

## A Study of Clinico-Etiological Profile of Neonatal Seizure: A Tertiary Care Hospital Based Study

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### I. Introduction

Seizures are the most common and distinct clinical manifestation of neurological dysfunction in the newborn infant.<sup>1</sup> Neonatal seizures are a common neurological problem in neonates with a frequency of 1.5-14/1000 neonates.<sup>2</sup> The occurrence of neonatal seizures per se has been positively correlated with structural brain damage and its consequent sequels at later stages in life. Historically seizures were divided in following clinical categories viz. focal clonic, multifocal clonic, tonic, myoclonic, & subtle seizures.<sup>1</sup> Diverse medical conditions in the newborn can be associated with neonatal seizures. Hypoxia-ischemia is nonetheless traditionally considered the most common cause of neonatal seizures.<sup>1,4</sup>

Cerebral infarction and stroke the second most common cause of neonatal seizures occurs in otherwise well term infants, without previous risk factors<sup>5,6</sup> and involves left middle cerebral artery territory and presents with right sided clonic seizures. Intracranial hemorrhage is implicated in 10% to 15% of seizures, and amongst them Intra-ventricular hemorrhage or Periventricular hemorrhagic infarction is the most common Intracranial hemorrhage in preterm infants and constitutes around 45% seizures in preterm.<sup>7,8</sup>

Central nervous system infections during intrapartum or postnatal period can be associated with seizures<sup>9</sup>. Biochemical disturbances occur frequently in neonatal seizures either as an underlying cause or as an associated abnormality.<sup>10,11</sup> Metabolic disturbances could be more commonly transient and rapidly correctable or less commonly inherited as persistent causes.

Infants of diabetic mothers, small for gestational age infants, infants with birth asphyxia are at more risk of hypoglycemia. Late onset hypocalcaemia due to use of high phosphate infant formula has been cited as common cause of seizures.<sup>12,13</sup> However commonly hypocalcaemia occurs in infants with trauma, hemolytic disease, asphyxia and IDM and usually coexists with hypoglycemia and hypomagnesemia<sup>14</sup> and presents at 2-3 days of life.

Hypomagnesaemia with serum <1.5 mg/dl can occasionally manifest with tetany and seizures at 2-4 weeks of age and has secondary hypocalcaemia associated.

Hypophosphatemia may be caused by ingestion of milk formulas containing high amounts of phosphorous, excessive parenteral administration of phosphorus, impaired renal function, and hypoparathyroidism.<sup>15</sup>

Hyponatremia as a result of fluid overload renal compromise and SIADH (syndrome of inappropriate ADH secretion) can be a frequent complication of birth asphyxia and could complicate the management of seizures in this condition.<sup>16</sup>

### II. Method

A hospital based prospective observational study was undertaken in the Department of Paediatrics, HI-TECH Medical College & Hospital, Bhubaneswar, Odisha Hospital.

**Estimation of sample size:** Sample size was calculated on the basis of prevalence of neonatal seizures in hospitalised children reported from previous studies of around 4%. The total sample size calculated was around 65, however we decided to take at least 100 patients.

After taking an informed written consent from the attendants of babies who were admitted in our neonatology section, a total of 100 consecutive neonates within the age group of 0-28 days presenting with seizures from December 2014 to August 2015 were enrolled in the study. The study was approved by the ethics committee of the institution.

**Inclusion criteria**

Detailed and unequivocal description of neonatal seizures by the mother and attending doctor.  
Occurrence of first seizure up to 28 days of life.

**Exclusion criteria**

Uncertain clinical manifestations.  
Those who had first seizure > 28 days

**Data collection procedure**

Detailed antenatal history, i.e. maternal age, past medical history, parity, gestational age, history of illness during pregnancy, medication during pregnancy; natal history viz. evidence of foetal distress, Apgar score, type of delivery, medication given to mother during delivery were recorded. Baseline characteristics of convulsing neonate including sex, gestational age, weight, head circumference & length were recorded at admission. Clinical details of each seizure episode were recorded i.e. age at onset of seizures, duration of seizure, number and type of seizure. Seizure were classified into subtle, focal clonic, multifocal clonic, tonic, and myoclonic as per criteria by Volpe.<sup>1</sup> Before instituting specific treatment blood glucose, total serum calcium levels, Na<sup>+</sup>, K<sup>+</sup>, Mg and P-levels were determined.

**Criteria for diagnosing various biochemical abnormalities:<sup>16</sup>**

Hypoglycemia: blood sugar <40mg/dl (normal range 40- 150 mg/dl)  
Hypocalcaemia: total serum calcium <7 mg/dl (normal range 7-10 mg/dl) Or Ionized calcium <4 mg/dl (normal range 4-5.5 mg/dl)  
Hypomagnesaemia: serum magnesium <1.5 mg/dl (normal range: 1.5-1.8 mg/dl)  
Hypernatremia: serum sodium >150 meq/dl (normal range 130-150 meq/dl)  
Hyponatremia: serum sodium <130 meq/dl  
Hypokalemia: serum potassium <3.5 meq/dl (normal range 3.5-5.5 meq/dl)  
Hyperkalemia: serum potassium >5.5 meq/dl  
Hyperphosphatemia: serum phosphorus >8 mg/dl (normal range 6-8 mg/dl).  
In addition complete blood counts, band cell count, absolute neutrophil count, micro-ESR, blood culture, USG cranium, MRI/CT, and CSF analysis were done as per the requirement in individual cases.

**Statistical analysis:**

Data was described as mean ± SE and %age. Software used for data analysis was SPSS 16.0 (statistical package for social sciences) and MS Excel.

**III. Results**

A total of 2550 neonates were admitted during the study period (from the start of study till enrolment of last patient). A total of 100 consecutive babies developed seizures in the study period hence accumulative frequency of around 3.9% was recorded in neonatal seizures in our set up.

**Table 1; Seizure Incidence**

Neonates	Total	Seizure	Percentage
Inborn	1100 (43.1%)	28	2.54
Outborn	1450 (56.8%)	72	4.96
<b>Total</b>	<b>2550 (100%)</b>	<b>100</b>	<b>3.9</b>

A total of 2550 neonates were admitted during the study period. Out of them 1450 were referred to us from peripheral institutions (outborn), while around 1100 neonates were born in our institution (inborn). Seizure frequency of around 2.54% was recorded in inborn neonates, while it was around 4.96% in outborn group. Cumulative frequency of around 3.9% was hence recorded in neonatal seizures in our set up.

**Table 2: Socio-demographic characteristics of the neonates with seizures.**

Socio-demography	n	%
Age on Admission (day) mean ± SE 2.2 ± 0.5 (0, 25)		
Gender	Male	60 60.0
	Female	40 40.0
Residence	Rural	84 84.0
	Urban	16 16.0

**Table 3: Presenting characteristics of the neonates with neonatal seizures.**

Characteristic	n %
Apgar Score at 5min	< 7 44 44.0
	7 to 10 56 56.0
Gestational Age (NBS)	Preterm 35 35.0
	Term 65 65.0
Weight	Appropriate for Gestation Age 68 68
	Large for Gestation Age 6 6
	Small for Gestation Age 26 26
Age of Onset of seizure (day) mean ± SE	3.7 ± 0.4 (1, 25)
Head Circumference (cm) mean ± SE	33.8 ± 0.1 (30, 37)
Length (cm) mean ± SE	47.5 ± 0.3 (42, 53)

Age on admission for neonates who presented with seizures or later on developed seizures in the hospital varied between 0 days to 25 days with a mean value of 2.2±0.5 days. Among the neonates convulsing in the hospital 60% (n=60) comprised of males and 40% (n=40) comprised of females. 84% (n=84) belonged to rural areas, while as around 16% were hailing from urban localities. The first day on which the seizures presented had a significant correlation with etiology, on an average presented on 3.7±0.4 days and varied from as early as 1 day to as late as 25 days. Majority of HIE patients presented with neonatal seizures in the first 72 hrs. Intracranial hemorrhage in preterm neonates had a slightly delayed age of presentation usually at or greater than first 72 hrs. Primary metabolic seizures except for late hypocalcaemia had presentation in the first half of first week. Late hypocalcaemia presented around the end of first week.

**Table 4: Maternal characteristics of the neonates**

Characteristic	N %
Maternal Age	≤ 18 10 10.0
	19 to 29 29 29.0
	30 to 39 42 42.0
	≥ 40 19 19.0
Maternal Parity	Nulliparous 62 62.0
	Parous 38 38.0
Delivery Status	In Born 28 28.0
	Out Born 72 72.0
Delivery Type	Caesarean Section 28 28.0
	Operated Vaginal 24 24.0
	Routine Vaginal 48 48.0
Antepartum Risk Factors	Pre-eclampsia 5 5.0
	Oligohydramnios 5 5.0
	Diabetes Mellitus 3 3.0
Intrapartum Risk Factors	Premature Rupture of Membrane 7 7.0
	Maternal Fever 12 12.0
Labour Record of Foetal Distress	11 11.0

**Table 5: Etiology of the neonatal seizures**

Etiology	n	%
Hypoxic Ischemic Encephalopathy	44	44
Intra Cranial Haemorrhage	13	13
Meningitis	15	15
Undiagnosed	4	4
Primary Metabolic	17	17
Septicemia	7	7

The overall etiological profile comprised of hypoxic ischemic encephalopathy, intracranial haemorrhage, meningitis, metabolic disorders and sepsis in that order. Seizure type and their relative occurrence in different etiologies recorded by clinical observation have been depicted in table 6 and in figure respectively. Tonic seizures and focal clonic seizures each comprised 53.8% (n=7) and 46.1% (n=6) among intracranial haemorrhage.

**Table 6: Seizure Characteristic**

Seizure Type	N %
Focal Clonic	30 30
Multi Focal Clonic	17 17
Subtle	28 28
Tonic	25 25

Focal clonic seizures were commonest seizure type in neonates with meningitis 40% (n=6). 17 neonates (31%) had primary metabolic seizures and 37 (69%) neonates had metabolic abnormalities superimposed or coincident on a primary illness like hypoxic ischemic encephalopathy, ICH, meningitis, sepsis etc.

#### IV. Discussion

The occurrence of seizures may be the first indication of neurological disorder and the time of onset of seizures has a correlation with the etiology of seizures and prognosis. Biochemical disturbances occur frequently in neonatal seizures either as an underlying cause or as associated abnormalities and are often underdiagnosed. Hence the need for this study to determine etiology and biochemical abnormalities in neonatal seizures which would help in early recognition and treatment and hence better prognosis in neonatal seizure. The study group included the babies with seizures who were admitted not only in neonatal intensive care unit (NICU) but also in level 2 care nursery. Our center has no facility for continuous EEG monitoring, and we are limited to assessing babies with seizures on clinical grounds alone. Hospital staff and doctors have differing abilities to recognize suspicious behaviours; this variability will lead to over diagnosis or underdiagnosed in the absence of confirmatory continuous videographic EEG. However our incidence rate is similar to 3% shown in studies by Mentet al.<sup>17</sup> and 4.1% by Asindi et al.<sup>18</sup>

In our study focal clonic seizures constituted 30% while as subtle seizures were present in 28% of neonates with tonic seizures in 25% of neonates. Taksandeet al.<sup>19</sup> showed subtle seizures as the commonest type of fits occurring in 50% of neonates. Tonic seizures were found in 16 preterm neonates with ICH (GM/IVH) as compared to 9 term neonates comprising 45% (16/35) in the preterm and 13% (9/65) in term group respectively.

In our study 83 neonates (83%) presented with seizures within the first 72 hours of life and most of them could be attributed to perinatal asphyxia. Roseet al.<sup>13</sup> also found early onset seizures in 75 (50.33%) babies whereas Coen RW et al.<sup>20</sup> found that 81% of babies had early onset seizures.

Our etiological studies were limited in the sense that we don't have elaborated investigational panels for specific diagnosis of inborn errors of metabolism although they can be assumed to be rare. In our study 13 neonates had convulsions after 7 days of life, with meningitis in 5, septicemia in 2 and primary metabolic disorders in 3 neonates and 3 had seizures of unknown etiology. Holden KR et al.<sup>21</sup> reported that 36 (13%) babies had convulsions after 8 days, which were due to sepsis and meningitis.

Frequency of birth asphyxia as a cause of seizures was 44% in our study. Sood A et al.<sup>11</sup> and Kumar A et al.<sup>16</sup> reported that birth asphyxia as the etiology of seizures was seen in 45.71% and 48.2% cases respectively, which are quite comparable to results of our study.

In our study infection as a cause, whether as meningitis or sepsis, for neonatal seizures accounts a total of around 22% (n=22). A study conducted by Legido A et al.<sup>22</sup> reported that out of 40 babies 17.2% had some kind of infection leading to fits. Bushraet al.<sup>23</sup> reported it as 34% comparable to our study. The difference between the results of Legido et al.<sup>22</sup> and ours is partly because of high incidence of infections in our set up due to poor obstetric and early neonatal care facilities.

Intraventricular haemorrhage was there in around 13% (n=13) in our study. Bushraet al.<sup>23</sup> reported that ICH was there in around 9.5% of case. 12 preterm and 1 term neonate had intraventricular haemorrhage in our study. Incidence of intraventricular haemorrhage was much higher in preterm than term neonates. Roseet al.<sup>13</sup>, Scher MS et al.<sup>24</sup> also reported higher incidence of intraventricular haemorrhage in preterm.

#### V. Conclusion

Hypoxic ischemic encephalopathy was the commonest etiology of neonatal seizures and in them most of the seizures had an onset in the first 72 hours. Overall focal clonic and subtle seizures were the commonest seizure types encountered. Hypocalcemia was the commonest biochemical abnormality in primary metabolic seizures. Biochemical abnormalities were commonly associated with other etiologies like asphyxia, intracranial hemorrhage and meningitis; hence these should be actively sought for and treated for optimal seizure control.

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