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Original Article

Clinicoetiological profile of neonatal seizures in a tertiary care hospital

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ABSTRACT

Background: Seizure is one of the most frequently observed clinical sign in neonatal period and may be the only sign of a central nervous system disorder. Its recognition is of paramount importance and a newborn with seizures is in a true medical emergency requiring prompt intervention. **Objective:** To determine the clinical and etiological profile of seizures among neonates admitted to neonatal unit in a tertiary care hospital. **Materials and Methods:** It was a prospective, observational, hospital-based study conducted over a period of 1 year (December 2014-November 2015). Nearly, 63 babies either admitted with neonatal seizures or who developed seizures after admission were studied to find the clinical and etiological profile. Detailed history including gestational age, mode of delivery, birth events, Apgar scores and antenatal problems, age of onset, and frequency of seizures was also noted. Seizures were classified on the basis of detailed description by pediatric resident on duty in a predesigned pro forma. Informed written consent of parents was taken before enrolling a baby in study. **Results:** Sepsis was the most common cause of neonatal seizures (64.9%), followed by birth asphyxia, i.e., hypoxic ischemic encephalopathy (HIE) (48.3%). Hypoglycemia was seen in 21.6% and hypocalcemia in 18.3% cases. Subtle seizures were the most common type of seizures seen in 65% babies, followed by tonic (31.6%), myoclonic (16.6%%), and clonic (6.67%) type. Subtle seizures were commonly seen in cases of HIE. **Conclusion:** The recognition of clinicoetiology of neonatal seizures is often helpful with respect to prognosis and treatment. The most common etiology for neonatal seizure is sepsis. Onset of seizures during first 3 days of life has significant correlation with HIE as etiology. Subtle seizures are the most common type of clinical seizures, which is difficult to identify; therefore, careful observation of at risk newborns is necessary.

Key words: *Seizures, Hypoxic ischemic encephalopathy, Hypoglycemia, Hypocalcemia, Sepsis*

Seizures in newborns are qualitatively different from those in older children and adults because of anatomical as well as physiological immaturity of the central nervous system. The international classification of epileptic seizures does not apply to newborn seizures because neonates are unstable to sustain organized discharges and do not manifest generalized tonic-clonic seizures and any abnormal, repetitive, and stereotypic behavior in neonates also needs to be evaluated as possible seizure [1]. Neonates are at particular risk for the development of seizures, because metabolic, toxic, structural, and infectious diseases manifest more during this time than in any other period of life [2]. The National Neonatology Perinatal Database of National Neonatology Forum of India for year 2002-2003 recorded a seizure frequency of 1.03% [3].

Seizure incidence has been reported to be 57.5 per 1000 in babies with birth weight <1500 g. Incidence markedly decreased to 2.8 per 1000 in babies weighing between 2500 and 3999 g.

The reported frequency in international studies (Eghbalian et al. [4] and Scher et al. [5]) is above 2%. Such variability in reports is not surprising if we take into account the population studied – preterm versus term babies, the magnitude of the problem of birth asphyxia which is a sensitive indicator of perinatal seizures in a unit and criteria used for diagnosis of seizures – clinical only or clinical with electroencephalogram (EEG) as well. Further with improvement in perinatal care many a conditions causing seizures in neonates may be prevented; thus, a temporal change with reduction in frequency of seizures over a period of time is not surprising (1.03% in 2002 vs. 0.77% in 2013). Among conditions which present as seizures, hypoxic ischemic encephalopathy (HIE) has been the most common cause of seizures in most Indian studies followed by hypoglycemia, hypocalcemia, infections, intracranial hemorrhage (ICH), bilirubin encephalopathy, etc., which have different frequency in different studies [6-8]. Etiology of seizures, to some extent, depends on the age of the baby at the time of onset of seizures [9]. The aim of this study was to determine the clinicoetiologic association of seizures in neonates for more precise and prompt diagnosis and treatment.

MATERIALS AND METHODS

This prospective, observational, hospital-based study was conducted over a period of 1 year (December 2014-November

2015) after getting approval from the Ethical Committee of the institution. All neonates admitted to neonatal unit of Shri Ram Murti Smarak Institute of Medical Sciences, Bhojipura, Bareilly having seizures either at presentation or during their stay were investigated to establish clinical presentation and etiology of seizures. Neonates with isolated subtle motor movements or apnea without tachycardia or hypertension, having jitteriness, titanic spasms, and benign myoclonic jerks were excluded from the study. Detailed history including gestational age, mode of delivery, birth events, Apgar scores, and antenatal problems was recorded. Age of onset of seizures and frequency was also noted. Seizures were classified as subtle, clonic, tonic, or myoclonic on the basis of detailed description by the pediatric residents in a predesigned pro forma. Informed written consent of parents was taken before enrolling a baby in the study.

All neonates underwent a detailed examination including vitals, general physical examination, and neurological examination. HIE was defined as neurological dysfunction (e.g., seizures, encephalopathy, tone abnormalities) with evidence of multiple organ involvement such as kidneys, lungs, liver, heart, and intestine with Apgar score ≤3 at 5 min or later or suggestive laboratory investigations (arterial pH <7 from cord blood or immediately after birth) +/end organ dysfunction [10]. Sepsis screening was considered positive, if any one of the 2 criteria was positive: Total leukocyte count <5000/mm^3, immature to mature neutrophil ratio >0.2, C-reactive protein >1 mg/dl, micro-erythrocyte sedimentation rate >15 mm in 1st h [11-13]. Hypoglycemia was diagnosed if random blood sugar was <45 mg/dl. Serum sodium <130 and >150 mEq/l were taken as hyponatremia and hypernatremia, respectively. Hypocalcemia was diagnosed with serum calcium level <8.0 mg/dl (ionic calcium <4 mg/dl in preterm and <4.8 mg/dl in term). Hematocrit, creatinine kinase, liver function tests, renal function tests, cerebrospinal fluid (cells-8 [0-30]/mm^3, polymorphonuclears – 60%, protein – 90 [20-170] mg/dl, glucose – 52 [34-119]), EEG, ultrasound, computed tomography/magnetic resonance imaging, TORCH screen, and arterial blood gas analysis were done wherever indicated. Babies were followed up until discharge/death. Analysis of data was done using the SPSS version 17.

RESULTS

There were 63 neonates in the study (16 were female and 44 were male). Three neonates (two female and one male) were excluded from the study. 29 babies were born by normal delivery and 31 by lower segment cesarean section. More than 80% neonates were term (Table 1). Seizures were observed more commonly in male babies than female. In 35% cases, seizures occurred within 24 h of birth, 66% by 72 h and in 81.6% cases, within the first week (Table 2). Subtle seizure (lip smacking, staring look, and cycling movements) was the most common type of neonatal seizure seen in about 57% cases, followed by tonic seizures (31.6%) as shown in Table 3. Sepsis was the most common cause of neonatal seizures (64.9%), followed by HIE (48.3%). Hypoglycemia and hypocalcemia were seen in 21.6% and 18.3% cases, respectively. Subtle seizures were commonly seen in neonates having birth asphyxia leading to HIE, tonic seizures were mostly seen in sepsis (33.3%) (Table 4). Mortality in our study was 1.7% (1/60).

DISCUSSION

Neonatal seizures are the most frequent and distinctive clinical manifestation of the neurological dysfunction in the newborn infant. Infants are at a high risk of neonatal death or neurological impairment and epilepsy disorders in later life. Although mortality due to neonatal seizures has decreased from 40% to about 20% over the years, the prevalence of long-term neurodevelopment sequelae has largely remained unchanged at around 30% [14]. More than 80% babies in our study were term. Moayedi et al. [15] also found neonatal seizures in 83.6% term babies and 12.7% in preterm. Similar findings were shown in study by Suryavanshi et al. [16] who enrolled 52 babies with seizures and out of which, 23.75% were preterm, and 76.25% were term babies. Mohammad Kazem et al. studied 102 neonates and found 26.5% were preterm and 73.3% were term which is also similar to our study.

Neonates have immature brain which is more excitable. They are more likely to develop seizures due to delay in Na^+- K^+ ATP maturation and increased NMDA and AMPA receptor density as well as delay in development of inhibitory GABAergic transmission. About 30% babies developed seizure within 12 h and 35% by 24 h of birth. By 72 h, approx. 70% neonates had

Table 1: Frequency of seizure

Sex	Total cases			Gestation Number (%)		
	n	LSCS	NVD	Preterm	Term	Postterm
Female	16	10	6	3 (18.8)	13 (81.3)	0 (0)
Male	44	21	23	4 (9.1)	38 (86.4)	2 (4.5)
Total	60	31	29	7 (11.7)	51 (85.0)	2 (3.3)

NVD: Normal vaginal delivery, LSCS: Lower segment cesarean section

Table 2: Age of onset of seizures

Age of onset of seizures	Total cases (n)	Gestation Number (%)		
		Preterm	Term	Postterm
<12 h	17	1 (5.9)	15 (88.2)	1 (5.9)
12-24 h	4	2 (50)	2 (50)	0 (0.0)
24-72 h	19	0 (0.0)	18 (94.7)	1 (5.3)
72 h-7 days	9	2 (22.2)	7 (77.7)	0 (0.0)
7-30 days	11	2 (18.2)	9 (81.8)	0 (0.0)
Total	60	7 (11.7)	51 (85.0)	2 (3.3)

Table 3: Type of seizures

Seizure	Total cases (n)	Gestation Number (%)		
		Preterm	Term	Postterm
Subtle	34	4 (11.8)	28 (82.4)	2 (5.9)
Tonic	19	3 (15.8)	16 (84.2)	0 (0.0)
Clonic	4	0 (0.0)	4 (100)	0 (0.0)
Myoclonic	10	1 (10.0)	9 (90.0)	0 (0.0)

Table 4: Etiological profile of neonatal seizures

Diagnosis	Total cases	Type of seizures	Cases
	Number (%)		
Sepsis	42 (70)	Subtle	16
		Tonic	14
		Clonic	3
		Myoclonic	8
HIE	29 (48.3)	Subtle	17
		Tonic	8
		Clonic	2
		Myoclonic	2
Metabolic			
Hypoglycemia	15 (25)	Subtle	7
		Tonic	5
		Myoclonic	3
Hypocalcemia	13 (21.6)	Subtle	8
		Tonic	3
		Clonic	1
		Myoclonic	1
Intracranial hemorrhage	2 (3.34)	Tonic + subtle	2
Miscellaneous			
Meconium aspiration syndrome	11 (18.3)	Subtle	9
		Clonic	2
Polycythemia	7 (11.67)	Subtle	3
		Tonic	1
		Clonic	1
		Myoclonic	2
Disseminated intravascular coagulation	1 (1.67)	Subtle	1
Acute bilirubin encephalopathy	1 (1.67)	Tonic	1
Communicating hydrocephalus	1 (1.67)	Subtle + myoclonic	1

HIE: Hypoxic-ischemic encephalopathy

developed seizures. Moayedi et al. followed up 110 neonates and found almost similar results. Farid et al. [17] studied 159 neonates and also found 30.18% neonates had developed seizures within 24 h and 55% by 72 h of life. Arshad et al. [18] followed up 96 neonates and found 85.41% of the neonates had seizures within 7 days of life; the author though has not grouped onset of seizures on hourly basis. GABA in immature brain is excitatory and opening up chloride channels in immature brain leads to depolarization. Such activity is the more common in male babies. Hence, male babies are more prone to seizures. We found 80% male babies had seizures, similar observation have been made by others [16-18].

Volpe and Hill [19] modified the classification of neonatal seizures in 1994 into four types: (1) Subtle, (2) Tonic (Generalized, Focal), (3) Clonic (Multifocal, Focal), (4) Myoclonic (Focal, Multifocal, and Generalized). The common changes seen on the EEG include burst suppression pattern, focal sharp waves, and hypsarrhythmia. Myoclonic seizures carry the worst prognosis in terms of neurodevelopment outcome and seizure recurrence. Focal clinic seizures have the best prognosis. We found subtle seizures in 34 cases (56.6%) in which 30 were term and four were preterm babies. In a study conducted by Soo Jung Lim et al. [20] which consisted of 63 neonates, subtle seizures was the most common seizure type found in 35 (43.75%) which included 12 preterm babies (37.7%) and 23 term babies (63.15%), tonic extension was seen in nine babies (11.25%) out of which two were preterm (10.54%) and seven (11.47%) were term. Moayedi et al. also observed subtle seizures in 39.1% neonates. Farid et al. found subtle seizures in 39.6% cases. Other types of seizures are not commonly seen. In some neonates, multiple seizures types coexisted such as subtle, tonic, and clinic.

Depolarization results into excessive excitatory amino acid glutamate release and/or deficiency of GABA. Although HIE is the most common cause of neonatal seizures but we found 70% cases had sepsis. These babies exhibited subtle type in 38% and tonic type in 33% cases. Being a tertiary care hospital, many babies from nearby health facility are transferred for treatment. HIE disrupts the ATP dependent sodium-potassium pumps and leads to depolarization. HIE causes neonatal seizures in term and preterm neonates equally. Usually, subtle and tonic type is more common. HIE led to seizure in 48.3% cases. Subtle seizure was the more common than tonic seizure. Shah [21] studied 90 neonates and found subtle seizure more in HIE cases. Taksande et al. also found HIE as the most common cause of neonatal seizure. However, Maya Prasad et al. [22] found clonic type more commonly in babies having HIE, of which no obvious cause has been given by the author. Metabolic causes such as hypoglycemia and hypocalcemia can occur in HIE and sepsis cases as well. We found 28 cases (46.6%) due to hypoglycemia and hypocalcemia of which 17 were associated with sepsis and 11 were associated HIE. In these cases also, subtle seizures were the most common followed by tonic type. Maya Prasad et al. found hypoglycemia and hypocalcemia in 21.5% cases each whereas Bhatt et al. [23], in study of 172 neonates, found metabolic causes in 13.3% cases.

ICH was diagnosed on basis of CT/MRI findings. Although subarachnoid hemorrhage (SAH) was the most common type, we did not find any case due to SAH. We had only two cases of ICH in our study and both were preterms. Sahana et al. in study of 109 neonates found ICH in two term and four preterm babies. Bhatt et al. found ICH in 3 (1.7%) preterms. Our study shows how varied a clinical presentation can be for a particular etiology; therefore, all relevant investigations must be done for ruling out the cause of seizure. There are some limitations of our study, for example, clinically evident seizures only were included in the current study; hence, very subtle and electrical seizures might have been missed as no EEG was done. A true incidence of neonatal seizure based on total live births could not be calculated as most of the cases were referred from peripheral hospitals. We could not get many advanced investigations (metabolic screens,

EEG etc.) in our study; therefore, sepsis and HIE remain the important common causes.

CONCLUSION

Multiple causes may contribute to seizure in the same newborn. The most common etiology for neonatal seizure is sepsis. Onset of seizures during first 12 hrs of life was due to HIE and by 3rd day, sepsis was the most common cause. Subtle seizures were the most common type of clinical seizures, which are difficult to identify; therefore, careful observation of at risk newborns is necessary.

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