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Clinico-etiological profile of neonatal seizures and factors determining outcome in a tertiary referral center of North India

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ABSTRACT

Background: Neonatal seizures continue to contribute significantly to neonatal mortality and morbidity in terms of sequelae and cerebral palsy. **Aims and Objectives:** The objectives of the study were as follows: Study of clinical and etiological profiles of neonates. To study the time of onset of seizures and its relation to etiology and to observe short-term outcomes related to various factors associated with neonatal seizures. **Materials and Methods:** The study was done to study etiology, onset, type of seizures, and factors determining outcome in a tertiary medical college hospital. It was a prospective observational study enrolling 135 neonates with seizures. History, time of onset, number, type of seizures, examination, and relevant laboratory investigation were documented. Treatment and outcome were documented and analyzed to determine the predictors of outcome. **Results:** One hundred thirty-five neonates were studied. Neonates were predominantly male (57.7%), term (82.9%), and more than 1.5 kg (93.9%) born by vaginal route (71.8%). Generalized tonic seizures were predominantly seen in 48.14% followed by subtle type (27.40%) and focal tonic type (20.0%). Seizures caused by hypoxic-ischemic encephalopathy (HIE) (45.18%), meningitis (22.96%), metabolic (hypoglycemia [15.55%] and hypocalcemia [6.66%]). HIE, hypoglycemia, intraventricular hemorrhage (IVH), and malformations presented early on day 1 and had a poor prognosis. Meningitis and hypocalcemia presented on day 3–day 7. Metabolic causes had a good prognosis. Multiple (>5) seizures had a poor prognosis. **Conclusion:** Neonatal seizures had a mortality of 22.9% with HIE having the worst and hypocalcemia best prognosis. Targeted interventions to reduce mortality and morbidity are the need of the hour.

Key words: Hypoxic-ischemic encephalopathy; Neonatal seizures; Meningitis; Morbidity; Mortality

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INTRODUCTION

Seizures are the most common and distinct manifestation of underlying neurological pathological condition in a newborn. The incidence of neonatal seizures is approximately 1.5–3.7/1000 live births in term babies and 6–12% in babies weighing <1500 g.[1] As the immature brain is less capable of propagating organized electrical discharges, the clinical presentation of neonatal seizures differs from that of adults. In newborns, due to brain immaturity, there is a depolarizing rather than hyperpolarizing effect of gamma-aminobutyric acid which makes it more at risk to seizures as compared to older brains.

There is a strong association of neonatal seizures with low gestational age and low birth weight. Birth asphyxia and cerebral edema are important risk factors leading to the death of newborns with neonatal seizures.[2] The mortality rate can go as high as up to 27% commonly in neonates with hypoxic ischemic encephalopathy (HIE).[3] In addition

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neonatal seizures have also been associated with other permanent neurological diseases such as mental retardation and cerebral palsy.

Considering the above information, the study of etiology, onset, and clinical manifestations of neonatal seizures has a significant role in the management of neonatal seizures for a favorable outcome.

Aims and objectives

- Study of clinical profile of neonatal seizures.
- Study of etiology of neonatal seizures and observe short term outcome of seizures.

MATERIALS AND METHODS

This was a prospective observational hospital-based study done in our hospital over a period of 18-month duration from September 2022 to March 2024.

All consecutive patients admitted to the sick newborn care unit fulfilling the inclusion criteria were enrolled with written and informed consent.

Institutional ethical clearance was taken before the study and informed consent was obtained from the attendants of all the neonates. (664/GMC/IEC/2022/Reg no. 662/IEC/R-November 20, 2022 dated January 11, 2023).

Definitions used for the purpose are

Inborn if delivered in the medical college hospital and Outborn if delivered outside the medical college or at home.

HIE: This refers to the objective proof that hypoxia and ischemia are causing clinical characteristics of encephalopathy that were previously defined.[4]

Hypoglycemia was diagnosed if Random Blood Sugar (RBS) is <40 mg/dL.[5]

Hypocalcemia was diagnosed if serum calcium level is <8.0 mg/dL.[6]

Hyponatremia was diagnosed if serum sodium level is <130 mEq/L and hypernatremia if serum sodium is >145 mEq/L.[7]

Intraventricular Hemorrhage – Diagnosed on cranial ultrasonography.

Meningitis – A cerebrospinal fluid (CSF) white blood cell count of 20 cells/mm^3 (both term and preterm) and CSF protein level of 170 mg/dL (in preterm) and 120 mg/dL (in term).[8]

Sample size 135

Prevalence of reference study 8.89 % (Sau et al.)[9]

The sample size (n) is calculated according to the formula: $n=z^2\times P\times (1–P)/e^2$

Where: z-1.96 for a confidence level (α) of 95%, P-proportion (expressed as a decimal), e-margin of error.

z-1.96, P-0.0889, e-0.05

$n=1.962\times0.0889\times(1–0.0889)/0.0025$

$n=0.0311/0.0025–124$

n=124

Non-response rate-10%

Final sample size-135

One hundred thirty-five neonates presenting with seizures were included in this study with written and informed consent taken from the parents. Infants with age more than 28 days, seizure-like activity like jitteriness, tetanic spasm, or subtle seizures without apnea or autonomic symptoms were excluded from the study. A detailed history and examination were done. Laboratory investigation pertaining to the common causes such as RBS, electrolyte, and lumbar puncture was done. Computed tomography and Magnetic resonance imaging where indicated were done and noted in performa. Treatment was done as per standard protocol. Seizure type, etiology, number of anticonvulsant therapy, and outcome were duly documented.

RESULTS

Table 1 shows demographic data of the study population Seizure profile. It shows that in the study population of 135 neonates outborn (n=86) were more than inborn (n=49), male outnumbered female by ratio 1.4:1. The neonate delivered vaginally was significantly more than delivered by lower segment C-section (LSCS).

Table 2 shows type of seizure in neonates in the present study. The most common type of seizure in neonate was the generalized tonic type in both preterm and term neonate followed by subtle seizures in full term followed by focal tonic type in preterm neonates.

Table 3 shows etiology of neonatal seizure with HIE being the most common cause followed by meningitis and hypoglycemia. Congenital malformations, TORCH group of infections, and IVH were seen in a small percentage.

Table 4 shows etiology of seizure according to day of seizure with HIE, hypoglycemia, hypocalcemia congenital malformation, and torch manifesting on day 1 of life. The cause of seizure on days 3–7 and later was predominantly hypocalcemia and meningitis.

Table 5 shows that HIE and meningitis have adverse outcomes in spite of treatment. Congenital malformation and torch infection presenting early also have adverse outcomes. Metabolic causes such as hypoglycemia and hypocalcemia have good outcome.

Table 6 shows the outcome of neonatal seizure based on the type of seizure with maximum mortality seen in generalized type of seizure. Good outcomes were seen in cases of subtle seizure.

Table 7 Mortality was seen more in case of multiple episodes (>5) of convulsion indicating more brain insult with each episode of convulsion and poor outcome.

DISCUSSION

This study was conducted at the sick neonatal care unit of our hospital.

One hundred thirty-five neonates presenting with neonatal seizures were enrolled, and proper history examination investigation, imaging was done and treatment given according to standard protocol.

The present study demonstrates the incidence of neonatal seizures in male (57.7%) more than females (42.2%) with

Table 1: Demographic profile on neonatal seizure

Parameter			P-value
Status of baby	Outborn 63.7%	Inborn 36.2%	0.002
Gender	Male 57.7% (n=78)	Female 42.2% (57)	0.085
Period of gestation	Preterm 17.03% (n=23)	Term 82.9% (n=112)	0.001
Birth weight	<1.5 kg=5.9% n=8)	>1.5 kg=93.9% (127)	0.001
Mode of delivery	@LSCS 28.1% (n=38)	Nvd 71.8% (n=97)	0.001

@LSCS: Lower segment c-section, @Nvd: Normal vaginal delivery

Table 2: Distribution for type of seizure

Type of seizure	Pre-Term (n)	Term (n)	Frequency (overall)	Percent	P-value
Generalized tonic	13	52	65	48.1	<0.001
Subtle	4	33	37	27.4	<0.001
Focal tonic	6	21	27	20.0	<0.001
Focal clonic	0	5	5	3.7	0.691
Myoclonic	0	1	1	0.74	0.016
Total	23	112	135	100.00	

Table 3: Distribution for cause

Cause	Frequency	Percent
HIE@	61	45.18
Meningitis	31	22.96
Hypoglycemia	21	15.55
Hypocalcemia	9	6.66
IVH#	1	0.74
TORCH * infection	1	0.74
Congenital malformation	1	0.74
Others	10	7.40
Total	135	100.000

@HIE: Hypoxic ischemic encephalopathy, #IVH: Intraventricular hemorrhage, *TORCH: Toxoplasmosis, others, rubella, cytomegalovirus, herpes simplex virus

Table 4: Etiology according to day of seizure

Cause	Day 1	Day 2	Day 3-7	Day >7	Total	P-value
Congenital malformation	1	0	0	0	1	<0.001
HIE@	49	4	7	1	61	
Hypoglycemia	6	3	0	0	9	
Hypocalcemia	14	1	5	1	21	
IVH#	0	0	0	1	1	
Meningitis	6	1	8	16	31	
others	8	0	1	1	10	
Torch infection*	1	0	0	0	1	
Total	85	9	21	20	135	

@HIE: Hypoxic ischemic encephalopathy #IVH: Intraventricular hemorrhage *TORCH: Toxoplasmosis, others, rubella, cytomegalovirus, herpes simplex virus

Table 5: Outcome as per etiology

Outcome	Death	Discharge	LAMA	P-value
Congenital Malformation	1 (3.22)	0 (0.00)	0 (0.00)	0.003
HIE@	23 (74.19)	33 (36.26)	5 (38.46)	
Hypocalcemia	0 (0.00)	9 (9.89)	0 (0.00)	
Hypoglycemia	2 (6.45)	14 (15.38)	5 (38.46)	
IVH#	0 (0.00)	1 (1.09)	0 (0.00)	
Meningitis	4 (12.9)	24 (26.37)	3 (23.07)	
Others	0 (0.00)	10 (10.9)	0 (0.00)	
TORCH infection*@	1 (3.22)	0 (0.00)	0 (0.00)	
Total	31 (100)	91 (100)	13 (100)	

@HIE: Hypoxic ischemic encephalopathy, #IVH: Intraventricular hemorrhage, *TORCH: Toxoplasmosis, others, rubella, cytomegalovirus, herpes simplex virus

Table 6: Outcome as per seizure type

Type of seizure	Death	Discharge	LAMA	P-value
Focal clonic	0	5	0	<0.001
Focal tonic	0	20	7	
Generalized tonic	30	30	5	
Myoclonic	1	0	0	
Subtle	0	36	1	

Table 7: Outcome according to no of episodes

Outcome	Death (%)	Discharge (%)	LAMA (%)	P-value
1–2	4 (12.9)	43 (47.2)	1 (7.6)	<0.001
2–3	1 (3.2)	7 (7.6)	3 (23)	
3–4	1 (3.2)	10 (10.9)	0 (0.0)	
4–5	1 (3.2)	6 (6.5)	4 (30.7)	
Multiple	24 (77.4)	25 (27.4)	5 (38.4)	
Total	31	91	13	

no statistical significance on gender in relation to neonatal seizure. Similar results were also demonstrated in other studies also such as Nemati et al., Nawab and Lakshmipathy et al., Garg et al., Sau et al., Shah et al., Verma et al., Bari et al.[9-15] All studies showed the prevalence of male more than female.

Other demographic parameters such as, period of gestation showed that term (82.9%) and AGA (weight more than 2.5 kg) were 52.5%, were more affected than preterm (17.03%) and low birth weight babies (47.32%). Similar study results were also shown by Nemati et al., Sau et al., Nawab and Lakshmipathy et al., Tekgul et al., Verma et al.,[9-11,14,16] showing the predominance of neonatal convulsion in term babies. Other studies conducted by Shah et al., Kumar et al., and Kuldeep et al.,[13,17,18] showed the contrary finding suggestive of more rates of convulsion in low-birth-weight babies compared to normal birth weight babies.

In the present study, seizures were predominantly seen in normal vaginal delivery (71.85%) than LSCS (28.14%) with a statistically significant P value (0.001). Similar findings were seen in the study by Reddy et al.[19] This result underscores the importance of good antenatal monitoring, timely referral of high-risk pregnancies, and timely intervention if mortality and incidence of perinatal asphyxia is to be reduced.

Our study documents the distribution of various seizure types which showcased that generalized tonic types predominate (48.14%), followed by subtle seizure (27.40%) and focal tonic (20.0%). Myoclonic seizures were the least common type of seizure. Similar results were also seen in studies conducted by Garg et al.[12] Contradictory results were seen in the case of studies conducted by Bari et al., Verma et al., and Sau et al., [9,14,15] showcasing the predominant subtype being subtle seizure.

Among the etiological factors predisposing to neonatal seizure HIE was the most important culprit striking at 44.18%, followed by meningitis/sepsis in 22.96% and hypoglycemia in 15.55%. Other less prevalent causes seen were hypocalcemia, IVH, TORCH group of infection, and congenital malformation. Similar results were seen in studies conducted by Nemati et al., Garg et al., Verma et al., and Kumar et al.[10,12,14,17] All these studies concluded HIE as the predominant factor responsible for neonatal seizures.

HIE was responsible for seizures within 24 h of life and the majority of seizures seen in 1st day of life were generalized tonic type.

Limitations of the study

EEG or aEEG was not available at our center. Some rare causes of inborn error of metabolism could not be tested due to resource limitation.

CONCLUSION

HIE contributes to 37.7% of neonatal mortality. Seizure type, early onset (within 24 h), and multiple seizure episodes are key prognostic factors for morbidity and long-term effects. Meningitis and hypoglycemia are preventable causes of neonatal seizures, requiring prompt diagnosis and management. Congenital malformations and TORCH infections can lead to fatal outcomes if they occur in the early neonatal period. High mortality rates highlight the need for better antenatal monitoring, timely delivery, and potential use of therapeutic hypothermia to reduce long-term neurological sequelae and improve outcomes.

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PS- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **RR**- Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **BD**- Design of study, statistical analysis, and interpretation; **AK**- Coordination and manuscript revision.

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