ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 8, Issue – 6, November – 2023 , Page No. : 102 – 108

Neurodevelopmental Outcome of Neonatal Seizure during Infancy

[1]Dr Sohrab Shakeel, Ex Resident Doctor Deen Dayal Upadhyay Hospital Hari Nagar, New Delhi

[2]Dr Rekha, Aassociates Professor Deen Dayal Upadhyay Hospital Hari Nagar New Delhi

Corresponding Author: Dr Sohrab Shakeel, Ex Resident Doctor Deen Dayal Upadhyay Hospital Hari Nagar, New Delhi

Citation this Article: Dr Sohrab Shakeel, Dr Rekha, "Neurodevelopmental Outcome of Neonatal Seizure during Infancy", IJMSIR- November - 2023, Vol – 8, Issue - 6, P. No. 102 – 108.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Newborn with neonatal seizures is at risk of neurodevelopmental delay. The present study was undertaken to evaluate the neurodevelopmental outcome of neonatal seizures among term neonates during infancy and access relationship with age at onset of seizure, type of seizures and etiology till one year of age.

Method: A total of 140 babies who had clinical seizure within 28 days of life and were admitted in the Neonatal unit of DDU Hospital, New Delhi during the study period from Aug 2016 to Jan 2018 was enrolled. Among them, 37 did not come for follow up so were excluded from study. So, 103 terms newborn were analyzed only by clinical neurodevelopmental examination on at discharge, 1,3,6,9 and 12 months of follow up.

Results: Out of 103 babies, 58(56.31%) were male and 45(43.69%) were female. In 52.42% baby's 1st seizure developed within 24 hours of life. Most common seizure was subtle (66.99%) and most common etiology was perinatal asphyxia (45.63%). Persistent seizure was found in 10(28.57%) babies, microcephaly in 1(2.8%), developmental delay in 18(51.42%), hearing defect in 2(5.7%) and persistent seizures with developmental delay found in 4(11.4%) babies. The abnormal outcome was found in 30% and 35% babies at 1st month and after 12 months of follow up respectively.

Conclusion: The abnormal outcome was more in babies with early onset of seizure and with tonic seizures. Babies with ICH and kernicterus had poor neurodevelopmental outcome. Mortality was more if seizures occurred within 24 hours of life.

Keywords: Neonate, Seizures, Neurodevelopmental, Etiology, Asphyxia, Microcephaly, Kernicterus, Mortality.

Introduction

Neonatal seizure is the commonest neurological dysfunction in the neonatal period and can occur at any gestational age [1]. Estimate of the incidence of neonatal seizure vary according to case definition, method of ascertainment and definition of the neonatal period, and range from 0.95 to 3.5 per 1000 live births [2]. 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 amino butyric acid (GABA) [3]. Neonatal seizures are dissimilar to those in a child or adult because generalized tonic-clonic convulsion doesn't occur during the first month of life that is due to the

arborization of axons and dendritic processes as well as myelination is incomplete [4].

The most common seizures type in neonatal are focal or multifocal clonic, tonic, myoclonic, and Subtle [5], the subtle seizures comprise a variety of motor and autonomic phenomena [6]. The major causes of neonatal seizures are Hypoxic-Ischemic Encephalopathy (HIE), which represents about 50% of the causes of neonatal seizures followed by cerebral malformations and metabolic disturbances, Intrauterine infection caused by cytomegalovirus is the most common of the intrauterine infections that affect the central nervous system leading to brain atrophy with sever neurological sequelae [7].

The recurring question uppermost in both parents and pediatrician's mind is what will be the long-term neurological outcome in a baby with neonatal seizures. For many decades, it has been clear that the etiology of neonatal seizures is one factor critical in determining outcome. Newborns with transient correctible metabolic abnormalities, focal ischemia and without clear etiology do well, while those with HIE, CNS infections and cerebral dysgenesis regularly do poorly [8]. In India, where perinatal care is uneven, transient metabolic disturbances like hypocalcemia and hypoglycemia still account for about a fifth of the neonatal morbidity [9]. Also, the outcome of hypoglycemia is not necessarily favorable [10, 11]. Neonates with seizures are at risk of death, whereas survivors are at risk of neurological sequelae, developmental delay, later epilepsy and cognitive impairment so, we need to initiate an early diagnostic work up to determine the causes, depending upon the facilities available, Mortality following seizures has improved in the last decade especially in full term babies, but the prevalence of adverse neurodevelopmental sequelae remains relatively stable [12]. Therefore, the present study is proposed to evaluate the neuro developmental outcome of these newborns till one year of age.

Materials and Methods

This prospective, hospital based, observational study was carried out in new born babies who had clinical seizure within 28 days of life and were admitted in the Neonatal unit of Deen Dayal Upadhyay Hospital, New Delhi during the period from Aug 2016 to Jan 2018 after getting written informed consent from parents/guardians. Neonates with obvious congenital malformation, preterm newborn (<37wk), neonates whose parents did not give consent, post term new born (>42wk) were excluded from the study.

A detailed history in all cases was taken with emphasis on the onset of first seizure, number of seizures, type of seizure, antenatal, natal and post-natal risk factors. The detailed were entered on case report form (proforma). Patients were followed in High-Risk Clinic for clinical examination and neurodevelopmental assessment at 1, 3, 6, 9 and 12 months of age. The patients with developmental delay were assessed and referred to CDC (child development clinic) center for management. For the determination of etiology, relevant clinical information included maternal history (hypertension, diabetes, chronic disease etc), antenatal history (1st trimester history of rash, fever, lymphadenopathy etc. suggestive of TORCH infection, 3rd trimester history of maternal fever, urinary tract infection etc), drug intake during pregnancy (morphine, pethidine, antiepileptic drug etc), pregnancy induced hypertension (PIH) or gestational diabetes, peripartum and neonatal history were recorded. Essential investigations such as blood glucose, serum calcium, sodium, urea and creatinine and serum bilirubin levels, Hb TLC, DLC, PS for band cells, CRP (C-Reactive Protein), ultrasonography (USG) of cranium, electroencephalography (EEG), ABG (arterial

blood gas) / VBG(venous blood gas), blood culture and CSF examination were done in all case. (CSF examination was done only when the neonates have clinically abnormal finding biochemistry, microscopy and culture). If required Additional investigations like CXR (chest x-ray), serum magnesium, metabolic screening for inborn error of metabolism, TORCH titre as well as Radiology (CT- Scan Brain, MRI Brain) were done.

Statistical Analysis

Statistical testing was conducted with the statistical package for the social science system version SPSS 20.0. Continuous variables were presented as mean ± SD. Categorical variables were expressed as frequencies and percentages. Nominal categorical data between the groups was compared using Chi-squared test or Fisher's exact test as appropriate. The comparison of normally distributed continuous variables between the groups were performed using Student's t test for all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Observations and Results

During the study period of one and half years from Aug 2016 to Jan 2018, total 140 babies with seizure were enrolled, among them 37 babies did not come for follow up so were excluded from study. Thus, the data 103 term newborn with seizures were analyzed only by clinical neurodevelopmental examination on at discharge, 1,3,6,9 and 12 months of follow up.

Out of 103 babies, 58 were male (56.31%) and 45 were female (43.69%). Most of the babies (52.42%) developed 1st seizure at the age of <24 hours of life followed by >72 hours of life (30.09%). Most common seizure was subtle (66.99%) and most common etiology was perinatal asphyxia (45.63%), (Table 1).

Table 1: Distribution of neonates according to age at first seizure, type of seizures and etiology (N=103)

Onset of seizure	No. of babies	Percentage
<24hrs	54	52.42%
24-48hrs	8	7.76%
48-72hrs	10	9.7%
>72hrs	31	30.09%
Type of seizure	No. of babies	Percentage
Subtle	69	66.99%
Clonic	28	27.18%
Tonic	6	5.82%
Myoclonic	0	0
Etiology	No. of babies	Percentage
Perinatal asphyxia (HIE)	47	45.63%
Meningitis	17	16.5%
Hypocalcemia	15	14.5%
Hypoglycemia	9	8.73%
ICH	7	6.79%
Kernicterus	1	0.97%
Unknown etiology	7	6.97%

Outcome

On clinical examination at the time of discharge, out of 103 babies, 66 (64.07%) were clinically normal and 30 babies (29.12%) were abnormal. The mortality occurred in 7 babies (7%). On 12 months of follow up weight, length and head circumference of each baby were measured and clinical neurodevelopmental assessment was done as Per porforma, out of 96 babies 61(63.54%) babies were normal and 35 (36.45%) babies were abnormal. Out of 35 babies, persistent seizure was found in 9 (25.12%) babies, microcephaly was found in 2 (5.7%) baby, developmental delay was found in 20 (57.14%) babies, hearing defect was found in 2 (5.7%)

babies and persistent seizure with developmental delay were found in 2 (5.7%) babies.

Table 2 show the relationship of outcome with age at onset of seizure, type of seizures and etiology till one year of age. Among survivors, abnormal outcome was found in 30% and 35% babies at 1 month and after 12 months of follow up respectively.

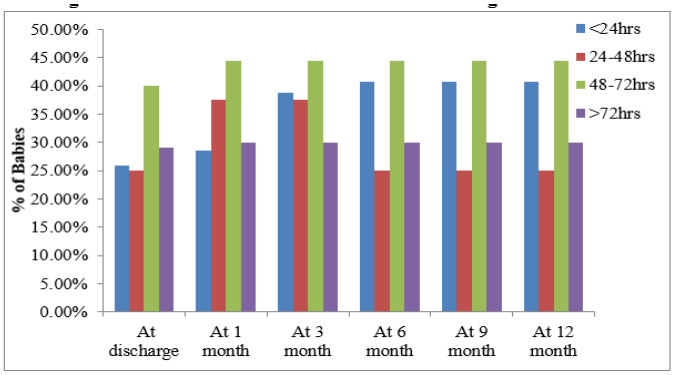
Table 2: Relationship of outcome with age at onset of seizure, type of seizures and etiology till one year of age

Onset of Seizure	At time of discharge			1 Month		3 Months		At 6, 9 and 12 Months	
	Nor. N (%)	Abn. N (%)	Exp. N (%)	Nor. N (%)	Abn. N (%)	Nor. N (%)	Abn. N (%)	Nor. N (%)	Abn. N (%)
0-24hrs	35 (64.8)	14(25.9)	5(9.25)	35 (71.4)	14 (28.5)	30(61.2)	19(38.7)	29(63)	20(40.8)
24-48hrs	6 (75)	2(25)	0(0.0)	5 (62.5)	3(37.5)	5(62.5)	3(37.5)	6(75)	2(25)
48-72hrs	5(50)	4(40)	1(10)	5 (55.6)	4(44.4)	5(55.6)	4(44.4)	5(55.6)	4(44.4)
>72hrs	21(67.7)	9(29)	1(3.2)	21 (70)	9(30)	21(70)	9(30)	21(70)	9(30)
P value	0.647			0.837		0.756		0.545	
Seizure type	Nor. N (%)	Abn. N (%)	Exp. N (%)	Nor. N (%)	Abn. N (%)	Nor. N (%)	Abn. N (%)	Nor. N (%)	Abn. N (%)
Clonic (25)	19(67.8)	6(21.4)	3(10.7)	18(72)	7(28)	17(68)	8(32)	17(68)	8(32)
Subtle (66)	46(66.6)	20(28.9)	3(4.35)	46(69.6)	20(30.3)	43(66.5)	23(34.8)	43(66.5)	23(34.8)
Tonic (5)	2(33.3)	3(50)	1(16.6)	2(40)	3(60)	1(20)	4(80)	1(20)	4 (80)
P value	0.211			0.372		0.123		0.123	
Etiology	Nor. N (%)	Abn. N (%)	Exp. N (%)	Nor. N (%)	Abn. N (%)	Nor. N (%)	Abn. N (%)	Nor. N (%)	Abn. N (%)
HIE	29(61.1)	12(25.5)	6(12.7)	28(68.3)	13(31.7)	23(56.09)	18 (43.9)	23(56.09)	18 (43.9)
Hypocalcemia	15(100)	0(0.0)	0(0.0)	15 (100)	0(0.0)	15 (100)	0(0.0)	15 (100)	0(0.0)
Hypoglycemia	8(88.9)	1(11.1)	0(0.0)	8 (88.9)	1(11.9)	8 (88.9)	1 (11.1)	8 (88.9)	1 (11.1)
ICH	0(0.0)	6(85.7)	1(14.3)	0(0.0)	6 (100)	0(0.0)	6 (100)	0(0.0)	6 (100)
Kernicterus	0(0.0)	1(100)	0(0.0)	0(0.0)	1 (100)	0(0.0)	1 (100)	0(0.0)	1 (100)
Meningitis	11(64.7)	6(35.3)	0(0.0)	11(64.7)	6 (35.3)	11(64.7)	6 (35.3)	11(64.7)	6 (35.3)
Unknown	4(57.3)	3(42.9)	0(0.0)	4 (57.1)	3 (42.9)	4 (57.1)	3 (42.9)	4 (57.1)	3 (42.9)
P Value	0.001			<0.001		<0.001		<0.001	

Nor- Normal, Abn. - Abnormal, Exp. – Expired, N- No. of patients

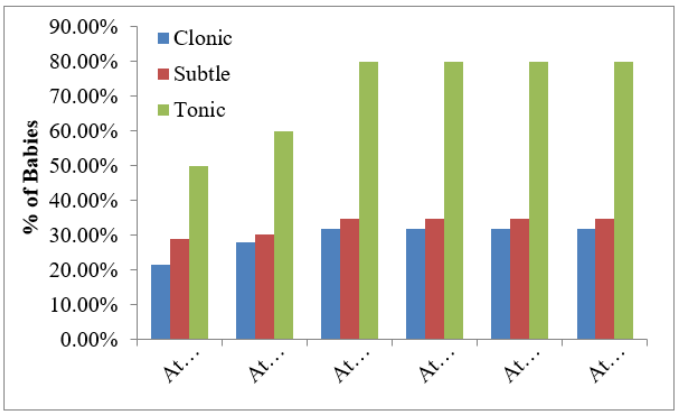
Abnormal outcome was more in babies whom 1st seizure developed within 24 hours of age and least in babies in whom 1st seizure developed at 48-72 hours of age than >72 hours of age as shown in figure 1.

Figure 1: distribution of abnormal outcome with age at 1st seizure



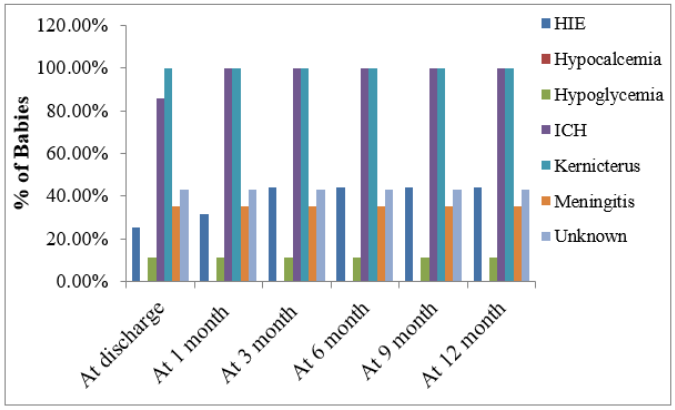
Abnormal outcome was highest in babies with tonic seizure and least with clonic seizure as depicted in figure 2.

Figure 2: Distribution of abnormal outcome with seizure type



All babies of ICH and kernicterus were abnormal while no abnormality found was hypocalcemia babies as shown in figure 3.

Figure 3: Distribution of abnormal outcome with seizure etiology



Discussion

Seizures are still the most important clinical manifestation of neurological disorders in the neonatal period [13]. In the present study total 103 neonates presented with seizures were analyzed, of them 58(56.31%) were male and 45(43.69%) were females with male to female ratio of 1.28:1. Thus, male preponderance was seen which is consistent with other studies [14, 15]. Neonates were more affected with subtle seizures (66.99%). However subtle seizures pattern reported more common in some studies like Kolkar et al [14] and Scher et al [16]. Overall, 60% cases had seizures during first 48 hours of life. Perinatal asphyxia, in this study, in agreement with other series, was the most frequently etiology related to neonatal seizures [4, 13, and 17].

Overall, 29.12% cases had developmental delay with mortality in 7% and lost to follow up in 26.42% cases. The reported rate of mortality in the literature is 9-15% [18]. The mortality was 9.25% in babies in which 1st seizure occur within 24 hours of life, 10% in which 1st seizure occur in 48-72 hours of life and 3.2% in which 1st seizure occur >3 days of life. The mortality was 4.34% with subtle seizures, 10.7% in babies with clonic seizure and 16.7% in babies with tonic seizures. These findings are in accordance with the study conducted by Bergman et al [19]. Mortality was 12.76% in babies in whom cause of seizure was perinatal asphyxia and 14.3% in whom cause of seizure was ICH which is comparable with the study done by Bergman et al [20]. In other cause of seizures, no mortality occurred.

The abnormal outcome was found in 28.98% babies with subtle seizure, at the time of discharge while among survivors, it was found in 30.30% at 1 month follow up, 34.84% at 3, 6, 9 and 12 month follow up. In babies with clonic seizures abnormal outcome was found in 21.42% at time of discharge whereas among survivors, it was found in 28% babies at 1 month follow up, 32% at 3, 6, 9 and 12 month follow up. In babies with tonic seizures abnormal outcome was found in 50% babies at time of discharge, 60% at 1 month follow up, 80% at 3, 6, 9 and 12 month follow up. Abnormal outcome was found in 25.53% babies with perinatal asphyxia at time of discharge, 31.71% at 1 month, 43.90% babies at 3, 6, 9 and 12 month follow up. It was found in 35.5% babies

with meningitis at time of discharge. Among the survivor's abnormal outcome was found in 34.2% babies at 1 month follow up, 35.5% babies at 3, 6, 9 and 12 month follow up. According to Agustin et al [21] and Iype et al [22] unfavorable outcome was found in 50% and 26.4% respectively in cases of hypoglycemia. Likewise in present study abnormal outcome was found in 11.1% in babies with hypoglycemic seizures at time of discharge, among the survivor's abnormal outcome was found in 11.1% babies at 1 month follow up, 11.1% babies at 3, 6, 9 and 12 month follow up. The babies in whom cause of seizure was ICH, the abnormal outcome was found in 85.7% babies at the time of discharge while among survivors it was found in 100% babies at 1,3,6,9 and 12 month follow up. Similarly in babies with kernicterus, all babies (100%) were found to be abnormal at the time of discharge and on follow up. The abnormal outcome was found in 42.9% babies in whom cause of seizure was of unknown etiology at the time of discharge and at 1, 3, 6, 9 and 12 months follow up which is comparable with the study conducted by Agustin et al [21]. There was significant relationship found in etiology of seizure and outcome (p-<0.001).

Limitations of the study

1. Unavailability of synchronized video EEG and EEG might have resulted in inclusion of newborns with seizure mimics.
2. Other modalities like CT and MRI in the diagnosis of neonatal seizures could not be performed in an unstable infant, and sometimes was best deferred until the acute clinical situation resolved.
3. Clinical evident seizures only were included in the current study hence, very subtle and electrical only seizure might have been missed.

Conclusion

In the present study, perinatal asphyxia was the most common cause of neonatal seizure. Abnormal outcome was more in babies with early onset of seizure and with tonic seizures. Babies with ICH and kernicterus had poor neurodevelopmental outcome. Mortality was more if seizures occurred within 24 hours of life.

The study recommended that the proper antenatal check-up and early registration, early diagnosis of chronic illness in mother like PIH, Bleeding, Premature illnesses, rupture of membranes should be done and prompt treatment should be initiated. Neonatologist should anticipate babies who are predisposed for neonatal seizures through maternal diseases, gestation, birth weight, etc. and should undertake closer monitoring of such newborns. Intensive training of the residents of Department of Obstetrics and Gynaecology in relevant domains of Neonatology namely Neonatal resuscitation, prevention of Birth Asphyxia and safe deliveries is mandatory. The residents of Neonatology should also be trained in anticipating, monitoring and observation for subtle and treatment protocols of neonatal seizures.

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