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Pediatrics

ETIOLOGY AND SHORT-TERM OUTCOMES OF NEONATAL SEIZURES IN A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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ABSTRACT

Background: Neonatal seizures are the most common manifestation of neurological disorders in the newborn period and early detection of predictors of adverse outcome will be helpful for neonatologists to plan management, follow up and rehabilitation in advance so that neurological disability can be minimized.

Objectives: To determine the etiology, incidence of various clinical seizure types, and prognostic factors associated with poor short-term outcome among neonates admitted with neonatal seizures.

Methods: This is a nested case control study in a descriptive cohort, conducted in Department of neonatology, Dr Mehta's Hospital Chennai between May 2011 to November 2012.All the neonates who presented with clinically identifiable seizures were enrolled in the study. Seizure etiology was based on positive clinical data, laboratory findings, EEG and /or imaging studies of the brain (ultrasonography, CT Scan, or MRI).

Results: Hypoxic ischemic encephalopathy, radiological findings and EEG findings were significantly associated with outcome.

Conclusion: Hypoxic Ischemic Encephalopathy was the most common cause of neonatal seizure and most common seizure type was multifocal clonic type. The most common diagnosis associated with neonatal seizure that carry worse mortality were hypoxic ischemic encephalopathy and inborn errors of metabolism.

KEYWORDS : Hypoxia-ischemia, neonatal seizures, newborn, prognosis

Introduction

Neonatal seizure is a relatively common pediatric emergency and it is critical to determine the etiology and other factors that determine the outcome. Even with advanced perinatal care, mortality and morbidity of neonatal seizure remains high. There are a number of problems in diagnosis and management of neonatal seizures underscoring the dynamic nature of the study of neonatal seizures [1]. Etiology is the most important factor reported to determine the outcome after neonatal seizures. Other than etiology, factors reported with adverse outcome are type of seizure, status epilepticus, early onset of seizures, gestational age, Apgar score, birth weight, need for resuscitation, neurological examination at onset of seizure, electroencephalogram (EEG) and radiological finding. Reliability of most of these factors is limited [2]. The purpose of this study was to determine the clinical profile of neonatal seizure and to determine the factors associated with unfavorable outcome of neonates admitted with seizures in neonatal Intensive Care Unit (NICU). It is important to identify the early predictors of adverse outcome because it could be a valuable tool in providing advanced care and for an early referral for long-term follow-up and rehabilitation.

Materials and Methods

This is a nested case control study in a descriptive cohort, conducted in Department of neonatology, Dr Mehta's Hospital Chennai between May 2011 to November 2012. All neonates with clinical seizures (at admission or during hospital stay) during the study period formed the study group. Neonates presenting with or developing at least one type of the following seizure type during the hospital stay- Generalized tonic clonic/ multifocal clonic/focal clonic/ myoclonic/ subtle seizures were included. Those newborns whose parents denied consent and those with history of seizures prior to admission and without proper documentation were excluded. Evaluation included a thorough search for etiology, including detailed clinical history, maternal and perinatal risk factors. Data were collected regarding time of onset of seizure, type, duration and frequency of seizure, neurological examination at the onset of the seizure. Maternal and perinatal history including gestational age, type of delivery, birth weight, Apgar score at 1 and 5 min and need for and type of resuscitation at the time of birth were recorded. Routine chemistries, including blood sugar, sepsis screen, lumbar puncture, serum electrolytes such as sodium, calcium, magnesium, EEG, neuroimaging (ultrasonography/computerized tomography/magnetic resonance imaging [USG/CT/MRI]), TORCH screen and screen for inborn errors of metabolism were done wherever indicated. We followed-up the babies throughout the hospital stay till discharge/death and conducted a retrospective analysis to identify the variables that were significantly associated with adverse outcome. Association between the variables and outcome was analyzed by Chi-square test to find the statistical significance (degree of freedom = 1). The variables with $P < 0.05$ are considered to significantly affect the outcome after neonatal seizures [2]. For the statistical analysis resuscitation maneuvers were grouped into two categories: 1 (routine) = routine care/oxygen supplementation; and 2 (extra) = resuscitation >1 min with positive pressure ventilation+/endotracheal intubation+/cardiac massage+/drug therapy. Multiple seizure types often coexisted in the same patient. Hence, patients were categorized as having one or multiple type of seizures. Status epilepticus was defined as seizure for 5 min or recurrent seizure that lasted for >30 min without definite return to baseline neurological condition between seizures. EEG was considered severely abnormal when there were asymmetries in the voltage or frequencies, low-voltage activity or a permanent discontinuous activity. USG/CT/MRI findings were considered severely abnormal when there was IVH of degree 3 or 4, intraparenchymal hemorrhage, periventricular hemorrhage or brain malformations. The outcome was categorized into two categories: 1 = favorable outcome, which included normal neurological examination, mild muscle tone+/reflex abnormalities; 2 = adverse outcome, which included death, severe neurological impairment [2].

Results

Total number of cases admitted to NICU during the study period was 1436 among which 107 newborns had seizures (7.5%). Table 1 shows the baseline characteristics of the 107 patients who had neonatal seizures. There was a male preponderance in this study (60.7%). Majority were term infants and appropriate for gestational age babies (78.5% and 81.3%). HIE (42.1%), was the most common etiology. Second most common cause was hypoglycemia and meningitis (15% each). Hypocalcemia was present in 9 (8.4%) and inborn error of metabolism 3 (2.8%) neonates. Intracranial hemorrhage, bilirubin encephalopathy and electrolytes imbalance constituted 1(0.9%) each. It was not possible to determine etiology of seizures in 15 patients. In terms of seizure type, out of 107 neonates, 72 babies (67.3%) had multifocal clonic seizures, 15 neonates (14.0%) had subtle seizures, 14

(13.1%) babies had focal clonic seizure, 4 babies (3.7%) had GTS and 2 (1.9%) had myoclonic seizure. The short-term outcomes were neonatal mortality and abnormal neurological examination at discharge. 10 babies died during their hospital stay (9.3%). Two more babies died within two months of life (1.9 %). Outcome mortality in this study was 12 (11.2%). Moderate to severe neurological impairment was present in 8 (8.4%) cases and mild neurological impairment in 59 (62.1%) cases. Association between the variables and outcome was analyzed by Chi-square test and results showed that hypoxic ischemic encephalopathy, radiological findings and EEG findings were significantly associated with outcome. (Table 2)

Discussion

Incidence of neonatal seizure in this study was 7.5%. Most of the cases were referred from peripheral hospitals. Hence, a true incidence based upon total live births cannot be calculated. Newborns with seizures are included based on clinical criteria without synchronized video EEG recording. Hence, newborns with very subtle or electrical only seizures might have been excluded. [3]

The reported incidence ranges from 0.5% to 22.2%. Hospital based studies including high risk cases show higher incidence of neonatal seizures than population study including infants in general nurseries and less ill. There is a male preponderance and majority were term babies in this study. Most of the studies show higher incidence in preterm babies. [4,5,6]. Most common etiology reported remains HIE and sepsis in this era of advanced perinatal care. Mortality in the present study is 11.2% and reported in literature is 9-15%. [7] It is important for the neonatologists to have early and accurate predictors of outcome to plan the management. The variables selected in this study are easily available including the instrumental investigations.

Etiology, severe EEG and radiological (USG/CT/MRI) abnormality were found significantly associated with adverse outcome in this study. Prognostic factors reported in literature are etiology, seizure type, early onset of seizure, prolonged and recurrent seizure, gestational age, birth weight, Apgar score at 5 min, need for resuscitation maneuvers, neurological examination, EEG, and USG findings. [2,8,9] Mode of delivery, Apgar at 1 min, resuscitation maneuver, seizure type, neurological examination at onset of seizure are not found significantly associated with adverse outcome in this study. Some studies report that newborns with generalized tonic, myoclonic and subtle seizures have poor outcome compared with those with clonic seizures but recent studies report that prognostic significance of seizure type is not reliable as multiple seizure type often coexist in same patient. [2] Apgar score at 5 min than at 1 min is described as reliable predictor of neurological outcome. [10,11] Need for resuscitation correlates with Apgar at 1 min both of which are found not significantly associated with adverse outcome in the present study. Preictal neurological examination is described significantly associated with outcome. In this study, we have analyzed only the neurological examination after the onset of seizure, which is found not significantly associated with outcome. Neonatal status epilepticus, which is most often of symptomatic origin with extensive structural brain injury is likely to have significant influence on outcome than prolonged or recurrent seizure, which is often associated with favorable prognostic factors like hypocalcemia. [2]

The inclusion of newborn with seizures was based on clinical criteria without synchronized video EEG recording. This might have resulted in inclusion of newborns with seizure mimics which have different prognosis. Recurrent seizure thought to be associated with adverse outcome was not included. Accurate seizure duration determination is a time-consuming process and it requires a systematic data collection of the duration of each seizure episode. MRI, which is a helpful tool in determining periventricular white matter lesions, is not done in majority of cases due to financial constraints in this study. It has inherent difficulties in patient preparation, safety, and timing. [2] This study includes short-term follow-up only; further follow-up is required to evaluate long-term neurological follow-up.

Conclusion

Neonatal seizure contributes to 7.5 % of admission in NICU. Most seizures occurred on first day of life. Multifocal clonic seizure was the predominant seizure type. HIE was the commonest etiology. HIE, abnormal neuroimaging and abnormal EEG were significantly associated with unfavorable outcome.

Table 1- Baseline characteristics of patients with neonatal seizures

Variable	Favorable outcome (87)	Unfavorable outcome (20)	P value
Mode of delivery	29	3	0.25
Vaginal	5	1	
Instrumental	53	16	
LSCS			
Gestational age	7	1	0.64
30-34 wks.	11	4	
35-36 wks.	69	15	
≥37 wks.			
Intrauterine growth status	73	14	0.28
AGA	10	5	
SGA	4	1	
LGA			
APGAR at 1 min	46	8	0.299
<5	41	12	
≥5			
APGAR at 5 min	43	12	0.39
<7	44	8	
≥7			
Resuscitation at birth	26	1	0.06
Nil	46	14	
Routine	15	5	
Extensive			
Seizure onset	35	6	0.14
<24hrs	28	4	
24-72 hrs.	24	10	
>72 hrs.			
Type of seizure			0.15
Subtle	14	1	
Tonic	2	2	
Clonic	70	16	
myoclonic	1	1	
Duration of single seizure			0.5
<5 min	85	19	
>5 min	2	1	
AED		14	0.47
Monotherapy	53	5	
Double therapy	14	1	
Triple therapy	11		
Number of seizures	27	4	0.32
Single	60	16	
Multiple (≥2)			
Neuroimaging before			0.00001
discharge	82	6	
Normal	5	14	
Abnormal			
EEG	48	1	0.00004
Normal	39	19	
Abnormal			
Etiology	33	12	0.04
HIE	20	6	
Metabolic	34	2	
Others			

Table 2- Association between variables and outcome

Variables	N (%)
Sex	60(60.7)
Male	42(39.3)
female	
Birth weight	1(0.9)
<1 kg	3(2.8)
1-1.5 kg	26(24.3)
1.5-2.5 kg	77(72)
>2.5 kg	
Gestational age	23(21.5)
<37 weeks	84(78.5)
>37-42 wks.	
Intrauterine growth status	87(81.3)
AGA	15(14)
SGA	5(4.7)
LGA	

Family history of seizures	4(3.7)
Type of seizures Multifocal clonic	72(67.3)
Subtle	15(14)
Focal clonic	14(13.1)
Tonic	4(3.7)
Myoclonic	2(1.9)
Causes of seizures HIE	45(42.1)
Hypoglycemia	16(15)
Sepsis/Meningitis	16(15)
Idiopathic	15(14)
Hypocalcemia	9(8.4)
IEM	3(2.8)
ICH	1(0.9)
Bilirubin Encephalopathy	1(0.9)
Electrolyte abnormalities	1(0.9)
Treatment offered No anticonvulsive drugs	9(8.4)
Only Phenobarbitone	67(62.6)
Phenobarbitone + phenytoin	19(17.8)
Phenobarbitone + Phenytoin + Midazolam	12(11.2)

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