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Incidence of Neonatal Seizures and it's Clinico-Etiological Profile in A Tertiary Care Hospital in Western India

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ABSTRACT

Introduction: Neonatal seizure is defined as paroxysmal electrical discharge from the brain. The immature brain seems more prone to seizures. The incidence was found to increase with decreasing gestation and birth weight- preterm neonates (20.8 vs. 8.4 per 1000 live-births) while very low birth weight neonates had more than 4-fold higher incidence (36.1 per 1000 live-births).

Objective: The study was conducted to estimate the incidence, etiological factor, time of onset, clinical types, and biochemical abnormalities among the different types of neonatal seizures.

Methods: This is a hospital based prospective observational study conducted in NICU, Department of Pediatrics, SMIMER during the period of January 2020 to March 2021.

Results: Total patients with neonatal seizures were 90 in our study. Incidence of neonatal seizures in our study was 1.1%. Incidence was higher in pre-term neonates (4.8%) and more in males (56.67%). Incidence of neonatal seizures was higher in LBW babies (4.3%) and more common in SGA babies (51.11%). Incidence among vaginal delivered babies was 0.9%, LSCS was 1.7% and forceps was 1.1%. Birth asphyxia (41.1%) was the most common cause of all neonatal seizures followed by hypoglycemia (17.8%), neonatal meningitis/septicemia (14.5%), hypocalcemia (12.2%), ICH (7.8%). Subtle seizures (44.4%) were the most common type of seizure followed by tonic (38.9%), focal clonic (11.1%), multifocal clonic (5.6%). 33.3% of neonatal seizures occurred in < 24hrs & 40% in 24-72 hrs. The most common biochemical abnormality was hypoglycemia (17.8%) followed by hypocalcemia (12.2%).

Conclusion: Incidence of neonatal seizures was 11.1/1000 live births (1.1%) & more common in preterm, LBW & LSCS deliveries. Birth asphyxia was the most common cause and subtle seizures were the most common type of seizure. Subtle seizures were more common in 24-72 hours of life. Most common biochemical abnormality was hypoglycemia followed by hypocalcemia.

INTRODUCTION

The neonatal central nervous system is particularly susceptible to seizures due to a combination of enhanced excitability and low levels of the inhibitory neurotransmitter gamma-aminobutyric acid.[1] Neonatal seizures are clinically significant as they may be suggestive of an underlying disorder or primary epileptic condition. The occurrence of seizure may be the first indication of a neurological disorder, and the time of onset of seizure

has a relationship with the etiology of seizures and prognosis.[2] Neonatal seizures can be divided into epileptic and nonepileptic seizures; neonatal seizures of epileptic origin are generated by hypersynchronous cortical neuronal discharges. There are age-dependent properties of the immature brain that enhance seizure initiation, maintenance of the seizure discharge, and propagation of the seizure discharge. Nonepileptic seizures occur in the absence of electrical seizure activity.[3] Volpe classified seizures into five clinical types, namely subtle, multifocal clonic, focal clonic, generalized tonic, and myoclonic.[4] Seizures in neonates are different from those seen in older children. The differences are perhaps due to the neuroanatomic and neurophysiologic developmental status of the newborn infant. In the neonatal brain glial proliferation, neuronal migration, the establishment of axonal deposition, dendritic contacts, and myelin deposition are incomplete. For this reasons, clinical presentation differs. [5]

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.[2],[3] Cerebral infarction and stroke are the second most common cause of neonatal seizures occurring in otherwise well term infants, without previous risk factors. Hypoglycemia is a well-known cause of neonatal seizures. Infants with sepsis and meningitis frequently have hypoglycemia which can be attributed to inadequate intake, increased metabolic rate and impaired ability to metabolize glucose. Hypocalcemia is total serum Ca levels <7mg/dl although the exact level at which seizure occurs is debatable. Late onset hypocalcemia due to use of high phosphate infant formula has been cited as common cause of seizures.[6],[7]

However. commonly hypocalcemia occurs in infants with trauma, hemolytic disease, asphyxia and IDM and usually coexist with hypoglycemia and hypomagnesemia and presents at 2-3 days of life. Hypomagnesemia with serum <1.5mg/dl can occasionally manifest with tetany and seizures at 2-4 weeks of age and has secondary hypocalcemia associated. Mg depletion is known to predispose to decreased PTH secretion. Hyperphosphatemia may be caused by ingestion of milk formulas containing high amounts of phosphorous, 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 complication of birth asphyxia. Outcome is predicted by the underlying etiology.[8] Patients with hypoxic ischemic encephalopathy (HIE), intraventricular haemorrhage and structural brain malformation have the worst prognosis.[8]while those with transient metabolic abnormalities and benign idiopathic or familial etiologies have the best prognosis.[9] The objectives of the study were to estimate the incidence, etiological factor, time of onset, clinical types and biochemical abnormalities among the different types of neonatal seizures.

METHODOLOGY

The study type was a hospital based prospective observational study and carried out in Neonatal ICU, department of pediatrics, SMIMER during period of Jan 2020 to March 2021.Cases were selected by applying the inclusion and exclusion criteria irrespective of gestational age and gender of the neonates. All intramural babies admitted with clinically identified as seizure before 28 days of life were included. Followings are the exclusion criteria: Uncertain clinical manifestations, seizures more than 28 days of life, Seizure mimics (e.g., jitteriness), Extramural babies. Informed written consent was obtained from the parents of neonates admitted in the NICU. Data collection was done by using a structured case recording form to enter the patient details, detailed clinical history including maternal antenatal history, intrapartum history and baseline characteristics of convulsing neonates. Clinical details of each seizure episode observed by the mother and subsequently observed by the resident doctors recorded. Venous blood collected as soon as possible and blood glucose, total serum calcium, sodium, potassium and phosphate level will be done immediately after the baby has had seizures and before instituting any treatment. Venous blood collected & sent for investigation [blood glucose, serum calcium (Ionized calcium if needed), serum electrolytes, serum magnesium, (serum phosphate if needed); USG skull & neuroimaging if needed]. All treatment protocols were as per standard guidelines. Criteria for diagnosing various biochemical abnormalities:-[10],[11]

Hypoglycemia: <40 mg/dl, Hypocalcemia: <7 mg/dl, Hypomagnesemia: <1.4 mg/dl, Hyponatremia: <135 meq/l, Hypernatremia:>145 meq/l

This study was approved by the institutional ethical committee and Descriptive statistics applied – qualitative data represented by number and percentage.

RESULT

The observational study was conducted during January 2020 to March 2021 in a tertiary health care hospital to study the clinico-etiological profile of neonatal seizures.

INCIDENCE: Total number of livebirths during this study period in our setup was 8107. The **incidence** of neonatal seizures in our study is **11.1/1000** live-births (**1.1%**). Total number of NICU admission was 907 among them 647 were intramural and 260 were extramural neonates. Extramural patients were excluded from my study. Total number of patients which develop neonatal seizures were 90. The proportion of neonatal seizures among NICU admission of inborn patients were 13.9%.

Out of 90 babies of neonatal seizures, 51 (56.67%) were males and 39 (43.33%) were females in the ratio of **1.3:1**, with male preponderance (Table 1).

During the study period, out of 8107 livebirths 90 developed neonatal seizures (11.1/1000 livebirths).

Table 1: - Sex wise distribution of neonatal seizures.

Gender	Cases (n=90) (%)
Male	51 (56.67)
Female	39 (43.33)

Table 2: -Gestational age, Birth weight and Mode of delivery wise distribution of neonatal seizures.

Variables	Livebirths (n= 8107)	Neonatal seizures (n=90) (%)	Incidence
Gestational Age			
Pre-Term	964	47 (52.2)	4.8
Term	6883	40 (44.5)	0.5
Post-term	160	3 (3.3)	1.8
Birth weight			
<2.5 kg	1114	49 (54.4)	4.3
>=2.5 kg	6993	41 (45.6)	0.5
Mode of delivery			
Vaginal delivery	6118	56 (62.2)	0.91
LSCS	1809	32 (35.6)	1.7
Forceps delivery	180	2 (2.2)	1.1

Table 3: -Distribution of neonatal seizures according to Intra-uterine status, time of onset, type of seizure and etiology.

Variables	Cases (n=90) (%)
Intra-uterine status	
SGA	46 (51.11)
AGA	41 (45.56)
LGA	3 (3.33)
Time of onset	
<24 Hrs	30 (33.3)
24-72 Hrs	36 (40)
>72 Hrs	24 (26.7)
Types of neonatal seizures	
Subtle	40 (44.4)
Tonic	35 (38.9)
Focal clonic	10 (11.1)
Multifocal clonic	05 (5.6)
Myoclonic	00 (00)
Etiology of neonatal seizures	
Birth asphyxia	37 (41.1
Hypoglycemia (isolated)	16 (17.8
Neonatal meningitis/Septicemia	13 (14.5
Hypocalcemia (isolated)	11 (12.2
Intracranial haemorrhage (ICH)	7 (7.8
Bilirubin encephalopathy	2 (2.2
Hypoglycemia+Hypocalcemia	1 (1.1
Hypocalcemia+Hypomagnesemia	1 (1.1
Unknown	2 (2.2

It was found that 4.8% of pre-term babies, 0.5% of term babies and 1.8% of post-term babies were having neonatal seizures. Neonatal seizures found to be more prevalent in pre-term babies (Table 2).

In this study out of 90 babies, 49 neonates (54.4%) were of <2.5kg birthweight and 41 (45.6%) were of >=2.5kg birthweight. When compared to overall live births 4.3% of LBW neonates and 0.5% of neonates of birth weight >=2.5kg developed seizures (Table 2).

In this study it was found that out of 90 cases of neonatal seizures, 56 (62.2%) cases of neonatal seizures were of vaginal delivery, 32 (35.6%) cases of neonatal seizures were of LSCS and 2(2.2%) cases were of forceps delivery. The incidence of neonatal seizures according to mode of delivery, in vaginal delivery it was 0.91%, in LSCS it was 1.7% and in forceps delivery incidence was 1.1% (Table 2).

In this study, it was found that out of 90 cases, 46 (51.11%) babies were Small for Gestation Age(SGA), 41 (45.56%) babies were Appropriate for Gestation Age(AGA) and 3 (3.33%) babies were Large for Gestation Age(LGA) which showing that neonatal seizures found to be more prevalent in Small for Gestation Age(SGA) babies (Table 3).

Out of 90 neonates, in 36 (40%) neonates seizure occur between 24-72hrs whereas in 30 (33.3%) neonates seizure occur in <24hrs and in 24 (26.7%) babies seizure occur in >72hrs which shows that most of seizures were observed between 24-72hrs of life (Table 3).

In this study, out of 90 cases, neonates with subtle seizures were 40(44.4%), neonates with tonic seizures were of 35(38.9%), neonates with focal clonic were of 10(11.1%) and the multifocal clonic seizures were of 5(5.6%). This shows that subtle seizures were common followed by tonic seizures and no any case of myoclonic seizure was found in this study (Table 3).

It was found that out of 90 cases of neonatal seizures in this study, 37(41.1%) cases were of birth asphyxia, 16 cases were of isolated cause of hypoglycemia, in addition to this there was 1 case of combined cause of hypoglycemia & hypocalcemia which is taken here as a separate number from isolated cause of hypoglycemia which is 16 in number. Out of 90 cases, 13(14.5%) cases of neonatal meningitis/septicemia, 7(7.8%) cases of ICH, 2(2.2%) cases of bilirubin encephalopathy. There were 11(12.2%) cases of isolated cause of hypocalcemia and in addition to this there was 1 case of combined cause of hypocalcemia & hypomagnesemia which is counted as a separate in number. There were 2 cases of unknown causes of neonatal seizures. (Table 3)

OUTCOME: Out of 90 cases, 28 (31.1%) babies died in our study, and 62 (68.9%) babies were discharged in our study (Table 4).

In this study among babies with biochemical abnormalities, Hypoglycemia (isolated) was noted in 16 babies contributing to about 17.8%, followed by hypocalcemia (isolated) in 12 neonates (12.2%), hyponatremia in 5 neonates (5.5%), hypomagnesemia in 3 neonates (3.3%). Out of 16 cases of hypoglycemia, 10 cases of subtle seizures & 6 cases of tonic seizures. In addition to this there was 1 case of combined cause of hypoglycemia

with hypocalcemia and 1 case of hypocalcemia with hypomagnesemia. There were 5 cases of neonatal seizures showing hyponatremia among them 2 cases of subtle seizures, 2 cases of tonic seizures and 1 case of multifocal clonic seizure. There was 1 case of neonatal seizure showing hypernatremia (Table 5).

Table 4: Outcome of neonatal seizures and number of cases

Outcome	Cases (n=90) (%)
Discharge	62 (68.9
Death	28 (31.1
Total	90 (100

Table 5: Biochemical abnormalities in neonatal seizures

Biochemical parameter	Types of seizures				Total
	Subtle	Tonic	Focal clonic	Multifocal clonic	
Hypoglycemia (isolated cause)	10	6	0	0	16
Hypocalcemia (isolated cause)	5	5	2	0	12
Hypomagnesemia	3	0	0	0	3
Hyponatremia	2	2	0	1	5
Hypernatremia	0	1	0	0	1
Hypoglycemia + Hypocalcemia	0	0	1	0	1
Hypocalcemia + Hypomagnesemia	0	1	0	0	1

DISCUSSION

The incidence of neonatal seizures found in **our study** was 11.1/1000 live births (1.1%) which is like studies conducted by **Ajay Kumar et al [12]** (11.7/1000), **Shah GS et al [13]** (10.3/1000), **Amar et al [14]** (16.6/1000) live births. **Bergman et al [15]** (1983) and **Eriksson et al [16]** (1979) reported incidence rates of seizures range from 1.5 to 5.5 in1000 neonates. **Cloherty et al [17]** stated that in earlier reports, seizures occurred in up to 3 in 1,000 full-term infants and up to 60 in 1,000 premature infants. However, the reported incidence of neonatal seizures varies widely across studies, a variability that is primarily the result of inconsistent diagnostic criteria, as well as the often-subtle clinical manifestations of neonatal seizures, and their potential confusion with non-epileptic neonatal behaviours. It showed preponderance towards male babies of 56.67%, while females contributing with 43.33% with male to female ratio of 1.3:1 in our study. This is comparable to **Shah GS et al** [13], **Ajay et al** [12], **Cockburn et al**, **Fredrichsen et al** and **Mc.Intyre et al** all showed male preponderance. **Sanjeev Kumar digra et al** [18] (Jammu, India) reported male: female ratio of 2.4:1. Out of 90 neonatal seizures, 52.2% were pre-term, 44.5% were term and 3.3% were post-term, which was about 4.8% of all live pre-term and 0.5% of all live term babies and 1.8% of all live post-term babies respectively. This is like **Ajay et al** [12], who reported as incidence in term babies was 0.69% and 6.14% in preterm. **Rennie JM et al** [19], **Bernes and Kaplan** [20] in PCNA (1990) and **Laroia et al** [21] reported varying incidence in term from 0.1 to 0.5% and 10 – 22.7% in preterm which is attributed due to the involvement of multiple factors like maternal medical illness, socio-economic status, health facilities available etc. **Meharban Singh** [22] reported incidence of 0.5% – 0.8% in term babies and 6-12% in babies weighing <1500g.In present study, 54.4% neonates were of <2.5kg birth weight and 45.6% neonates were of >=2.5kg birth weight, which is 4.3% of all LBW babies and 0.5% of babies weighing >=2.5 Kg respectively. **Kumar et al** [12] reported 11.65% in LBW and 0.59% in normal birth weight babies. **Shah GS** [13] reported the incidence of neonatal seizures was 2 times higher in LBW babies. **Lanska et al** (1995) [23] reported seizure occurrence to be greatest in pre-term or LBW babies compared with babies born at term. They found an incidence of seizures in all neonates to be 3.5 in 1000 but 57.5 in 1000 in VLBW (<1500g), 4.4 in 1000 LBW (1500-2499) and 2.8 in 1000 in normal birth weight neonates. Similarly, **Kohelet and colleagues** (2004) found an overall incidence of seizures in a cohort of VLBW infants to be 5.6%. In the present study it was found that more incidence of seizures in LSCS deliveries (1.7%). **Maheswari et al**, [24] AIIMS, New Delhi in her study found that a greater number of babies delivered by forceps develop seizures when compared to normal deliveries. **Pradhan et al**, [25] **Birmingham UK**, reported that vaginal breech and emergency LSCS babies were significantly more likely to have low 5 min Apgar score require admissions in NICU and showed increased susceptibility towards birth trauma, birth asphyxia, neonatal seizures, and death. In this study, 51.1% babies were SGA, 45.5% AGA. The occurrence of neonatal seizures is more in SGA than AGA, which is like **Ajay et al** [12] (52.2%). Though equal number of deaths have occurred in both groups, SGA babies are more likely to go for complications because of underlying metabolic disturbances like hypoglycemia, hypocalcemia, hypothermia etc. Out of 90 cases of neonatal seizures, 33.3% neonates developed seizures in <24hrs, 40% neonates developed seizures in 24-72 hrs and 26.7% neonates developed seizure in >72hrs. **Sanjeev et al [18]** reported seizures occurring more in <24 hrs. However, 73.3% of cases had seizures in <72hrs of life. This is like **Ajay et al** [12] &**Shah GS et al [13]**. Out of 90 cases of neonatal seizures subtle seizures (44.4%) were the commonest of all types followed by tonic seizures (38.9%). **Shah GS et al**,[13] **Mizrahi & Kellaway [26]**, **Scher et al [27]**, **Cloherty [17]** and **Meharban Singh [22]** reporting subtle seizures are the

commonest type accounting for over 50% of seizures. **Ajay et al [12]** reported multifocal seizures as commonest of all types. It was found that out of 90 cases of neonatal seizures in this study, 37(41.1%) cases were of birth asphyxia, 16 cases were of isolated cause of hypoglycemia, in addition to this there was 1 case of combined cause of hypoglycemia & hypocalcemia which is taken here as a separate number from isolated cause of hypoglycemia which is 16 in number. Out of 90 cases, 13(14.5%) cases of neonatal meningitis, 7(7.8%) cases of ICH, 2(2.2%) cases of bilirubin encephalopathy. There were 11(12.2%) cases of isolated cause of hypocalcemia and in addition to this there was 1 case of combined cause of hypocalcemia & hypomagnesemia which is counted as separate in number. There were 2 cases of unknown causes of neonatal seizures. Birth asphyxia (41.1%) was the most common cause of neonatal seizures in the present study, like the studies described below. This is because ours is a tertiary center and cases were referred with improper antenatal care, untreated or partially treated PIH, ante partum haemorrhage, varying presentations of baby, fetal distress with meconium-stained liquor, undue prolongation of stages of labour. Hypoglycemia (17.8%) and hypocalcemia (12.2%) were the metabolic disturbances observed in our study, which is similar to **Shah GS et al [13]**, **Ajay et al [12]**, **Bergmen I et al** [15] and **Westerlaine [27].** In this study, out of 90 cases, 28 (31.1%) babies died in our study, which is like **Shah GS et al** [13] who reported 15% in his study. **Ajay et al [12]** reported 10% deaths, **Tinuadeogunlesi et al [28]** reported 43.6% and **Andre M et al [29]** reported 22% mortality. **Harris et al [30]** in Australian pediatric journal 1998 reported mortality to be around 31% and stated that the leading risk factors were prematurity, LBW and severe birth asphyxia.

In this study among babies with biochemical abnormalities, Hypoglycemia (isolated) was noted in 16 babies contributing to about 17.8%, followed by hypocalcemia (isolated) in 12 neonates (12.2%), hyponatremia in 5 neonates (5.5%), hypomagnesemia in 3 neonates (3.3%). In addition to this there was 1 case of combined cause of hypoglycemia with hypocalcemia and 1 case of hypocalcemia with hypomagnesemia. In a study by **Sood et al** [31] on 59 neonates, hypoglycemia was found in 48.27%, hypocalcemia in 48.27%, hyponatremia in 17.25%, hypomagnesemia in 17.24%. In a study of **Kumar et al** [12] on 35 neonates, hypoglycemia was found in 50(31.8%) cases, hypocalcemia was found in 7 (31.8%) cases, hyponatremia was found in 10 (45.5%) cases and hypomagnesemia was found in 1 (13.63%) case.

CONCLUSION

The Incidence of neonatal seizures was 11.1/1000 live births (1.1%). Neonatal seizures were more common in preterm, LBW. Also higher among those delivered by LSCS deliveries. Birth asphyxia was the most common cause of all neonatal seizures followed by hypoglycemia. Subtle seizures were the most common type of seizure observed followed by tonic. Subtle seizures were more common in 24-72 hours of life. Most common biochemical abnormality found in neonatal seizures is hypoglycemia followed by hypocalcemia.

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