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Pediatrics

KEY WORDS:

Neonatal Seizures and Outcomes at 12 months of age: A Nested Case Control study

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ABSTRACT

Background: Neonatal seizures are often associated with short term and long term adverse outcomes in young infants. Incidence and Risk factors determining outcome in neonatal seizures are not well known.

Objective and Methods: To measure neurodevelopmental outcomes at 12 months of age and analyse factors associated with adverse outcomes in babies with clinical seizures. A descriptive cohort with a nested case control design was used

Results: Of 436 neonates admitted to our NICU, 107 neonates had seizures. Study cohort had 92 babies as 12 babies expired and 3 were lost to followup. We noted mental development delay in 29 (31.5%), motor development delay in 24(26.1%), recurrent seizures in 17 (18.5%), failure to thrive in 12 (13%), hearing impairment in 5 (5.4%) and vision impairment in 4 (4.3%) on long term followup. The risk factors for mental delay were low APGAR score at 1 minute [(6.6(2.47-17.2)] and 5 minutes [6.02(2.28-15.89)], hypoxic ischemic encephalopathy [7.11(2.68-18.90)], abnormal neurological examination at discharge [29.54(8.55-102)] and abnormal post neonatal EEG [37.6(7.7-183.6)] and MRI [33.8(3.89-293.3)]. The risk factors predicting poor motor DQ were- abnormal neonatal EEG [2.68(1.02-7.2)], post neonatal EEG [66(12.7-341.24)], abnormal neurological examination at discharge [16.2(4.84-55.55)], abnormal post neonatal MRI [45.5(5.14-402.7) and abnormal neonatal neurosonogram [4.5(1.08-18.56)]. By multivariate regression analysis, MRI alone appeared to the significant modality to predict recurrent seizures and neurodevelopment delay.

Conclusion: Neonatal seizures are associated with significant morbidity in the form of predominantly neurodevelopment delay at 1 year of age.19 % of survivors are at risk for repeated seizures in infancy. Significant risk factors of poor neurological outcome at 1 year are low APGAR score at 1 and 5 minutes, presence of HIE, abnormal neurological examination at discharge and abnormal post neonatal EEG and MRI.

Introduction

Neonatal seizures are a marker of brain dysfunction in the newborn. Population based studies from the West [1] suggest a relatively low incidence of 2.6/1000. The incidence in outborn babies admitted to Indian NICUs is close to 12%, and reflects the actual reality in our country where babies are mostly born in small hospitals and nursing homes [2]. Neonates with seizures are at risk of various adverse short term and long-term outcomes including poor neurodevelopment outcome and epilepsy. Newborns with transient correctible metabolic abnormalities, focal ischemia and without clear etiology usually do well, while those with hypoxic-ischemic encephalopathy (HIE), CNS infections and cerebral dysgenesis develop long term sequelae [1,3]. The incidence and risk factors for adverse neurodevelopment sequelae following neonatal seizures are yet not well described in the available literature. We planned this study to measure the long-term outcomes (12 months of age) following neonatal seizures, incidence and factors associated with adverse long-term outcomes.

Materials and methods

This nested case control study was done at the Department of Neonatology, Mehta Children's Hospital over a period of 18 months from 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. Neonates with history of seizures prior to admission and without proper documentation and whose parents denied consent were excluded. The institutional ethics committee approved the study. Ethical principles as dictated by Declaration of Helsinki, which provides guidance to physicians and other participants in medical research involving human subjects was strictly followed.

Data collection and statistical tests

Data regarding seizures-type, duration, onset and number- was collected as per observations of NICU staff and confirmed by neonatologists. Relevant history, clinical details, blood investigations, radiological investigations and special investigations were collected. A consistent institutional management protocol was used for management of neonatal seizures.

Collected data was entered in Microsoft excel sheet. Subsequent visits and neurodevelopment follow up details were added to the same. Simple descriptive statistics were used to describe the demographic characteristics. Poor prognostic factors for long term outcomes (at 12 months) were assessed using univariate Odds Ratio (95% CI), Chi square test and Fisher's exact as applicable.

Parameters studied

Long term outcomes were studied. These included - neurodevelopment at 1 year corrected age, recurrent seizures, vision impairment, hearing abnormalities and failure to thrive. Neurodevelopment assessment was done using Amiel Tison's neurological examination at discharge from NICU, at 3, 6 and 9 months. Formal development assessment was done by the principal investigator along with an experienced clinical psychologist trained in DASII (Developmental Assessment Scales for Indian Infants) at 1 year of age. Motor and Mental delays were defined as the corresponding DQ <85

Definitions used

Recurrent seizures: > 1 unprovoked seizure episode after neonatal period (28 days of life). Hearing impairment: Abnormal BERA done at 3 and 6 months of corrected age. Vision impairment: corrected best visual acuity worse than either 20/60 or 20/40 as ascertained by trained Pediatric Ophthalmologist. Failure to Thrive: Weight for age, less 5th centile on multiple occasions or weight deceleration crossing two major centiles.

Special tests used for assessment and follow up
Electro Encephalogram (EEG): EEG studies were recorded for all neonates prior to discharge and at follow up. Inter ictal EEG was classified as: Normal or Abnormal: Sharp waves with normal background, Sharp waves with abnormal background (low voltage)

Neuroimaging studies- Neurosonogram was done for all enrolled cases during hospital stay. CT scan/MRI brain were done as per the requirement in individual cases. Abnormal MRI was defined as (1 or more of the following): Extra parenchymal Lesion, diffuse cortical lesion, focal cortical lesion

Results

A total of 1436 neonates were admitted to the NICU during the study period. Out of these, 107(7.5%) had neonatal seizures. Table 1 shows the baseline characteristics of the 107 patients who had neonatal seizures. Majority of the cases were males and 72% had birth weight of more than 2.5 kg. Nearly four fifths were born at a gestational age of 37-42 weeks and were appropriate for gestational age. Family history of seizures was present in 3.7%. Multifocal clonic seizures were the commonest type of seizures and the major etiology for seizures was hypoxic ischaemic encephalopathy.

Twelve cases expired during the study period and three were lost to follow up. Thus, 92 patients formed the study cohort. On long term follow up, the following abnormalities were noted in the study cohort- mental development delay in 29 (31.5%), motor development delay in 24(26.1%), recurrent seizures in 17 (18.5%), failure to thrive in 12 (13%), hearing impairment in 5 (5.4%) and vision impairment in 4 (4.3%). 83% of patients (24/29) with neurodevelopment delay showed involvement of both motor and mental faculties while 17% had only mental delay. Figure 1 shows the morbidities noted in cases with and without neurodevelopment delay.

The risk factors for recurrent seizures included- abnormal neurological examination at discharge, abnormal neonatal and post neonatal MRI and abnormal post neonatal EEG (Table2). The risk factors for mental delay were low APGAR score at 1 minute and 5 minutes, hypoxic ischemic encephalopathy, abnormal neurological examination at discharge and abnormal post neonatal EEG and MRI. (Table 3). The risk factors predicting poor motor DQ were- abnormal neonatal and post neonatal EEG, abnormal neurological examination at discharge, abnormal post neonatal MRI and abnormal neonatal neurosonogram (table 4), By multivariate regression analysis, MRI alone appeared to the significant modality to predict recurrent seizures and neurodevelopment delay.

Discussion

The incidence of neonatal seizures was 7.5%. This is higher compared to other Indian studies which report an incidence ranging from 1.17-3.9% [4,5]. Poor long-term outcomes were noted in 35% of the study group. The major long-term outcomes in decreasing order of incidence included- neurodevelopment delay, recurrent seizures, failure to thrive, hearing and vision impairment. The significant risk factor for poor long-term outcomes were seizure etiology and post-neonatal EEG. This is similar to results reported in the earlier studies [3].

Etiologies associated with unfavourable outcome were low APGAR scores at 1 and 5 minutes, presence of hypoxic ischemic encephalopathy. HIE remains the commonest etiology for neonatal seizures in India [6,7] and is associated with poor long-term outcome. There was no significant difference detected in clinical seizure type/ duration of seizure and long-term outcome. This was similar to study by Tekgul et al [3]. However, Brunquell PJ et al [8] reported that clinical semiology is predictive of outcome in neonates with seizures and suggests the presence of unique pathophysiologic processes for different seizure types. Abnormal neurological examination at discharge, abnormal post neonatal EEG and neonatal and post neonatal MRI were significant risk factor for poor long-term outcome. Similar findings have been reported by various studies [3,9,10]

The present study underscores the importance of early recognition and management of neonatal seizures. It highlights the need for structured neurodevelopment follow up in all cases of neonatal seizures. The study further points to the role of clinical examination, EEG and MRI as associated risk factors of neurodevelopment outcome and identifying high risk neonates who require early interventions. The present study has a few pitfalls as well. It is a descriptive study where single point EEG was done and continuous EEG monitoring could not be done. Risk factors for term and preterm have been analysed separately. Follow up for 2 years should have been done to pick up persistence of long term abnormalities

Conclusion

Neonatal seizures are associated with significant morbidity in the form of predominantly neurodevelopment delay at 1 year of age.19 % of survivors are at risk for repeated seizures in infancy. Significant risk factors of poor neurological outcome at 1 year are low APGAR score at 1 and 5 minutes, presence of HIE, abnormal neurological examination at discharge and abnormal post neonatal EEG and MRI.

Table 1- Baseline characteristics of patients with neonatal seizures

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

Table 2- Risk factors for Recurrent Seizures

Risk factors	Cases n (%)	Controls n (%)	OR (95% CI)	Significance
Abnormal Neurological examination at Discharge	11(64.7)	25(33.3)	3.66(1.21 -11.06)	0.02*
Abnormal Post-neonatal EEG	14(82.3)	4(54)	82(16.67 -411.48)	<0.0001*

Abnormal MRI - Neonatal	7(41.2)	2(4)	10.5(1.36 -81.05)	0.02*
Abnormal MRI -Post Neonatal	10(58.8)	4(5.3)	15.5(3.47 -69.16)	0.0003*

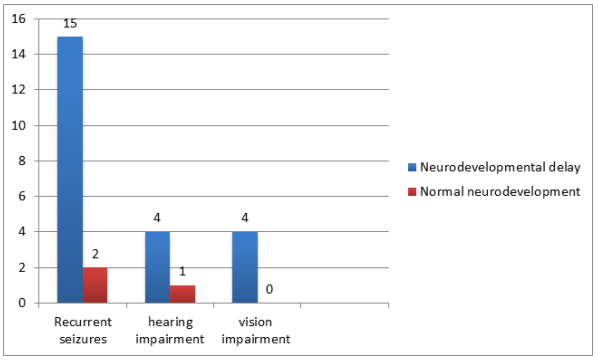
Table 3- Risk factors for Developmental Delay (Mental DQ)

Risk factors	Cases n (%)	Controls n (%)	OR (95% CI)	Significance
Low APGAR<5 at 1 min	20(68.9)	16(25.4)	6.6(2.47-17.2)	0.0001*
Low APGAR <7 at 5 min	17(58.62)	19.04)	6.02(2.28-15.89)	0.0003*
HIE	20(68.9)	15(23)	7.11(2.68-18.90)	0.0001*
Abnormal Neurological Examination at Discharge	25(86.2)	11(17.4)	29.54(8.55 -102)	<0.0001*
EEG- Post Neonatal	16(25.3)	2(3.17)	37.6(7.7-183.6)	<0.0001*
Post Neonatal - MRI	13(56.52)	1(1.58)	33.8(3.89-293.3)	0.0014*

Table 4- Risk factors for Developmental Delay (Motor DQ)

Risk factors	Cases n (%)	Controls n (%)	OR (95% CI)	Significance
Abnormal Neurological Examination at Discharge	20(83.33)	16(23.52)	16.2(4.84-55.55)	<0.0001*
EEG- Neonatal	16(66.7)	29(42.6)	2.68(1.02-7.2)	0.04*
EEG- Post Neonatal	16(66.7)	2(2.94)	66(12.7-341.24)	<0.0001*
Abnormal Post Neonatal MRI	13(51.46)	1(3.44)	45.5(5.14-402.7)	0.0006*
Abnormal Neurosonogram	5(20.83)	4(6.15)	4.5(1.08-18.56)	0.04*

Figure 1-Morbidities in cases with neurodevelopment delay and normal neurodevelopment



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