

Original Research Article

Study on etiology and clinical course of neonatal seizures and their outcome

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ABSTRACT

Background: The aim was to explore etiology, clinical course of neonatal seizure and their outcome in Narayana Medical College Hospital, Nellore, Andhra Pradesh, India.

Methods: Retrospective study of 65 neonates from 1 month to 1 year diagnosed with epilepsy between November 2016 to August 2018.

Results: Most common type of seizures seen are subtle (40%), followed by multifocal clonic (20%), tonic (21%), focal clonic (9.2%), clonic (7.7%) and myoclonic (1.6%). Most common cause of neonatal seizures was HIE (41.5%), followed by hypoglycemia (13.8%), intracranial bleed (10.8%), septicemia (10.8%), hypocalcemia (7.7%). The mortality percentage is high (18.2%) when seizures occurred before 12 hours, when seizures occurred between 24-48 hrs it is 14.3%, and mortality was least when seizures occurred between 2-6 days (12.5%). Seizures are common in stage IIHIE (81.5%) compared to Stage I & Stage III. Seizures with adverse outcome are generalized myoclonic and focal clonic seizures. Focal clonic and focal tonic seizures are most often associated with focal injury. Generalized tonic seizures, motor automatism and some myoclonic seizures are associated with diffuse brain injury. Prolonged seizure activity, seizures lasting for many days, repetitive seizures, and the need for multiple anticonvulsants to control seizure activity are associated with an increased mortality.

Conclusions: Authors conclude that prompt recognition, evaluation and treatment of these neonatal events are important in improving the survival of neonates with seizures.

Keywords: Myoclonic, Neonates seizure, Septicemia

INTRODUCTION

Neonates are at particular risk for the development of seizures because of metabolic, toxic and infectious diseases, and are more likely to be manifested during this time than at any other period of life. Neonatal seizures are common and may be the first manifestation of neurological dysfunction after insult. Seizures are usually related to significant illness. Seizures may interfere with cardiorespiratory function and with nutrition and may have detrimental effects on neurological development.

Neonatal seizures are dissimilar from those in a child or adult because generalized tonic clonic seizures tend not to occur in the first month of life. The arborisation of axons and dendritic processes as well as myelination is incomplete in the neonatal brain. A seizure discharge therefore cannot readily be propagated throughout the neonatal brain to produce a generalized seizure. Neonatal seizures are powerful predictors of cognitive and developmental impairment. Recurrent seizures may result permanent significant changes in nervous system, increased risk of epilepsy and long-term cognitive disabilities.

Seizures are the most frequent clinical manifestation of central nervous system dysfunction in the newborn with the incidence varying from 1-5%.¹ Neonates are at higher risk for seizures compared to older children. It has been shown that immature brain is more susceptible to seizures than mature brain.^{2,3} Neonatal seizures are poorly classified, under-recognized, and often difficult to treat.

The presence of neonatal seizures often signals an underlying ominous neurological condition, most commonly hypoxia-ischemia. The other common etiologies of neonatal seizures are stroke, intraventricular hemorrhage or intraparenchymal hemorrhage, meningitis, sepsis, and metabolic disorders. In sick neonates, seizures are not easily recognized clinically, and usually go untreated. Seizures can permanently disrupt neuronal development, induce synaptic reorganization, alter plasticity and “prime” the brain to increased damage from seizures later in life.⁴

Prompt recognition, evaluation and treatment of neonatal seizures is important. Recent advances in diagnostic technology have provided important insights into neonatal seizures.

Techniques such as bedside video-electroencephalogram (EEG) monitoring and MRI have challenged earlier beliefs and raised fundamental questions regarding the diagnosis, etiology and management of seizures in the newborn infant.

Vast majority of seizures in the newborn are symptomatic of a specific etiology. With these diagnostic advances, etiology is increasingly identifiable. In addition, these advances have further highlighted the essential differences between the seizures in the newborn infants and older patients including their response to conventional anticonvulsant agents. Neonatal seizures are powerful predictors of long-term cognitive and development impairment.

At present, there are no established evidence-based guidelines for the appropriate workup or management of neonatal seizures, e.g. the use of EEG and brain imaging, choice of anti-epileptic drugs, treatment of intractable neonatal seizures, duration of treatment, and more.

New animal research suggests that neonates may exhibit some neuroprotection from seizures, but brief, recurrent seizures result in significant, permanent changes in the central nervous system, an increased risk of epilepsy, and long term cognitive disabilities.⁵

Coen RW et al, Holden KR et al, came to conclusion in their studies that 53% of newborns with seizures due to hypoxia-ischemia and/or ICH had severe or moderate neurological impairment at follow up.^{6,7}

Holden KR et al, neonatal convulsions are not a risk factor for later epilepsy unless the epilepsy is part of a

chronic brain syndrome that includes cerebral palsy, mental retardation or both.⁸

Ellenberg JH et al, found that approximately 20% of neonates with seizures had one or more non febrile seizures later in life, nearly 2/3rd occurred within first 6 months applied and 374th with in first year.⁹

Ortibus EL et al, indicated that the predicted outcome, less reliable when based solely on EEG variables from a single recording obtained at seizure onsets than when based on a combination of imaging, clinical and EEG data.¹⁰

However, all variables relate to single factors, the degree of brain injury at the time of seizure occurrence, and this related to etiology.

Scher MS et al, reported post-natal epilepsy following neonatal seizures in six (17%) of 36 preterm survivors and six (30%) of 20 term survivors.¹¹

Recently, Orbitus EL et al, reported 28% of survivors of neonatal seizures with post neonatal epilepsy.⁹

The present study was undertaken to delineate the various aspects of neonatal seizures, with special reference to etiology, clinical spectrum, and outcome in the Neonatal Intensive Care Unit (NICU) of a tertiary care center, Narayana Medical College and Hospital, Nellore Andhra Pradesh, India.

METHODS

In this study, babies with neonatal seizures admitted to NICU (Neonatal Intensive Care Unit) attached to the Neonatology Division of Narayana Medical College and Hospital, Nellore, Andhra Pradesh, India formed the subjects.

Babies with neonatal seizures admitted in NICU were evaluated and managed as per NICU protocol. Gestational age assessment is done by modified Ballard's scoring system and detailed neurological assessment is done during NICU stay.

Blood sugar, serum calcium is routinely done and CBC, CSF study, neuro sonographic evaluation and other investigations were done as and when indicated. A total of 65 babies with neonatal seizures which were admitted in NICU of Narayana medical college and General hospital during two-year time formed the study population. Proforma was used to collect the relevant data.

Inclusion criteria

All the babies born in Narayana Medical college Hospital and admitted into NICU with complaints of neonatal seizures.

Exclusion criteria

Babies born outside and brought to Narayana medical college and hospital NICU. Baby who were identified to have seizure like events but not seizures. Cases left against medical advice. Cases where're quired investigations could not bed on due to various reasons.

RESULTS

Total of 65 babies with neonatal seizures admitted in NICU of Narayana Medical College and Hospital, Nellore, Andhra Pradesh, India during 2-year time formed the study population and the neonatal outcome was noted.

Table 1: Types of neonatal seizures.

Types of seizure	No. of neonates	%
C	5	7.7
FC-	6	9.2
MFC	13	20.0
Myoclonic	1	1.6
Subtle	26	40.0
T	14	21.5
Total	65	100.0

Amongst clinical types of seizures observed in our babies, the most common type was subtle seizures (40%). Subsequently tonic (21.5%), multifocal clonic (20%), focal clonic (9.2%), clonic (7.7%) and least common type was myoclonic seizures (1.6%) (Table 1).

Table 2: Etiology of seizures.

Etiology	No. of neonates	Percentage
HIE	27	41.5
Hypocalcemia	5	7.7
Hypoglycemia	9	13.8
IC bleed	7	10.8
Meningitis	3	4.6
Septicemia	7	10.8
BE	4	6.1
CNS+M	2	3.1
MAS+MA	1	1.6
Total	65	100.0

Most common cause is hypoxic ischemic encephalopathy (41.5%) followed by hypoglycemia (13.87%). Intracranial bleed (10.8%), septicemia (10.8%), hypocalcemia (7.7%), bilirubin encephalopathy (6.1%), meningitis (4.6%), CNS+M (3.1) and the least was MAS+MA (1.6%) (Table 2).

Table 3: Etiology in relation to type of seizure.

Type of seizure	No.	Etiology								
		HIE	Hypocalc	Hypogl	IC	Meni	Sept	BE	CNS+	MAS+M
C	5	3 (60%)	1 (20%)	-	1 (20%)	-	-	-	-	-
FC	6	4 (66.6)	-	-	-	-	1 (16.7)	-	1 (16.6)	-
MFC	13	8 (61.5)	-	-	1 (7.7)	1 (7.7)	3 (23.1)	-	-	-
Myoclonic	1	-	-	-	-	-	-	1 (100)	-	-
Subtle	26	12 (46.1%)	3 (11.5)	5 (19.2)	2 (7.7)	1 (3.8)	1 (3.8)	2 (7.7)	-	-
T	14	-	1 (7.1)	5 (28.6)	3 (21.4)	1 (7.1)	2 (14.3)	1 (7.1)	1 (7.1)	1 (7.1)
Total	65	27 (41.5)	5 (7.7)	9 (13.8)	7 (10.8)	3 (4.6)	7 (10.8)	4 (6.15)	2 (3.1)	1 (1.6)

Table 4: Outcome in relation to etiology of seizures.

Etiology	No. of cases	Deaths n (%)
HIE	27	2 (7.4)
Hypocalcemia	5	-
Hypoglycemia	9	-
IC bleed	7	3 (42.9)
Meningitis	3	-
Septicemia	7	2 (28.6)
BE	4	1 (25.0)
CNS+M	2	1 (50.0)
MAS+MA	1	1 (100)
Total	65	10

Association between HIE seizure revealed that seizures occur most often in stage II HIE (81.5%), less often in stage III HIE (18.5%). In this study, subtle (39.1%) and tonic (60.9%) type of seizures are very common in preterm, and full term subtle (40.5%), focal clinic (14.3%), multifocal clonic (30%) and clonic (11.9%) are common and rare type is myoclonic seizure (2.4%) (Table 3). Babies with myoclonic seizures had (100%) mortality, followed by focal clonic (33.3%), multifocal clonic (23%) and tonic seizure (21.4%) and least subtle seizure (3.8%). The worst outcome was with CMS malformation (50%) followed by intracranial bleed (42.9%), in HIE Bilirubin encephalopathy (25%), septicemia (28.6%), and the least was (7.4%) in HIE (Table 4).

Table 5: Outcome in relation to time of onset of seizure.

Onset of	No. of	Outcome
		Deaths n (%)
<12 hrs	11	2 (18.2)
12-24	13	-
24-48	14	2 (14.3)
2-6	24	3 (12.5)
7 days	3	3
Total	65	10 (15.4)

The death rate in relation to time of onset of seizure was described in Table 5. Onset of 7 days, there was 3 deaths were observed. In total 15.4% deaths were observed out of 65 cases (Table 5).

DISCUSSION

In the present study, 65 neonates were admitted to NICU with neonatal seizures. Babies are evaluated and managed as per NICU protocol and relevant investigations were done. Neonatal seizures form an important cause of NICU admission. Neonatal seizures are due to various causes like HIE, hypocalcemia, hypoglycemia, intracranial bleed, meningitis, septicemia, bilirubin encephalopathy and CNS malformations.

The study attempts to delineate the etiologic pattern of neonatal seizures in tertiary-care settings as also the outcome in relation to the type of seizure, etiology in relation to type of seizures, various etiologies of neonatal seizures, outcome in relation to etiology of seizures, types of seizure in relation to gestational age, immediate outcome in relation to time of onset of seizures and seizures in different stages of HIE.

Types of seizures

There were four recognizable clinical seizure types, subtle, clonic, tonic, and myoclonic, each of these types can be focal, multi focal or generalized. In the present study subtle seizures 26 (40%) were the most common

type of seizures observed followed by tonic 14 (21.5%), multi focal clonic 13 (20%), focal clonic 6 (9.2%), clonic 5 (7.7%) and the least common was myoclonic 1 (1.6%). Upadhyay A et al, observed subtle seizures to be the commonest type and it constituted 50% of all seizures.¹² The present study results for subtle seizures and clonic seizures (including both multifocal and focal) are correlating with their studies.

Outcome in relation to type of seizure

Seizure characteristics associated with adverse outcome are generalized myoclonic or tonic seizures, intractable seizures and burst suppression or persistent low voltage EEG states. In the present study the different types of seizures in relation to outcome are as follows.

- Subtle 26 - death 1 (3.8%) Clonic 5 - no death
- Focal clonic 6 - death 2 (33.3%)
- Multifocal clonic 13 - death 3 (23.1%)
- Myoclonic 1 - death 1 (100%)
- Tonic 14 - death 3 (21.4%).

Mizrahi EM et al, Kellaway P et al, in their study observed, clonic-abnormal 4 (28.6%) no death, myoclonic-abnormal 6 (35.3%) death 5 (29.4%), tonic - abnormal 7 (53.8) death 3 (23.1%), subtle (54.5%) death 4 (18.2%).¹³

Etiology in relation to type of seizures

In the present study, subtle seizures are observed in many of the etiological states like HIE 12 (46.2%), hypocalcemia 3 (11.5%), meningitis 1 (3.8%), septicemia 1 (3.8%), bilirubinencephalopathy 2 (7.7%) followed by tonic seizures - hypoglycemia 5 (28.6%), intra cranial bleed 3 (2.4%), septicemia 2 (14.3%).

In a study by Mizrahi EM et al, and Kellaway P et al, observed that in HIE related seizures- clonic 1 (7.1%), myoclonic 11 (64.7%), tonic 7 (53.8%) and subtle 12 (54.5%). In infections - clonic 3 (20.4%), tonic 5 (22.7%) and subtle 5 (22.7%).¹³

Generalized tonic seizures, motor automatism and some myoclonic seizures are associated with more diffuse brain injury e.g. HIE. bilateral infarcts or advanced CNS infections.

Etiology of seizures

Though various causes of neonatal seizures have been recognized, in the present study HIE is the most common cause contributing to 41.5%. Hypocalcemia (7.7%), Hypoglycemia (13.8%), IC bleed (10.8%), Septicemia (10.8%) Meningitis (4.6%) and Bilirubin encephalopathy (6.1%), CNS malformations (3.1%).

Types of seizures in relation to gestational age

Term neonates with seizures generally fare better than preterm neonates. In the present study most common seizures observed in preterm babies were tonic (60.9%) and subtle (39.1%) seizures. Whereas in full-term babies subtle (40.5%) and focal clonic (14.3%) were common followed by multifocal clonic (13%), clonic (11.9%) and the least was myoclonic (2.4%). The present study values of subtle type of seizures in both preterm, full-term neonates correlate with this study.

Outcome in relation to etiology of seizures

The outcome of neonatal seizures depends mainly on the etiology. Other factors have a significant bearing on the prognosis. HIE - death (7.4%) Intracranial bleed - death (42.9%) Meningitis - death (66.6%) Septicemia - death (28.6%) CNS malformation - death (50%). In a study by Bergman L et al, HIE with intracranial hemorrhage or both death or severe or moderate impairment (45%) <mild impairment (34%). Infections-16(7%) death Hypoglycemia- 7 (2%) death. Hypocalcemia - 2 (0%) death Hyperbilirubinemia-1 (1%) death Brain malformations - 5 (5%) death or severe impairment (0%) mild impairment. Some of these results are correlating with the present study.¹⁴

Outcome in relation to time of onset of seizures

Early onset of seizures is a predictor of bad prognosis in general, onset within 48 hours of birth indicates a grave prognosis, whereas seizures starting after 41 day of life have relatively better prognosis. The time of onset has been divided into <12 hours, 12-24 hours, 24- 48 hours, 2-6 days and 7-28 days.

In the present study onset of seizures <12 hours had an outcome of death 2 (18.2%)

- 12-24 hours - death 2 (14.3%)
- 24-48 hours - death 2 (14.3%)
- 2-6 days-death 3 (12.5%)
- >7 days-death 3 (100%)

In a NC PP follow-up study, they observed that onset of seizures <12 hours had a mortality rate (53%), 12-24 hours (39%), 24-48 hours (37%), 2-6 days (19%) and 7-28 days (31%). In a study by Clancy RR et al, and Legido A et al, 40 - mortality 33%, 30 (term), neurologic impairment 38%, normal 30%.¹⁵ Ortibus EI et al, observed 81-29% mortality, 49% neurologic impairment, 22 normal. In a study by Agustin Legido et al, 49 observed that the onset of seizures within the first day of life (p=0.2) and a severely abnormal neurologic evaluation (p=0.003) significantly predicted an unfavourable outcome.⁹ Prolonged seizure activity, seizures lasting for many days, repetitive seizures and the need for multiple anticonvulsants to control seizure

activity are associated with an increased mortality or abnormal neurologic outcome.

Neonatal seizures in different stages of HIE

Hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures. Often no seizures are seen in stage 0 and stage I hypoxic- ischemic encephalopathy. But seizures in stage II hypoxic- ischemic encephalopathy and stage III hypoxic-ischemic encephalopathy are known. In the present study seizures observed in stage II hypoxic-ischemic encephalopathy was 81.5% and stage III hypoxic-ischemic encephalopathy was 18.5%. A total of 75-85% of the cases of neonatal seizures have been attributed to hypoxic- ischemic insult.¹⁶

Evans D and Levene M in their study, observed hypoxic-ischemic insults accounted for about 50% of cases of neonatal seizures.¹⁷ Bergman I et al, observed in their study that the most common cause of neonatal seizures is hypoxic-ischemic encephalopathy.¹⁴ Leviton and Nelson¹⁸ in their study state that neonatal seizures are a part of the neonatal encephalopathy syndrome in its moderate or severe forms and may indicate serious risk of an adverse outcome

CONCLUSION

In the present study, in Neonatal seizures, mortality rates in various etiologies are 50% in CNS malformations, 42.9% in IC bleed, 28.6% in Septicemia and 7.4% in HIE. Early onset of seizures, prolonged, repetitive and the need for multiple anticonvulsants to control seizure activity are

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