

# Clinical Profile and Short-Term Outcome of Neonatal Seizures in a Tertiary Care Hospital, Kuppam – A Retrospective Study

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## ABSTRACT

### BACKGROUND

Neonates presenting with seizures require long term stay in hospital and have higher chances of neuro-developmental delay later. Seizures in neonates are mostly subtle and difficult to diagnose. We wanted to study the clinical profile and short-term outcome on term and later pre-term neonates presenting with seizures.

### METHODS

The study was a retrospective observational study done from November to December 2020 at PES Hospital, Kuppam. Retrospective data of neonatal seizures from May 2019 to April 2020 was considered for study. Details from the case records of neonates with seizures was collected.

### RESULTS

Neonatal seizures (NS) were most common in females (53.8 %, 72/134). Subtle seizures were most common form of seizures in neonates which was seen in 64.2 % (86/134) babies followed by tonic seizures in 22.4 % (30/134). Neonatal seizures were most commonly seen in babies with hypoxic ischemic encephalopathy in 63.4 % (85/134) followed by metabolic disturbances in 15.6 % (21/134) and meningitis in 13.5 % (18/134). In babies with hypoxic ischemic encephalopathy, metabolic and meningitis subtle seizures were observed to be more common. Seizures were seen most commonly in first 72 hours of life (82.85 %, 111/134). Seizures in babies with hypoxic ischemic encephalopathy, metabolic causes most commonly occurred within first 24 hours of birth. Seizures in babies with meningitis most commonly occurred after 7 days of birth. Babies with neonatal seizures with sequelae was seen in 17.96 % (24/134) and 11.94 % babies died (16/134).

### CONCLUSIONS

Subtle seizures were most common form and hypoxic ischemic encephalopathy was most common risk factor. Most neonatal seizures present within 72 hours of birth. Babies with meningitis presented with seizures most commonly after 72 hours of birth.

### KEYWORDS

Hypoxic Ischemic Encephalopathy, Neonatal Seizures, Newborn, Aetiology, Outcome

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**BACKGROUND**

Neonatal seizure (NS) is defined as a paroxysmal alteration in neurological function i.e. motor, behaviour and/or autonomic function in infants aged less than 4 weeks.<sup>1</sup> The incidence of neonatal seizures in India is about 10.3 per 1000 live births.<sup>2</sup> Seizures in newborn period differ from older children. It is difficult to recognize seizures in newborn period. The most common form is subtle.<sup>3</sup> Seizures are a frequent manifestation of neurologic disorders in neonates and are associated with high morbidity and mortality.<sup>4</sup> About 80 - 85 % of neonatal seizures are symptomatic and rest is idiopathic.<sup>5</sup> Amongst disorders of the central nervous system (CNS). Hypoxic ischemic encephalopathy accounted for 1.4 %, seizures 1.0 % and intraventricular haemorrhage 0.3 %.<sup>2</sup>

Common causes of neonatal seizures include hypoxic-ischemic encephalopathy (HIE), intracranial haemorrhage, meningitis, hypoglycaemia, hypocalcaemia, congenital malformation etc. Neonatal seizure carries a high risk of mortality, neurological impairment and epilepsy disorders in later life.<sup>1,4,6</sup> Mortality from neonatal seizures has decreased considerably from 40 % to about 20 % over the years. The long-term neurodevelopment problem hasn't changed much and is around 30 %.<sup>7</sup>

The incidence of seizures is about 1 to 3.5 per 1000 live births in neonatal period, but its incidence in neonatal intensive care unit (NICU) is as high as 10 - 25 %, where 15 % ones die and 35 - 40 % of them have prominent neurological disability.<sup>8,9</sup>

Hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures amounting to about 50 %.<sup>10</sup> Common metabolic disorders were hypomagnesaemia, hypernatremia, hyponatremia, hypocalcaemia and hypoglycemia.<sup>11</sup> Other causes comprise of central nervous system malformations, intracranial haemorrhage, birth trauma, intracranial infections, drug withdrawal and metabolic disorders. The less frequent metabolic disorder is inborn error of metabolism (IEM).<sup>12,13</sup> Prolong nothing per oral or fasting may lead to metabolic abnormalities. Exact mechanism of seizures is not known in hypomagnesaemia, hypoglycaemia and hypocalcaemia. Proper fluid and electrolyte management can decrease these abnormalities of metabolic disturbance and the occurrence of seizures can decrease.<sup>12</sup>

Neonatal seizure is an emergency. Early diagnosis and treatment is necessary because any delayed treatment modality results in a long-term disability and unfortunate neurological outcome. Recent studies on animal model indicated that the neonate's CNS, to some extent, could be resistant to long-lasting seizures whereas the frequent short-term seizures could have long-term disability and detrimental effect in these patients.<sup>14-16</sup> Birth weight, Apgar score at 1st minute, neurologic examination, electroencephalography, ultrasound brain scans and the presence of neonatal status epilepticus were different between preterm newborns with favourable and adverse outcome.<sup>15</sup>

The present study was conducted to determine clinical profile and short-term outcome of neonates presenting with seizure.

**METHODS**

This study was a retrospective observational study done at Neonatal Intensive Care Unit (NICU) of PES Institute of Medical Sciences and Research, Kuppam, Andhra Pradesh. Retrospective data of neonates with seizures after meeting the inclusion and exclusion criteria for 12 months from May 2019 to April 2020 was taken after obtaining ethical committee approval (Certificate no: PESIMSR / IHEC / C-66/2020) from November 2020 to December 2020. The case records of neonates with seizures were assessed. Ethical committee approval was obtained from the institutional ethical committee before starting the study.

Late pre-term and term neonates presenting with seizure within 28 days of life were included in the study. Neonates with seizure mimics such as jitteriness, tetanic spasms, complex congenital malformations and syndromic features were excluded from the study. Neonates with isolated brain malformations were included in the study.

**Data Collection**

Details such as sex, gestational age, mode of delivery, birth weight were noted. The type of seizure was noted. They were classified as subtle, tonic, clonic and myoclonic. Investigation details such as serum glucose, calcium, magnesium, electrolytes, blood gas analysis were noted. The diagnosis of hypoxic ischemic encephalopathy (HIE) was made based on clinical details, arterial blood gas and neuroimaging (if available). Metabolic disturbances such as hypocalcaemia, hypoglycaemia, hyponatremia and hypernatremia were noted. Diagnosis of meningitis was based on clinical features, cerebrospinal fluid (CSF) cell count or culture. Presence of intracranial haemorrhage and brain malformations were noted. The duration of onset of seizures were noted. Short term outcome till discharge or death was noted. The short-term outcome noted were death, alive without sequelae or alive with sequelae.

**Statistical Analysis**

The results were entered in Microsoft excel sheet. The descriptive categorical data and variable data was analysed using percentage.

**RESULTS**

Late pre-term and term neonates with seizures included in the study were 134. Among these 46.2 % (n - 62 out of 134) were male and 53.8 % (n - 72 out of 134) were females). Late pre-term were 28.3 % (n - 38) and term neonates with seizure were 71.7 % (n - 96). Babies born by normal vaginal delivery were 56.8 % (n - 76) and by caesarean section were 43.2 % (n - 58). Babies with birth weight < 2500 grams (gms) were 14.9 % (n - 20/134), 2500 to 4000 gms were 78.4 % (n - 105) and > 4000 gms were 6.7 % (n - 9).

Subtle seizures were the most common form of seizures found in 64.2 % of total cases followed by tonic seizures in

22.4 %, clonic seizures in 11.9 % and myoclonic seizures in 1.5 % as shown in Table 1. The most common aetiology of seizure in neonates in our study was HIE in 63.4 % (85/134) followed by metabolic disturbances in 15.6 % (21/134) and meningitis in 13.5 % (18/134) in decreasing order of frequency (Table 2). Among the 85 HIE or perinatal asphyxia, 70 patients developed seizure within 24 hours after birth and 15 developed seizures after 24 hours. Majority patients with meningitis developed seizures after 72 hours of life (Table 2). In this study, majority of neonates presented with seizures within first 24 hours after birth (Table 3). In outcome of babies with neonatal seizures, 11.94 % (16/134) babies died in this study. Alive with no sequelae was seen in 70.1 % (94/134) and alive with sequelae was seen in 17.96 % (24/134).

Type of Seizure	Total Cases (N = 134)	Gestational Age	
		Late Preterm (n = 38)	Term (n = 96)
Subtle	86 (64.2 %)	29 (33.7 %)	57 (66.3 %)
Tonic	30 (22.4 %)	5 (16.67 %)	25 (83.33 %)
Clonic	16 (11.9 %)	4 (25 %)	12 (75 %)
Myoclonic	2 (1.5 %)	0 (0 %)	2 (100 %)

**Table 1. Type of Clinical Seizure in Babies with Neonatal Seizures (N = 134)**

Diagnosis	Total Cases (N = 134)	Type of Seizure	Seizure Onset
HIE	85 (63.4 %)	Subtle - 62	< 12 hrs - 34 (40 %)
		Clonic - 16	12 - 24 hrs - 36 (42.35 %)
		Tonic - 7	24 - 72 hrs - 14 (16.47 %)
		Myoclonic - 1	72 hrs - 7 days - 1 (1.18 %)
			7 - 30 days - 0 (0 %)
Metabolic disturbances	21 (15.6 %)	Subtle - 10	< 12 hrs - 8 (38.1 %)
		Clonic - 7	12 - 24 hrs - 10 (47.62 %)
		Tonic - 4	24 - 72 hrs - 3 (14.29 %)
		Myoclonic - 0	72 hrs - 7 days - 0 (0 %)
			7 - 30 days - 0 (0 %)
Meningitis	18 (13.5 %)	Subtle - 10	< 12 hrs - 0 (0 %)
		Clonic - 2	12 - 24 hrs - 0 (0 %)
		Tonic - 4	24 - 72 hrs - 0 (0 %)
		Myoclonic - 1	72 hrs - 7 days - 5 (27.78 %)
			7 - 30 days - 13 (72.22 %)
ICH (Intra cranial haemorrhage)	6 (4.5 %)	Subtle - 2	< 12 hrs - 0 (0 %)
		Clonic - 3	12 - 24 hrs - 2 (33.33 %)
		Tonic - 2	24 - 72 hrs - 2 (33.33 %)
		Myoclonic - 0	72 hrs - 7 days - 1 (16.67 %)
			7 - 30 days - 1 (16.67 %)
Brain malformations	2 (1.49 %)	Subtle - 1	< 12 hrs - 1 (50 %)
		Clonic - 1	12 - 24 hrs - 1 (50 %)
		Tonic - 0	24 - 72 hrs - 0 (0 %)
		Myoclonic - 0	72 hrs - 7 days - 0 (0 %)
			7 - 30 days - 0 (0 %)
Others	2 (1.49 %)	Subtle - 1	< 12 hrs - 0 (0 %)
		Clonic - 1	12 - 24 hrs - 0 (0 %)
		Tonic - 0	24 - 72 hrs - 0 (0 %)
		Myoclonic - 0	72 hrs - 7 days - 1 (50 %)
			7 - 30 days - 1 (50 %)

**Table 2. Aetiological Profile in Neonates with Seizure (N = 134)**

Hours (hrs)	Total No. (N = 134)	Late Pre-term	Term
< 12 hrs	43 (32.1 %)	11 (25.58 %)	32 (74.41 %)
12 - 24 hrs	49 (36.57 %)	12 (24.49 %)	37 (75.51 %)
24 - 72 hrs	19 (14.18 %)	5 (26.32 %)	14 (73.68 %)
72 hrs - 7 days	8 (5.97 %)	3 (37.5 %)	5 (62.5 %)
7 days - 30 days	15 (11.19 %)	7 (46.67 %)	8 (53.33 %)
<b>Total</b>	<b>134</b>	<b>38 (28.35 %)</b>	<b>96 (71.64 %)</b>

**Table 3. Onset of Seizures in Neonates with Seizure (N = 134)**

## DISCUSSION

The incidence of neonatal seizures in our study was 11.5 % (134/1162) for late pre-term and term neonates. The incidence of neonatal seizures was 18.6 % for term neonates

in study done by Chandan et al.<sup>1</sup> In study done by Srijana et al. the incidence was 12.26 % which is similar to our study.<sup>17</sup> The incidence in established intensive care units can be as high as 25 %.<sup>18</sup>

Neonatal seizures were slightly higher 53.8 % in females than males 46.2 % in our study. The seizures were more common in males (63.36 %) in study done by Srijana et al.<sup>17</sup> Male neonates with seizures were 30 % and female were 70 % in study done by Agarwal et al.<sup>19</sup>

Neonatal seizures were seen most common in full term babies 71.7 % (n = 96) in our study compared to late pre-term which was 28.3 % (n = 38). This was comparable to study done by Srijana et al. where seizures in full term babies were seen in 85.47 %.<sup>17</sup>

Majority on neonates with seizures in our study were born by vaginal route 56.8 % (n = 76) and by caesarean section was 43.2 % (n = 58). Agarwal et al. study shows that majority of newborns with seizures were delivered by vaginal delivery 86 % and remaining cases were delivered by caesarean section (14 %).<sup>19</sup> Srijana et al. study shows majority babies having neonatal seizures were delivered by vaginal route 62.39 %, which is similar to our study.<sup>17</sup>

Most neonates with seizures in our study were in birth weight group of 2.5 to 4 kilograms (kg) range (78.4 %, n = 105), 14.9 % (n = 20) in < 2.5 kg group and 6.7 % (n = 9) > 4.0 kg group. In Agarwal et al. study, 8 % were of birth weight 2499 - 1500 grams (gm) and remaining 92 % above 2499 gm (normal birth weight, overweight).<sup>19</sup>

Subtle seizures were the most common form of neonatal seizures found in 64.2 % (n = 86) in our study. Least common was myoclonic seizures 1.5 % (n = 2). In study done by Agarwal et al. most common type of neonatal seizure was subtle seizure (75.1 %). The other types are tonic seizure (17.3 %), clonic seizure (5.1 %), myoclonic seizure (2.5 %) which is comparable to our study.<sup>19</sup> According to John H. Menkes and Harvey B. Sarnat, subtle seizure were the most common (71 %) of seizures seen in term infant, and 68 % of seizures seen in preterm infants. According to Joseph J. Volpe in one study of infants more than 36 weeks of gestation subtle seizure was seen in 85 % and in another study subtle seizure account for 70 % to 75 % of all clinical seizure. Above studies shows that range of subtle seizure cases varies 68 - 85 %.<sup>20,21</sup> In study done by Abhishek et al. the most common type of seizure was subtle seizures 37.2 %, followed by focal clonic seizures 20.2 %, multifocal clonic seizures 15.9 % and myoclonic seizure 14.9 %.<sup>1</sup>

Majority of seizures occurred within the first 24 hours after birth in this study (32.1 % in < 12 hrs, 36.57 % in 12 to 24 hours). In 11.19 %, seizures occur after 7 days (Table 3). In study done by Abhishek et al. 28.7 % babies had neonatal seizures before 12 hours of life, 24.5 % between 12 hours to 24 hours of life, 12.8 % between 24 hours to 72 hours of life and 34 % after 72 hours of life.<sup>1</sup> Overall 66 % of neonates had seizures before 72 hours of age and the rest 34 % were reported after 72 hours of age.<sup>1</sup> In our study 82.85 % babies had seizures within 72 hours after birth and 11.19 % after 72 hours of birth. In study done by Agarwal et al. majority of neonates had seizures onset < 72 hours i.e., 53 % and remaining neonates had seizures onset > 72

hours i.e. 47 %.<sup>19</sup> Lanska et al. shows 82.8 % of neonatal seizures occur within first week, 91.4 % within first 2 weeks and 96.6 % within 3 weeks.<sup>22</sup> The onset of neonatal seizures mostly occurs within first 72 hours of life in studies done by Abhishek et al. Srijana et al. and Agarwal et al. which matches our study.<sup>1,17,19</sup>

Most common aetiology of seizures in neonates in our study was HIE in 63.4 % n - (85). It was followed by metabolic disturbances in 15.6 % (n - 21) and meningitis in 13.5 % (n - 18). Intra cranial haemorrhage was the cause in 4.5 % (n - 6). Subtle seizures were most common in neonates having HIE or metabolic disturbances or meningitis in our study. Neonates with HIE presented with seizures mostly within the first 24 hours of life. In all babies with above mentioned causes seizures occurred mostly within 72 hours of birth in our study (table 2). Neonates with meningitis most commonly had seizures after 72 hours of life in our study (table 2). Neonatal seizures due to hypocalcaemia and hypoglycaemia was seen in 6.72 %, hyponatremia in 1.49 % and hypernatremia in 0.75 % in our study. Birth asphyxia or HIE is most common cause of neonatal seizures in various studies.<sup>1,16,17,19,22</sup> In study done by Abhishek et al. perinatal asphyxia/HIE was the commonest risk factor for neonatal seizure (46.9 %). Second to HIE was septicaemia-meningitis (32.1 %). Other causes were hypocalcaemia (13.6 %), hypoglycaemia (11.1 %), hyponatremia (7.4 %). Hyperbilirubinemia with kernicterus was seen in 2.5 %.<sup>1</sup> Most common cause of neonatal seizures in full term neonates was birth asphyxia (77.17 %), followed by meningitis (8.70 %), hypoglycaemia 7.61 %, hypocalcaemia 3 %, intra cranial haemorrhage 2.17 % in Agarwal study.<sup>19</sup>

According to Volpe JJ (2008) HIE usually secondary to perinatal asphyxia, is the single most common cause of neonatal seizures in both full-term and preterm infants.<sup>21</sup> According to Bradley WG, Daroff RB, Fenichel GM and Jankovic J most common cause of neonatal seizure in both full term and preterm is HIE.<sup>23</sup> In a study done by Sahana et al. 57.80 % had perinatal asphyxia/HIE as the most common aetiology of neonatal seizure and second major common aetiology was infection in 14.67 %.<sup>24</sup> Shah et al. showed that the major aetiology of seizures were birth asphyxia in 44 %, septicaemia in 11 %, meningitis in 11 %, hypocalcaemia in 11 % and hypoglycaemia 22 %.<sup>25</sup>

Alive with no sequelae was seen in 70.1 % (n - 94), alive with sequelae was seen in 17.96 % (n - 24) and death in 11.94 % (n - 16) in our study. In study done by Glass HC et al. during the neonatal admission, 17 % of babies died and 49 % of survivors had abnormal neurologic examination at hospital discharge.<sup>4</sup>

Data from these 7 centers following American clinical neurophysiology society (ACNS) guidelines add to the literature that supports the ACNS recommendations to monitor at-risk neonates with conventional video-EEG for at least 24 hours of continuous monitoring to identify subclinical seizures and confirm electrographic correlates of paroxysmal events which is not available in most centers in India.<sup>4</sup> Greater seizure burden is associated with mortality, longer length of hospital stay, abnormal neurologic examination at the time of hospital discharge which is

independent of seizure aetiology and preterm birth. This shows the importance of detecting and characterizing neonatal seizures and the potential for improving outcome with better seizure control. Neonatal seizures are associated with a high need for specialized neurologic care, because more than one-half of subjects had  $\geq 7$  seizures that were refractory to initial loading doses of anti-seizure medication, received  $\geq 2$  anti-seizure medications. These babies were either deceased or had an abnormal neurologic examination at the time of discharge.<sup>4</sup>

In study done by Nawab T et al. on 110 neonates, birth asphyxia or hypoxic ischemic encephalopathy was the commonest cause of neonatal seizures in 66 (60 %) of the cases. This was followed by neonatal sepsis and metabolic disorders. Primary metabolic abnormalities were seen in 13 (11.8 %) cases of neonatal seizures, most common being hypoglycaemia 9 (69.3 %) followed by hypocalcaemia. Associated biochemical abnormalities were seen in 33 (30 %) cases with hyponatremia 13 (39.3 %) being most common followed by hypoglycaemia. These were most often seen with hypoxic ischemic encephalopathy.<sup>26</sup> In study done by Amudevi et al. onset of seizures in the first two days of life was seen in 62 (59.6 %) neonates, 3 - 4 days of life in 16 (15.4 %) neonates and 5 - 6 days of life 13 (12.5 %) developed convulsions. From 7 - 28 days of life 13 (12.5 %) neonates developed convulsions. Birth asphyxia or HIE was the commonest cause of neonatal convulsions in 67 (64.4 %) babies and 21 (20.2 %) neonates had central nervous system infection. Also, 10 (9.6 %) neonates had hypoglycaemia and 1 (1 %) baby had benign idiopathic neonatal seizures (BINS).<sup>27</sup> In the same study, 3 (2.9 %) of babies had convulsions due to hypocalcaemia and 2 (1.9 %) had convulsions due to intra ventricular haemorrhage (IVH). About 22 (21.2 %) neonates had mixed aetiology. Out of these, 13 (59.1 %) had birth asphyxia associated with hypoglycaemia and 9 (40.9 %) had birth asphyxia associated with hypocalcaemia.

In this study, 10 neonates had hypoglycaemic seizures, of these, 4 (40 %) had subtle, 4 (40 %) had multifocal, 1 (10 %) had focal and 1 (10 %) had generalized tonic seizures. In neonates with hypocalcaemia convulsions, 2 (66.7 %) babies had generalized tonic seizures, and 1 (33.3 %) baby had subtle seizures. In neonates with intra ventricular haemorrhage, both 2 (100 %) babies had multifocal seizures. Multiple causes for convulsions were noted in babies of birth asphyxia and septicaemia.

Out of 67 cases of birth asphyxia, 13 (19.4 %) had hypoglycaemia and 9 (13.4 %) had hypocalcaemia. Among babies of central nervous system infections 4 (19 %) cases had hypoglycaemia. Out of the 110 babies with moderate birth asphyxia, 53 (48.2 %) had convulsions and out of the 6 babies with severe birth asphyxia, 4 (66.7 %) had convulsions. Out of 397 total babies with birth asphyxia, 67 (16.8 %) had convulsions.<sup>27</sup>

The abnormal ultra sound findings were cerebral oedema, hydrocephalus and IVH. Out of the 104 cases, electro encephalography (EEG) was done for 72 cases which showed abnormal findings in about 18 (17.3 %) of cases. Abnormal EEG findings seen were slow waves, spike waves, ictal discharges and basal rhythm abnormalities. Out of 104

cases, computed tomography (CT) scan was done in 88 cases. Abnormal CT scan findings included cerebral oedema, hydrocephalus and intra ventricular haemorrhage.

In a case of intrauterine infection with cytomegalovirus peri ventricular calcification with hydrocephalus was seen.<sup>27</sup> In 104 neonates with seizures, 4 babies died with a mortality rate of 3.8 %. Out of these 4 deaths, 2 (50 %) neonates died due to severe birth asphyxia and 2 (50 %) babies died due to central nervous system infection. All deaths due to birth asphyxia were seen within 48 hours of life and deaths due to CNS Infection were seen after 7 days of life.<sup>27</sup> Study done by Nair BK et al. in 75 neonates admitted with neonatal seizure, 49 (65.33 %) were male and 26 (34.60 %) were female. Majority (52, 69.93 %) were term babies.

Subtle seizures (39.13 %) were most common in both pre-term babies (39.13 %) and term (53.85 %) babies. Age of onset was < 24 hours of life in 53.33 % of the babies. Hypoxic-ischemic encephalopathy (HIE) was the most common cause (52 %) of neonatal seizure.<sup>28</sup> Seizures in neonates are different from those seen in older children. These 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 these reasons, clinical presentation differs in neonates.<sup>28,29</sup>

## CONCLUSIONS

Most neonates with seizure presented within the first 72 hours of life. HIE was the most common cause of seizure overall and presented within first 24 hours of life. In neonates with meningitis seizures was common after 72 hours of life. Subtle seizures were the commonest seizure type observed.

## Limitation of the Study

Neonatal seizures are often subclinical, an EEG recording of electrographic seizures is crucial for estimation of true seizure burden which is not available in our setup. Long term follow-up was not done in this study.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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