases according to age at the time of onset of seizures

Age of onset	Frequency	%
Within 24 h	48	67.61
25–72 h	10	14.08
>72 h	13	18.31
Total	71	100.00

Table 5: Distribution of cases according to frequency of seizures

Frequency of seizures	Frequency	%
Single episode	41	57.75
Multiple episode	30	43.25
Total	71	100.00

Basic information and examination details were collected at the time of admission. At the time of discharge neurological examination, head circumference, history of antiepileptic drugs, and EEG were recorded. Three follow-up (at 1 month, at 3 month, and at 6 month) were done. At the follow-up visit recording of complain of seizures, neurological examination, head circumference and history of anti-epileptic drug, development assessment, assessment of tone Amiel Tyson method, EEG, and BERA findings were recorded. Neurodevelopment assessment was done by the Denver developmental screening test II (DDST). Obtained data were coded and entered into Microsoft Excel worksheet. This was analyzed using SPSS version 20 and Epi Info version 7.1.5.2. To find out the association of DDST with the study variables, Chi-square test and Fisher exact test was applied. The statistical significance was evaluated at 5% level of significance.

OBSERVATION AND RESULTS

Above table shows age-wise distribution of cases according to age of admission in nursery. Total 71 newborns were enrolled, out of them 21% (n=15) were admitted within 24 h of birth, 42% (n=30) were admitted within 24–72 h, and 37% (n=26) newborn admitted at >72 h of birth.

This table shows gender-wise distribution of newborn included in this study. Total number of male included were 56% (n=40) while female were 44% (n=31).

Table 6: Distribution of cases according to clinical type of seizure pattern

Types of seizures	No. of children	%
Subtle seizures	60	84
Tonic seizures	4	6
Clonic seizures	2	3
Subtle with clonic	5	7
Total	71	100

Table 7: Distribution of cases according to causes of seizures

S. No.	Cause of seizures	Number of newborns	%
1	Birth asphyxia	36	50
2	Hypoglycemia	9	12.6
3	Hypocalcemia	6	8.4
4	Meningitis	11	15.4
5	Kernicterus	2	2.8
6	IVH	1	1.4
7	Birth asphyxia, hypocalcaemia	2	2.8
8	Birth asphyxia, meningitis	2	2.8
9	Birth asphyxia meningitis, Kernicterus	1	1.4
10	Hypocalcemia, hypoglycemia, Kernicterus	1	1.4
	Total	71	100

Table 8: Distribution of newborn according to age at onset of seizure and DDST

Age at onset of seizures (in h)	DDST		Total
	Normal	Abnormal	
<24 h	31	14	45
24–72 h	3	1	4
>72 h	1	11	12
Total	35	26	61

p<0.001. DDST: Denver developmental screening test

This table shows distribution of cases according to birth weight. Out of total 71 newborn, 17% (n=12) were <1500 g, 55% (n=39) were from 1500 to 2500 g, and 28% (n=20) were >2500 g.

This table shows distribution of cases according to age at the time of onset of seizure. About 68% (n=48) cases had complain of seizure within 24 h of birth, 14% (n=10) cases had seizure from 24 h to 72 h of birth, and 18% (n=13) cases had seizure after 72 h of birth.

This table shows distribution of cases according to frequency of seizure. Out of 71 newborn, 58% (n=41) newborn had single episode of seizure, 42% (n=30) newborn had multiple episode of seizure.

This table shows distribution of cases according to type of seizure. Out of 71 newborn, 60 newborn (84%) had subtle seizure, 4 (6%) had tonic seizures, 2 (3%) clonic seizure, and 5 (7%) had subtle with clonic seizure.

This table shows distribution of cases according to causes of seizure. Out of 71 newborn, 50% (n=36) had seizure due to birth asphyxia, 13% (n=9) had seizure due to hypoglycemia, 9% (n=6) had hypocalcaemia, 15% (n=11) had meningitis, 3% (n=2) had developed acute bilirubin induced encephalopathy (kernicterus), 1.5% (n=1) had Intra-ventricular hemorrhage (IVH), and rest of them 9% had multiple etiology.

This table shows outcome (DDST-2 score) of newborn according to age at onset of seizure. In this study, total 71 newborn enrolled who have seizure in their neonatal life out of them 10 newborns did not attend follow-up, so we have followed only 61 newborn to see developmental

Table 9: Cross-tabulation between cause of seizure and age of onset of seizure

Cause of seizures	Age at onset of seizure					
	0–24 h	24–72 h	4–7 days	>7 days	Total	%
Birth Asphyxia	30	6	0	0	36	50.7
Hypoglycemia	6	1	2	0	9	12.6
Hypocalcemia	1	3	2	0	6	8.4
Meningitis	8	0	2	1	11	15.4
Kernicterus	0	0	0	2	2	2.8
IVH	1	0	0	0	1	1.4
Birth asphyxia, hypocalcemia	2	0	0	0	2	2.8
Birth asphyxia, meningitis	0	0	1	0	1	1.4
Birth asphyxia, meningitis, Hypocalcemia	0	0	0	1	1	1.4
Birth asphyxia, meningitis, kernicterus	0	0	0	1	1	1.4
Hypocalcemia, hypoglycemia, kernicterus	0	0	1	0	1	1.4
Total	48	10	8	5	71	100

p<0.001

outcome, out of them 45 newborns were having seizure within 24 h of life, in these newborn, 31 newborns was having normal development (<25 percentile), and 14 newborns was having abnormal developmental outcome. Four newborn admitted in hospital with complain of seizure within 24–72 h of their life, out of these four newborns three having normal development, and one having delay in development. Twelve newborn admitted in nursery with seizure in more than 72 h of life, out of them one newborn was normal development, 11 having abnormal DDST.

Above table shows corelation between causes of seizure and age of onset of seizure. Hence, out of 71 newborns, 36 newborns had birth asphyxia in them 30 had seizure within 24 h of life, six from 24 to 72 h of life. Nine newborns had seizure due to hypoglycemia, out of them six had seizure within 24 h, one from 24 to 72 h, and two newborn had seizure from 4 to 7 days of life. Six had hypocalcemic seizure; out of them 1 was be within 24 h of life, three from 24 to 72 h, and two from 4 to 7 days. Eleven had meningitis that eight had early onset (<24 h of life), two had seizure from 4 to 7 days, one had seizure at >7 days. Two newborns admitted in nursery at >7 days of life for complain of jaundice who had developed acute bilirubin-induced encephalopathy and convulsion. One had seizure due to IVH at 1st day of life while rest of them had multiple etiology.

DISCUSSION

Risk factors

There were 56% (n=40) males and 44% (n=31) females in the present study sample. There was some significant preponderance among male. This is in accordance with finding of Mwaniki *et al*., in 2003 who studied neonatal seizures in a rural Kenyan district hospital [3]; they studies etiology, incidence, and outcome of hospitalization in all cases of neonates. However, in 2010 Sanjeev Kumar Digra and Ashok Gupta conducted a study in all neonates <28 days of life, in SGMS Hospital, Government Medical College, Jammu for 6 month. They reported male preponderance in their results [4]. Being a long-term follow-up study, sample size is very small to draw any conclusion regarding any predilection of sex in neonatal seizures. In the present study, 17% (n=12) cases had birth weight <1500 g, 54% (n=39) were having birth weight between 1.5 kg to 2.5 kg, and 29% (n=20) had birth weight more than 2500 g. Incidence of neonatal seizures in higher in low birth weight babies. In 2009, Francesco Pisani et al development a scoring system for early prognostic assessment after neonatal seizures. They concluded that birth weight on one of the best outcome predictor on multiple logistic regressions [5]. In the present study, 67% (n=47) cases were born by vaginal delivery, while 33% (n-24) cases were born by LSCS delivery. Similar to this Finner *et al*., in 1981, have reported 65% vaginal delivery and 35% LSCS delivery in their study in which they followed up neonates with perinatal asphyxia [6]. Chandra *et al*., in 1997, done multivariate analysis of risk factors in hospital birth and found that cesarean section delivery is significantly associated with neonatal seizures with an odd ratio of 4.6 [8]. In the present study, out of 71 newborns, 18 (25%) were preterm and 53 (75%) were term. However, only 61 newborns attend the follow-up until 6 months of age, so, out of 61 newborn, 51 were term and in them, 66% (n=34) term newborn was normal, while 33% (n=17) term newborn was abnormal DDST, while, in preterm, total (n=10) newborn only 10% (n=1) was normal, 90% (n=9) was abnormal. Jennifer E. McGowan, et al. 2011 done study on late preterm infants (LPIs) born at 34 to 36 weeks gestation are increasingly regarded as being at risk for adverse developmental outcomes. Studies were heterogeneous, and poorer outcomes were reported among LPIs in relation to neurodevelopmental disabilities, educational ability, early-intervention requirements, medical disabilities, and physical growth in comparison to term-born children [8]. On analyzing various risk factors for neonatal seizures, meconium stained liquor (50%, n=36), obstructed labor (14.8%, n=10), and premature rupture of membrane (12%, n=9) were found to be most significantly associated with neonatal seizures. In 2001, Saliba *et al*. studied various risk factors for neonatal seizures. It was a population based study at Harris County in Texas from 1992 to 1994. They evaluated 116,048 infants among those 207 were diagnosed with clinical neonatal seizures. They assessed the relationship between seizures and birth weight between seizures and birth weight, gender, ethnicity, place of birth, mother's age, method of delivery, parity, and multiple births. For term infants, significant risk factors included birth by cesarean section (RR=2.2, 95% CI: 1.5; 3.2), small birth weight for gestational age (RR=1.9, 95% CI: 1.2; 2.9), and birth in a private hospital (RR=1.6, 95% CI: 1.1; 2.3). Birth by assisted vaginally delivery and primi parity was marginally significant form term infants [9]. The above observation reflects non-recognition of certain maternal-fetal risk factors at the early stage and inadequate fetal monitoring in such mothers as majority of perinatal asphyxia in the present study were associated with such risk factors. This also implies that if incidence of asphyxia and subsequent perinatal mortality and neurodevelopmental impairment in the surviving neonates are to be reduced, there is need to ensure the early recognition of mother with risk, more frequently institutional delivery, better fetal monitoring and adequate labor room facilities with availability of skilled personals, and trained properly for neonatal resuscitations.

In the present study, hypoxic ischemic encephalopathy was found to be the most common cause in 57.7% of cases (n=41), metabolic disorder were in 28% of cases (n=20), meningitis 20% (n=14), jaundice 5.6% (n=4), and IVH 1.5% (n=1).

In 1999, Sheth *et al*., examined the influence of gestational age on neonatal seizures in the neonatal intensive care until at Division of Pediatric Neurology, University of Wisconsin Medical School, US. A cohort of 4165 neonates admitted to a university intensive care unit between 1986 and 1995. They concluded that IVH was the principal etiology underlying the higher seizures rate for infants <30 weeks. HIE and congenital malformation were primary factor for infants more than

36 weeks. Nervous system infections were evenly distributed across gestational age [10].

In the present study of 71 cases, majority (67.7%, n=48) of them had seizures within 24 h of life. Out of which 12 had seizures within 6 h of life and 34 cases had seizures within 6–24 h of life. Only 14.8% (n=10) cases had seizures documented from 24 h to 72 h of life. Moreover, 13 newborns had seizure at >72 h of life. Manual of neonatal care (Cloherty *et al*.,) mentions that vast majority of post asphyxia seizures in the newborn occur within first 24 h after insult, 50% or more occurring within 12 h of birth [1]. Similar results were reported by Digra and Gupta in 2010 where they found that 71.4% neonates had early-onset seizures [11].

In the present study, out of 71 cases, most common cause of seizures came out to be HIE in 41cases (57.1%), of which 13 (31.5%) had abnormal neurodevelopmental outcome. Thirteen (19%) cases had metabolic disorder (hypocalcemia and hypoglycemia) out of them 4 (30%) having abnormal neurodevelopmental outcome, 13 (19%) cases had meningitis in them 6 (46%) having abnormal neurodevelopmental outcome. Iype *et al.,* from the Department of Neurology and Pediatrics, SAT Hospital, Medical College Trivandrum, Kerala, India in 2008 done study to determine sequelae of neonatal seizures in a cohort of newborns, recruited over a 6 month period. About 68% of the babies followed up were normal; 32% had an abnormal neurological outcome. Seven (7%) developed post-neonatal epilepsy. Hypocalcemia was significantly associated with mortality. No risk factors could be identified for post neonatal epilepsy. The presence of spike waves in the EEG was significantly related to abnormal neurological outcome [12].

CONCLUSION

In our study, we have found that preterm babies appear to have adverse neurodevelopmental outcome due to any brain insult occurred during neonatal period. Most common causes of seizure were birth asphyxia, meningitis, and hypoglycemia. Other common causes are hypocalcemia, kernicterus, and IVH. All the babies who developed seizure due to kernicterus (n=2) and IVH (n=1) were abnormal on DDST. Onset of seizure was found to be important predicting factor for developmental outcome. Frequency of seizure also has impact on developmental outcome, newborns who have single episode of seizure had good developmental outcome. Microcephaly or suboptimal head size was found to be particularly associated with adverse developmental outcome in our study.

ETHICAL CONSIDERATION

Ethical clearance was taken from the Institutional Ethical Committee of NSCB MedicalCollege Jabalpur.

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CONFLICTS OF INTEREST

None declared.

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