### **Original Research Article**

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# Clinico-epidemiological study of neonatal seizures from a tertiary care hospital of Western Rajasthan, India

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#### **ABSTRACT**

**Background:** Neonatal Seizures are frequent may be either symptoms of an underlying disorder and malfunction of the developing CNS or due to a primary epileptic condition. Their varied clinical presentations, delay in recognition and treatment results in poor neurological outcome. This study attempts to find out the clinical and etiologic profile of neonatal seizures and associated biochemical abnormalities in this geographical part of India.

**Methods:** A hospital based prospective observational study undertaken in a tertiary care pediatric hospital of Medical College Jodhpur India, on 202 consecutive neonates who presented with seizures during period of one year. A detailed antenatal history and baseline characteristics of convulsing neonate at admission and clinical details of each seizure episode reported by the mother and subsequently observed by doctors on duty were recorded. Venous blood sample was analyzed as soon as possible for blood glucose, total serum calcium levels and electrolytes, before instituting any treatment. Data were managed on Microsoft Excel spreadsheet, and analysis was performed using SPSS version.

**Results:** The overall frequency of neonatal seizures in our set up was recorded as 4.08%. Perinatal asphyxia with subsequent HIE was the most common (40.09%) cause of neonatal seizures while hypoglycemia was the most common metabolic cause (11.38%) observed specially in VLBW babies. Subtle seizures were the most common type (34.65%) and tonic seizures were the second most common (33.66%) type of seizures encountered. Hypocalcemia was the second commonest biochemical abnormality found in primary metabolic seizures. HIE, ICH and Hypoglycemia were the common seizure etiology in preterm neonates.

**Conclusions:** Perinatal asphyxia and subsequent HIE was the commonest etiology with subtle, tonic and multifocal seizures being the commonest clinical types encountered. Hypoglycemia and hypocalcemia were the most frequent biochemical abnormality found.

**Keywords:** Hypoglycemia, Hypocalcaemia, Hypoxic ischemic encephalopathy, Non-metabolic seizures, Primary metabolic seizures

#### INTRODUCTION

Seizures occur more frequently in the neonatal period than at any other time of life with an estimated incidence of neonatal seizures range from 0.95 to 3.5 per 1,000 live births. Seizures may be symptomatic of an underlying

disorder, signify serious damage or malfunction of the immature developing central nervous system or due to a primary epileptic condition. Various clinical conditions in the neonates can be associated with neonatal seizures and Hypoxia-ischemia is however conventionally considered the most common reason of neonatal seizures. Biochemical disturbances occur frequently in

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neonatal seizures either as an underlying cause or as an associated abnormality. Metabolic disturbances could be more commonly transient and rapidly correctable or less commonly inherited as persistent causes.<sup>3</sup> Premature infants are at especially high risk for asphyxia, seizures, and other conditions that cause hypoxia-ischemia. These events result in abnormal brain pathology and behavioral deficits that persist throughout adolescence and into adulthood.<sup>4</sup> Persistence of postanoxic encephalopathy stage 2 for more than seven days or failure of the EEG to revert to normal was associated with later neurologic impairment or death.<sup>5</sup>

Cerebral infarction and stroke are the second most common cause of neonatal seizures occurs in otherwise healthy newborn, without any previous risk factors, and usually involves left middle cerebral artery territory and presents with right sided clonic seizures.<sup>6,7</sup> Intracranial hemorrhage is implicated in 10% to 15% of seizures, and out of these Intra-ventricular hemorrhage or subsequent infarction particularly at periventricular area is the most common Intra cranial hemorrhage in preterm infants and contributes about 45% seizures etiology in preterm.<sup>8-9</sup>

Central nervous system infections during perinatal period can be associated with seizures. Biochemical disturbances occur more frequently in neonatal seizures either as an underlying etiology or as an associated abnormality. 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 also been noted as a common cause of seizures. <sup>13-14</sup> Nevertheless commonly hypocalcaemia occurs in infant's asphyxia, birth trauma, hemolytic disease and IDM and usually coexists with hypoglycemia and hypomagnesemia and presents at 2-3 days of life. <sup>15</sup>

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 high phosphate containing milk formulas, excessive parenteral administration of phosphorus, impaired renal function, and hypoparathyroidism. Hyponatremia as a result of fluid overload renal compromise and SIADH (syndrome of inappropriate ADH secretion) can be a frequent electrolyte abnormalities associated with birth asphyxia and could complicate the management of seizures in this condition. Since neonatal seizures can have varied presentations, delay in recognition and treatment results in poor neurological outcome. The objective of this study was an attempt to find out the clinical and etiologic profile of neonatal seizures in Western desert part of India to determine the etiological factors, clinical types

and various biochemical abnormalities associated with neonatal seizure.

#### **METHODS**

This hospital based prospective observational study was undertaken in the Postgraduate Department of Pediatrics, Umaid Hospital for women and children, which is a tertiary care hospital associated of Dr. S.N. Medical College, Jodhpur, Rajasthan. Sample size was calculated on the basis of prevalence of neonatal seizures in hospitalized children reported from previous studies and calculated study neonates were around 200 by sample size formula. A total of 202 consecutive neonates within the age group of 0-28 days presented with seizures for a period of one year were enrolled in the study. This study was approved by the local ethics committee of the institution.

#### Inclusion criteria

All the neonates with the detailed andclear description of seizures either by caregiver or attending doctor on its first occurrence

#### Exclusion criteria

Uncertain clinical manifestations and those who had first seizure >28 days.

#### Collection of data

A detailed antenatal history i.e. gestational age, maternal education, socio-economic status, history of maternal illness during pregnancy, natal history, labour records for evidence of fetal distress and Apgar score, type of delivery and medication given to the baby was recorded. Baseline characteristics of convulsive neonate; including sex, gestational age, weight; head circumference and length, was recorded at admission. Clinical details of each seizure episode reported by the mother or attendant and subsequently observed by resident doctors on duty was recorded, i.e. age at onset of seizures, seizure activity during occurrence of 1st seizure, duration of seizures, number and type of seizures. The neonatal seizures was classified according to Volpe's classification into subtle, multifocal clonic, focal clonic, tonic and myoclonic. The expanded new ballard scoring was used to estimate and confirm gestational age.

#### Collection of blood samples

Complete blood count, septic screening, blood glucose, total serum calcium and magnesium levels is done, immediately after baby had seizures and before institution of any specific treatment. Blood samples of newborn babies were collected by heel prick or from the vein of hands or feet or from femoral puncture and rarely from umbilical vein. Blood Sugar, Serum Calcium, Magnesium, Electrolytes, Arterial blood gas, TORCH serology and blood culture was done in relevant cases.

All the patients were treated according to the diagnosis as per standard protocols.

## Criteria for diagnosing various biochemical abnormalities<sup>17</sup>

Various criteria for diagnosing metabolic abnormalities was defined as.

Hypocalcemia: Total serum calcium <7.0mg/dl. Hypomagnesemia: serum magnesium <1.5mg/dl. Hyponatremia: Serum sodium <130mEq/L. Hypernatremia: Serum sodium >150mEq/L. Hypoglycemia: blood sugar <40mg/dl. Hypokalemia: serum potassium <3.5meq/dl (normal range 3.55.5 meq/dl), Hyperkalemia: serum potassium >5.5meq/dl, Hyperphosphatemia: serum phosphorus >8mg/dl (normal range 6-8 mg/dl).

CSF study was carried out in relevant cases to find out etiology. CSF was analyzed for color, turbidity, protein, sugar, total and differential cell count and culture. Neonatal meningitis was diagnosed when CSF culture showed growth of organisms. Ultrasound of cranium, CT scan and MRI Brain was done in the babies with neonatal seizures to rule out intracranial hemorrhage, hydrocephalus, congenital anomalies of brain and infarction of head whenever required.

#### Statistical analysis

Data was managed on Microsoft Excel spreadsheet; all the entries were double checked, and analysis was performed using SPSS version 15. Association of each of the categorical variable with neonatal seizures (outcome variable) was assessed with chi-square test. Yate's correction was applied, as the sample size was small. Significant values of X2 were seen from probability tables for degree of freedom.

#### **RESULTS**

The present study shows 72.27% were male and 27.72% were female and male to female ratio was 2.6:1. Therefore, seizures were more commonly observed in male babies (Table 1). Majority of cases were Hindu (84.15%) and others were Muslims (15.84%) and 70.79% cases belonged to rural areas as compare to 29.20% who were hailing from urban areas.

Table 1: Distribution of neonatal seizures cases according to sex.

Sex	No. Of cases	Percentage of
	(n = 202)	cases
Male	146	72.27 %
Female	56	27.72 %
Total	202	100 %

In present study, young age group of mothers (18-24 years) had more episodes of seizures in their babies and majority of neonates having seizures belonged to para 1st (57.42%). Therefore, it has been observed that the risk of having neonatal seizures decreases with increasing parity. Seizures were also more common in neonates of mother belonged to poor socioeconomic status. Maximum number of mothers were having anemia (11.88%) followed by prolonged labour (4.45%), PIH (3.96%) and twin delivery (3.46%). Therefore, antenatal and perinatal complications were the risk factors associated with neonatal seizures (Table 2).

Table 2: Association of maternal complication with neonatal seizures.

Maternal	Number of	Percentage
complication	cases(n=202)	of cases
APH	4	1.98 %
PROM	2	0.99 %
Eclampsia	3	1.48 %
CVS disease	1	0.49 %
Twin delivery	7	3.46 %
ВОН	2	0.99 %
Gestational Diabetes	4	1.98 %
Intrapartum fever	3	1.48 %
Obstructed labour	4	1.98 %
Transverse lie	1	0.49 %
Prolonged labour	9	4.45 %
Face Presentation	2	0.99 %
Anaemia	24	11.88 %
Cord prolapsed	1	0.49 %
PIH	8	3.96 %
Oligohydramnios	2	0.99 %
Breech delivery	2	0.99 %
Polyhydramnios	2	0.99 %

In the present study 56.93% of cases were term, 41.08% preterm and 1.98% post term. Out of these 8.91% of cases were VLBW, 50.48% of cases were LBW and 40.59% of cases were of normal weight. Majority of neonates (55.44%) had history of delayed cry and required resuscitation at birth thus; perinatal asphyxia was a main risk factor for neonatal seizures and most commonly observed cause of neonatal seizures (40.09%) where hypoglycemia was the most common metabolic cause of neonatal seizures (11.38%). In premature also the most common causes of seizures were birth asphyxia (31.32%) and hypoglycemia (9.63%).

However, hypoglycemia cases were more common in preterm neonates as comparison to term neonates and that was statistically significant (p value <0.001). Therefore, hypoglycemia was found as a major risk factor for neonatal seizures in VLBW babies also. Other etiological factors were meningitis (4.95%), septicemia (7.42%), hypocalcaemia (5.44%), hypomagnesaemia (0.99%), hyponatremia (0.99%), hypernatremia (1.48%), bilirubin

encephalopathy (4.45%), intracranial hemorrhage (3.46%) and brain malformation (0.49%), Whereas in 13.36% cases multiple etiological factors were found while in 5.44 % cases no etiological factor was found (Table 3). Over all subtle seizures were the most common type of seizures (34.65%) while tonic seizures were the second most common type of seizures (33.66%) in term

neonates. In preterm neonates, the most common type of seizures were subtle seizures (31.32%) followed by multifocal clonic seizures (27.71%) whereas in term neonates, the most common type of seizures were tonic seizures (40%) followed by subtle seizures (36.52%) (Figure 1, Table 3).

P. 1	Number of cases(n=202)			Percentage of cases		
Etiology	Total	Male	Female	Total	Male	Female
Birth asphyxia	81	59	22	40.09 %	29.2 %	10.89 %
Meningitis	10	9	1	4.95 %	4.45 %	0.49 %
Septicemia	15	8	7	7.42 %	3.96 %	3.46 %
Hypoglycemia	23	18	5	11.38 %	8.91 %	2.47 %
Hypocalcemia	11	7	4	5.44 %	3.46 %	1.98 %
Hypomagnesemia	2	2	0	0.99 %	0.99 %	0 %
Hyponatremia	2	2	0	0.99 %	0.99 %	0 %
Hypernatremia	3	3	0	1.48 %	1.48 %	0 %
Bilirubin encephalopathy	9	7	2	4.45 %	3.46 %	0.99 %
Intracranial hemorrhage	7	5	2	3.46 %	2.47 %	0.99 %
Multiple factors	27	17	10	13.36 %	13.36%	4.95 %
Brain malformation	1	1	0	0.49 %	0.49 %	0 %
Idiopathic	11	8	3	5.44 %	3.96 %	1.48 %

Table 3: Distribution of neonatal seizures cases according to etiology.

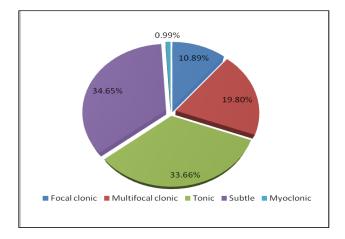


Figure 1: Distribution of neonatal seizures cases according to clinical type of seizure.

Maximum number of neonates both term and preterm developed seizures within 24 hours (43.06 %) and more than 50 % neonates (58.40 %) developed seizures within 48 hours of age and there was no statistically significant difference observed in preterm and term cases in their age of onset of seizures (p>0.05). Maximum cases of tonic seizures (47.05%) and subtle seizures (57.14%) occurred within 24 hours of age that was statistically significant (p<0.0001). In Perinatal asphyxia cases, the most common type of seizures were subtle followed by tonic seizures (statistically significant, X2=49.92, DF=4,

p<0.0001). In meningitis cases, the most common type of seizures were multifocal clonic followed by subtle seizures where as in septicemia cases, the most common type of seizures was subtle seizures (statistically not significant, X2=8.000, DF=4, p>0.09) In hypoglycemia cases, the most common type of seizures was multifocal clonic seizures (statistically significant, X2=13.304, DF=4, p<0.01), While in hypocalcaemia cases, out of 11 cases, multifocal clonic seizures and subtle seizures were developed in 4 cases (36.36%) each (statistically not significant, X2=7.636, DF=4, p>0.1). In intracranial hemorrhage cases the most common type of seizures was focal clonic seizures (statistically not significant, X2=5.143, DF=4, p>0.2). Whereas all cases of bilirubin encephalopathy, tonic seizures were present (statistically significant, X2=36.000, DF=4, p<0.0001) (Table 4).

In birth asphyxia cases, the most common type of seizures were subtle followed by tonic seizures that was statistically significant (p<0.0001). In hypoglycemia cases, the most common type of seizures was multifocal clonic seizures that were statistically significant (p<0.01). In all cases of bilirubin encephalopathy, tonic seizures were present that was statistically significant (p<0.0001). (Figure 2)In birth asphyxia cases, maximum cases (72.83%) developed seizures within 24 hours of age that was statistically significant (p<0.001). In meningitis cases, maximum cases (50%) developed seizures after 7 days of age and 40 % of cases developed seizures within 3-4 days of age that was statistically significant (p<0.05).

Etiology	Total (n=90)	Subtle (n=38)	Focal clonic (n=30)	Multifocal Clonic (n= 10)	Tonic (n= 10)	Myoclonic (n=2)
Birth asphyxia	40(44%)	20(50%)	10(25%)	5(12.5%)	3(7.5%)	2(5%)
Septicaemia	10(11%)	5(50%)	2(20%)	1(10%)	1 (10%)	1(10%)
Meningitis	10(11%)	6(60%)	1(10%)	1(10%)	1(10%)	1(10%)
Hypocalcaemia	10(11%)	7(70%)	1(10%)	0	1(10%)	1(10%)
Hypoglycaemia	20(22%)	13(65%)	5(25%)	0	1(5%)	1(5%)

Table 4: Correlation between etiology and type of seizures.

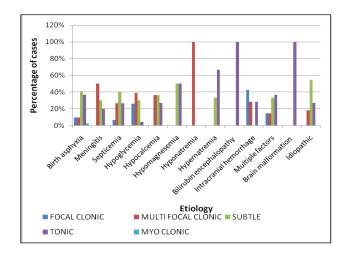


Figure 2: correlation between etiology and types of seizures.

#### DISCUSSION

we includes the neonatal seizures cases from NICU and referred cases from periphery, since our center is a tertiary care hospital we received cases from adjacent hospitals also therefore our incidence of seizures are seemingly less but Our incidence rate is similar to 3% shown in studies by Ment et al, and 4.1% by Asindi et al. 18,19 As our center doesn't have the facility for continuous EEG monitoring, therefore limited only to assessing babies with seizures clinically. Attending nurses and resident doctors have a contradictory ability to recognize altered neuro behavior have lead to some time under and over diagnosis or in the absence of confirmatory continues EEG monitoring. In our study Subtle seizures were the most common type of seizures (34.65%) and tonic seizures were the second most common type of seizures (33.66%) whereas in preterm neonates, the most common type of seizures were subtle seizures (31.32%) followed by multifocal clonic seizures (27.71%), while in term neonates, the most common type of seizures were tonic seizures (40%) followed by subtle seizures (36.52%). In the study of Taksande et al.<sup>20</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 this study out of 110 studied neonates, maximum cases of tonic

seizures (47.05%) and subtle seizures (57.14%) occurred within 24 hours of age and were attributed perinatal asphyxia cases. However, Rose et al, also found early onset seizures in 75(50.33%) babies whereas Coen RW et al, found that 81% of babies had early onset seizures. <sup>17,21</sup> In our study maximum cases of pyogenic meningitis (50%) and sepsis developed seizures after 7 days of age and 40% of cases developed seizures within 3-4 days of age. Holden KR et al, reported that 36(13%) babies had convulsions after 8 days, which were due to sepsis and meningitis. <sup>22</sup> Our etiological studies were limited as we don't have elaborated investigational panels for specific diagnosis of inborn errors of metabolism although they can be assumed to be rare.

The Frequency of birth asphyxia as a cause of seizures was 47.05% in our study. Whereas in the study of Sood A et al, and Kumar A et al, 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 this study. 11,16 In this is study infection as a cause, whether as meningitis or sepsis, for neonatal seizures accounts a total of around 28.2% (n=31). A study conducted by Legido A et al, reported that out of 40 babies 17.2% had some kind of infection leading to fits.<sup>23</sup> Bushra et al, reported it as 34% comparable to our study.<sup>24</sup> The difference between the results of Legido et al, and ours is partly because of high incidence of infections in our set up due to poor obstetric and essential neonatal care.<sup>22</sup> Bushra A et al, reported that ICH was there is around 9.5% of case.<sup>24</sup> 6 preterm and 1 term neonate had intraventricular haemorrhage in our study. Incidence of intraventricular haemorrhage was much higher in preterm than term neonates. Rose et al, Scher MS et al. 13,25 also reported higher incidence of intraventricular haemorrhage in preterm.

#### **CONCLUSION**

The recognition of the causes for the neonatal seizures is often helpful in respect to prognosis and treatment. Being the most common cause of neonatal seizures Perinatal asphyxia is frequently associated with perinatal complications, most of which are preventable if proper antenatal and perinatal care is given to the mother. Subtle seizures are commonest type of clinical seizures, which is difficult to identify, therefore careful observation of at risk newborns is necessary. Neonatal seizures themselves in addition to etiology for the seizures have a significant impact

on the developing brain. Therefore, it is critical to recognize neonatal seizures early, at least clinically where continuous video EEG monitoring facilities are not available, and to initiate the treatment. Hypoglycemia and hypocalcaemia which were one of the commonest causes should be suspected and detected as early as possible and treatment started, before it can cause any additional brain damage.

#### Recommendations

- Proper antenatal care so as to prevent intrapartum and postpartum asphyxia.
- Careful monitoring of preterm babies for seizures.
- Adequate and proper neonatal resuscitation at birth.
- To ensure Euglycemia and
- Eucalcemia in neonates.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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