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Original Research Article

Study of etiological factors and immediate outcomes of neonatal seizure among preterm and term neonate in a tertiary health centre of Northern India

Surbhi Yadav[1]*, Payal Agrawal[1], Vinod K. Sharma[2], Rekha[2], Sunder Lal Yadav[3]

[1]Department of Pediatrics, SGT Medical College Hospital and Research Institute, Budhera, Gurugram, Haryana, India
[2]Department of Pediatrics, Deen Dayal Upadhyay Hospital, Hari Nagar, New Delhi, India
[3]Medical Officer, Kanina, Haryana, India

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***Correspondence:**
Dr. Surbhi Yadav,
E-mail: surbhiyadav838@gmail.com

ABSTRACT

Background: Neonatal seizures result due to altered neurological functions like motor, behavioural and autonomic function. We conducted this study to assess the incidence, etiological factors, and immediate outcomes of neonatal seizures in term and preterm neonates.
Methods: This prospective observational study included all neonates delivered in a tertiary health centre of New Delhi from Nov 2015 to Oct 2016 and admitted in Neonatal Intensive Care Unit with clinically identified seizures up to 28 days of postnatal age.
Results: Out of 11,109 live births during the study period, 302 developed neonatal seizures with overall incidence of 2.71%. The early preterm (12.05%), very low birth weight babies (56.30%), and neonates in first 24 hrs of life (68.9%) had the highest incidence of neonatal seizures. The commonest seizure type was subtle seizures (52.3%). In early preterm commonest etiology was infection (31.3%) while in late preterm and term neonates most common etiology was Hypoxic ischaemic encephalopathy 59% and 72% respectively. Overall, HIE was the most common etiology (57%). Out of 302 cases, 81 (26.8%) cases have died. HIE was found to be the most common cause for mortality. Mortality was highest in early preterms (49.3%) and very low birth weight neonates (52.3%). Also, mortality was maximum among neonates having subtle seizures (29.1%) and seizures occurring within 24 hrs of life (30.8%).
Conclusions: Persistently high incidence of neonatal seizures requires further strengthening of antenatal, natal, and post-natal health services. Early identification of neonatal seizures and timely intervention are very important for better outcomes.

Keywords: Neonatal seizures, Incidence, Neonate, Term preterm, Etiology, Subtle, Hypoxic ischaemic encephalopathy

INTRODUCTION

Neonatal seizures result due to altered neurological functions like motor, behavioural and autonomic function and can affect neonate of any gestational age.[1,2] Enhanced excitability and low levels of inhibitory neurotransmitters (Gamma-amino butyric acid: GABA) makes the immature central nervous system susceptible for seizures.[3] Unlike seizures in children or adults, generalized tonic-clonic convulsions do not occur in neonatal period due to incomplete myelination and arborization of axons and dendritic processes.[4] The incidence of seizures varies

depending on the case definition, method of ascertainment, and definition of the neonatal period.[5] The incidence of neonatal seizures varies from 1.1 to 8.5 per 1000 live births. The wide range is because of variable incidence in different gestational ages, where preterm and very low birth weight neonates have the highest incidence. It may affect up-to 3.4% of neonates getting admitted in neonatal intensive care unit.[6]

Focal or multifocal, clonic, tonic, myoclonic, and subtle seizures are commonly seen in neonates with subtle seizure being the most common presentation.[7] The primary cause of neonatal seizures is Hypoxic-Ischemic Encephalopathy (HIE), which accounts for approximately 50% of cases, followed by metabolic abnormalities, infection, intracranial hemorrhage, developmental anomalies, and inborn errors of metabolism.[8-10] The latter being rare but their detection permits specific treatment (if available) and genetic counselling. Etiology of seizure depends on gestational age of the neonate. HIE is the most common cause in term neonates while intracranial hemorrhage and infections are more common in preterm neonates.[11] Electroencephalograph (EEG) is an important tool and can be used for detection as well as diagnosis of neonatal seizures, also it gives an estimate of perinatal brain damage. The variability of normal maturation of brain can influence its interpretation, also the restricted availability of equipment are its limitations.[12] The risk of mortality and associated morbidities like developmental delay, focal neurological deficits, and cognitive impairment, makes this clinical entity a matter of concern for clinicians. Early detection and timely intervention can reduce the morbidity profile.[12] This study was conducted to determine the incidence rate, etiology, and short-term outcome of clinically recognizable neonatal seizures.

METHODS

This prospective observational study was conducted at the department of pediatrics, Deen Dayal Upadhyay Hospital, New Delhi, over the course of one year, from November 2015 to October 2016, following approval from the institutional ethical committee and written consent from parents/guardians. The study included all neonates delivered in our hospital and admitted to the Neonatal Intensive Care Unit (NICU) with clinically identified seizures up to 28 days of postnatal age, excluding preterm neonates less than 28 weeks of gestational age, neonates with obvious congenital malformations, and those whose parents did not give consent.

A detailed history of the seizure episode including its onset, duration, type, number, and antenatal, natal, and postnatal risk factors were obtained for each case, followed by detailed clinical examination. Essential laboratory investigations were conducted, such as blood gas, blood glucose, serum calcium, sodium, magnesium, sepsis screen, serum bilirubin levels, serum urea and creatinine, blood culture, and CSF examination were done as required. Additional investigations included TORCH serology, serum parathyroid hormone, and metabolic profile for inborn errors of metabolism. Radiological investigations (chest X-ray, cranial ultrasonography, computed tomography, and magnetic resonance imaging of the brain) and EEG were performed if necessary. All the neonates were managed as per the standard treatment protocols.

Statistical analysis

Statistical analysis was conducted using SPSS 20.0 system version. The qualitative parameters were compared using the chi-square test/ Fisher's exact test, whichever is applicable, p value less than 0.05 was considered significant.

RESULTS

Out of 11,109 livebirths during the study period, 302 developed neonatal seizures. The incidence of neonatal seizures was found to be 2.71% in our hospital. However, the incidence in preterms was 5 times more (8.70%) than term (1.66%) and incidence in early preterms was 7 times more (12.05%) than term (1.66%) as shown in (Table 1).

Table 1: Incidence of neonatal seizures according to gestational age.

Gestational age (weeks)		No. of Neonates Delivered	No. of NDS*	Incidence of NDS (%)
Term (≥ 37)		9443	157	1.66%
Preterm (≤ 37)		1666	145	8.70%
Preterm	<34 (Early preterm)	556	67	12.05%
	34-36.6 (Late preterm)	1110	78	7.02%
Total		11,109	302	2.71%

*Neonates Developed Seizures- NDS

Neonatal seizures were found to be more common in male neonates (57%) and in low birthweight babies (56.30%). Un-booked cases (86.4%) and neonates delivered by normal vaginal delivery (NVD) (57.9%) were more affected. Seizures were more common in first 24 hrs of life (68.9%) and subtle seizures were found to be the most common type of seizures (52.3%) as shown in table 2. Out of 302 cases, 152 (50.4%) cases had associated maternal factors while 150 cases (49.60%) had no associated maternal factors. Amongst them pregnancy induced hypertension (PIH) was the most common (19.8%) followed by premature rupture of membrane (PROM) (16.5%) as depicted in (Table 2).

Hypoxic ischaemic encephalopathy (HIE) was found to be the most common etiological factor (57%) followed by infection (18.5%) (sepsis 9.6% and meningitis 8.9%),

metabolic causes (14.9%) and intra-cranial haemorrhage as depicted in table 3 and (Figure 1).

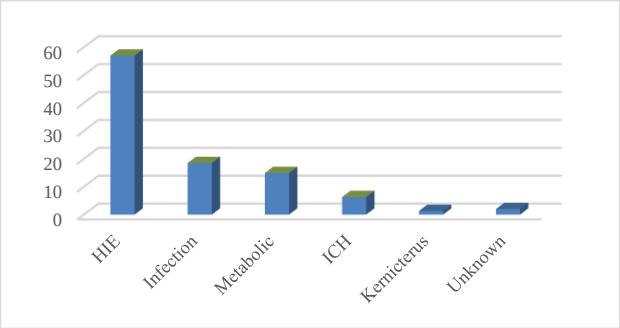

Figure 1: Distribution of neonates as per etiology.

As per the gestational age, most common etiology in early preterm neonates was infection (31.3%) while in late preterm and term neonates, the most common etiology was HIE 59% and 72 % respectively.

Table 2: Neonatal characteristics (n=302).

Neonatal characteristics		N	%
Gender	Male	172	57.0
	Female	130	43.0
Birth Weight (Grams)	<1.5	65	21.5
	1.5-2.499	105	34.8
	>2.5	132	43.7
Ante natal registration	Booked	41	13.6
	Un-booked	261	86.4
Mode of Delivery	LSCS	127	42.05
	NVD	175	57.9
Onset of Seizures according to age (Hrs)	0-24	208	68.9
	25-48	42	13.9
	49-72	25	8.3
	>72	27	8.9
Type of seizure	Subtle	158	52.3
	Clonic	104	34.4
	Tonic	38	12.6
	Myoclonic	2	0.7
Maternal risk factors	PIH	60	19.8
	PROM	50	16.5
	Placenta previa	14	4.63
	Multiple pregnancy	12	3.97
	Oligo-hydramnios	6	1.98
	Chronic maternal diseases	6	1.98
	GDM	4	1.32

HIE was found to be the most common cause of seizures among all weight groups. Outcomes of study showed that out of 302 cases, 81 (26.8%) cases were died and 221 (73.20%) were discharged. The most common cause of mortality was HIE while no mortality was noted in metabolic disturbances and kernicterus as shown in (Table 4).

Table 3: Distribution of neonates as per etiology (n=302).

Etiology	N	%
HIE (Hypoxic ischaemic encephalopathy)	172	57
Sepsis	29	9.6
Meningitis	27	8.9
Hypoglycemia	26	8.6
Hypocalcemia	19	6.3
ICH (Intra-cranial haemorrhage)	19	6.3
Kernicterus	4	1.3
Unknown	6	2
Total	302	100

The association of gestational age (GA), birth weight and outcome with etiology came out to be statistically significant with p value of 0.001. Comparison of mortality with other parameters showed that mortality was highest in early preterms (49.3%) and very low birth weight babies (52.3%). Also, mortality was more in babies in whom 1st seizure developed within 24 hrs of age (30.8%) and in neonates with subtle seizures than clonic, tonic, and myoclonic seizures as shown in (Table 5).

DISCUSSION

A seizure is defined as a paroxysmal involuntary disturbance of brain function. The various presentations of neonatal seizures are impairment in consciousness, abnormal motor, or behavioural activity, and sensory or autonomic disturbances.[1] Neonatal seizures can adversely affect neurodevelopment and may result in cognitive, behavioural, and epileptic complications in later life. As this could be the sole presentation of underlying CNS disorder, early recognition is very important.

In our study the overall incidence of neonatal seizures was 2.7% which is lower than the studies done by Sabzehei et al and Sahana et al while higher than the study done by Venkatesh et al which can be due to tertiary care status of our hospital where high risk and complicated deliveries are referred and most of them are un-booked deliveries (86.4%).[1,4,8,13] The incidence of neonatal seizures was 1.6 % in term neonates and 8.70% in preterm, among preterm neonates early preterm had 12.05% and late preterm had 7.02%. So total preterm (early and late) had a higher (5 times) incidence than term and among preterm early preterm had a higher incidence. These findings are consistent with other studies done by Tekgul et al and Kumar et al.[14,15] The overall incidence of prematurity in the current study was 15%. Preterm babies may have multifactorial etiology for neonatal seizures. Low birth weight, maternal illnesses, and metabolic causes could be the contributing factors. We found male predominance in our study which is consistent with other studies, we do not have any plausible mechanism behind that.

Table 4: Association of gestational age (GA), birth weight and outcome with etiology.

Variable		Cause of neonatal seizures (Etiology), N (%)						Total no. of neonates
		HIE	Infection	Metabolic	ICH	Kernicterus	Unknown	
GA (weeks)	28-33.6	13 (19.4)	21 (31.3)	15 (22.4)	17 (25.4)	01 (1.5)	00 (0.0)	67
	34-36.6	46 (59.0)	18 (23.1)	12 (15.4)	01 (1.3)	01 (1.3)	00 (0.0)	78
	>37	113 (72)	17 (10.8)	18 (11.5)	01 (0.6)	02 (1.3)	06 (3.8)	157
Birth weight	<1.5	24 (36.9)	19 (29.2)	11 (16.9)	09 (13.8)	01 (1.53)	01 (1.53)	65
	1.5-2.499	54 (51.4)	22 (20.9)	19 (18.0)	09 (8.5)	01 (0.95)	00 (0.0)	105
	>2.5	94 (71.2)	15 (11.3)	15 (11.3)	01 (0.75)	02 (1.51)	05 (3.7)	132
Outcome	Discharge	114 (51.6)	44 (19.9)	45 (20.4)	08 (3.6)	04 (1.8)	06 (2.7)	221
	Expired	58 (71.6)	12 (14.8)	00 (0.0)	11 (13.6)	00 (0.0)	00 (0.0)	81

Table 5: Relationship of outcome of neonatal seizures with GA, birth weight, age at onset of seizures and type of seizures.

Variable		Outcome N (%)		Total	P value
		Discharge	Expired		
GA (weeks)	28-33.6	34 (50.7)	33 (49.3)	67	0.001
	34-36.6	60 (76.9)	18 (23.1)	78	
	>37	127 (80.9)	30 (19.1)	157	
Birth weight	<1.5	31 (47.7)	34 (52.3)	65	0.001
	1.5-2.499	79 (75.2)	26 (24.8)	105	
	>2.5	111 (84.1)	21 (15.9)	132	
Onset of Seizure	0-24	144 (69.2)	64 (30.8)	208	0.001
	25-48	33 (78.6)	09 (21.4)	42	
	49-72	20 (80)	05 (20.0)	25	
	>72	24 (88.9)	03 (11.1)	27	
Type of Seizure	Clonic	76 (73.1)	28 (26.9)	104	0.001
	Myoclonic	02 (100)	00 (0.0)	02	
	Subtle	112 (70.9)	46 (29.1)	158	
	Tonic	31 (81.6)	07 (18.4)	38	

Neonatal seizures were more common in low birthweight babies (56.30%) as compared to normal birthweight babies (43.70%) which is comparable with the study conducted by Shah et al.[4,13,16,17] Low birth weight has many predisposing common factors for neonatal seizures namely maternal illnesses, neonatal infections, decreased metabolic stores, etc. We found seizures were more common in vaginally delivered babies. It may be assumed that vaginal delivery if difficult may cause asphyxia and subsequent complications and asphyxia remained the leading cause of seizures in our study. Most of the cases i.e., 82.8% had seizures during the first 48 hrs of life which is like the previous studies.[13,16,18] The most common seizure type was subtle (52.3%), this is consistence with the Chesti et al study.[16] Many underlying maternal risk factors have been described as important predisposing factors for neonatal seizures. Out of 302 cases, 152 (50.4%) cases had associated maternal factors, amongst which PIH was the major cause found in 19.8% of cases followed by PROM in 16.50%. The association of maternal factors with neonatal seizures was comparatively higher than the other studies, this could be because o the fact that most of the neonates who had seizures were delivered through un-booked pregnancies (85.6%) and our hospital is a tertiary care one and many high-risk delivery cases were being referred to the institute for the further management.[19,20] The overall most common etiology of neonatal seizure was HIE (57%) and second most common was infection (18.5%) and the least one was kernicterus (1.3%). Various studies reported the percentage of HIE varies from 38% to 66% which is similar to the present study.[13,18] In early preterms, infection (31.3%) and ICH (25.4%) were found to be common causes while in late preterms and terms, HIE and metabolic disturbances were more common. Previous studies show that the most common cause of seizures in preterm was ICH followed

by infections.[21,22] This difference in result may be because of the tertiary care status of our hospital, also our hospital serves mainly the lower socio-economic urban population. The high incidence of un-booked deliveries and high incidence of risk factors for neonatal sepsis in mothers belonging to poor socio-economic status are contributory. In all these studies HIE was the most common cause in late preterm and term neonates, like the present study. Out of 302 neonates, 81 (26.8%) expired and 221 (73.17%) were discharged which is comparable with the study done by Chesti et al and Singh et al.[16,18] However, mortality was higher than that reported in Tekgul et al (7%).[14] This may be due to the higher rate of un-booked deliveries as our hospital is a tertiary level health care referral centre with a large number of high-risk and complicated deliveries. The most common cause of death found was HIE, followed by Infections then ICH, there was no mortality in metabolic disturbances and kernicterus. Mortality was highest in early preterms and very low birth weight babies. In a previous study neonatal mortality was greatest in the infants of youngest gestational age with neonatal seizures. According to Holden et al neonatal mortality was 67% in <1500 gm birthweight babies.[19-24] Mortality was more in babies in whom 1st seizure developed within 24 hrs of age which is comparable with the study done by Holden KR et al.[24] Mortality was highest in subtle seizures and least in myoclonic. This is quite comparable with the Yin-Hsuan Lai et al study.[25]

Limitations

The major limitation of our study was short study duration because it is difficult to ascertain the causal relationship between etiological factors and the outcome. Also, long-term prognosis cannot be defined by our study, hence further long-term follow-up study is recommended.

CONCLUSION

Although there have been significant advancements in delivery services and neonatal care, there is still a lack of adequate perinatal care accessible to all communities. This deficiency in comprehensive care has resulted in a consistently high incidence of prematurity and related complications such as infections and ICH. Additionally, unattended antenatal periods can lead to unplanned, complicated deliveries, particularly in term neonates, which contribute to high rates of perinatal asphyxia, early and late neonatal sepsis, and intra-uterine growth retardation. Consequently, the prevalence of neonatal seizures is also high. Prompt recognition and management of neonatal seizures and their underlying causes can minimize neonatal morbidity and mortality. There is a need for further strengthening of antenatal, perinatal, and neonatal health facilities to ensure a better future.

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