RESEARCH PAPER

The Newborn with Seizures – A Follow-up Study

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ABSTRACT

Objective: *To determine the sequelae of neonatal seizures in a cohort of newborns, recruited over a six month period.* ***Design:*** *Prospective hospital based study.* ***Setting:*** *The neonatal intensive care unit (NICU) of a tertiary care hospital.* ***Participants:*** *135 babies were recruited of whom 10 died and 25 were lost to follow up.* ***Methods:*** *The cases were followed up over four months.* ***Result:*** *68% of the babies followed up were normal; 32% had an abnormal neurological outcome. Seven (7%) developed post-neonatal epilepsy. Hypocalcemia was significantly associated with mortality (OR: 21.9; 95% CI: 1.2-391.2). No risk factors could be identified for post neonatal epilepsy. Presence of spike waves in the EEG was significantly related to abnormal neurological outcome (OR: 3.5; 95% C.I. 1.2-10.8).* ***Conclusions:*** *Majority of neonates with seizures have a normal outcome with no developmental delay or neurological deficit. Predominantly spike waves in the EEG is predictive of abnormal neurological outcome.*

Key words: *Neonate, Neurodevelopment, Prognosis, Seizures, Sequelae.*

INTRODUCTION

Neonatal seizures are the most common overt manifestation of neurological dysfunction in neonates(1). The most important factor that predicts their outcome is the underlying etiology(2). Patients with hypoxic encephalopathy (HIE), intraventricular hemorrhage (IVH) and neuronal migration disorders (NMD) are reported to have the worst prognosis. Neurological deficits also predict poor outcome. EEG abnormalities, such as burst suppression, low voltage, or multifocal abnormal discharges are associated with abnormal neurological outcome(3).

The present study was a prospective follow-up of newborns with seizures to determine the predictors of an adverse outcome.

METHODS

This was a prospective study conducted in the Newborn Unit of a tertiary care hospital. Newborns having seizures unresponsive to restraining maneuvers and unprovoked by stimulation, occurring for the first time within 28 days age, were enrolled. Neonatal seizures were defined as paroxysmal events with at least one of the following clinical characteristics: changes in behavior, stereotyped or periodic motor activities or autonomic dysfunction(1). All enrolled newborns were followed up at 2 and 4 months of age. The outcome was defined as abnormal in any of three conditions: (*i*) death either while in the NICU or during follow up; (*ii*) post neonatal epilepsy (seizure recurrence); or (*iii*) abnormal neurodevelopment defined as the presence of a motor deficit, developmental delay or spasticity. A few neonates were followed up to 8 months of age.

Data were collected regarding maternal and perinatal history, type and frequency of seizure and EEG and CT scan findings. The initial EEG was recorded at the end of the first week of life. All babies underwent biochemical testing for random blood sugar, serum calcium and electrolytes. Brain stem auditory evoked responses and visual evoked responses were evaluated wherever

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indicated. A repeat EEG was done at the end of 3 months. Developmental delay was assessed using the Trivandrum Development Screening chart(4).

Statistical analysis: The statistical analysis was performed using SPSS 11. Multivariate analysis and logistic regression were employed to assess the predictors of outcome.

RESULTS

We enrolled 135 cases over a six-month period. Of these, 120 were followed up for 2 months, 100 for 4 months and 88 for 8 months. Ten babies died during the study period. 96.3% had a CT scan of the head.

***Table* I** shows the etiological profile of neonatal seizures. In almost a quarter of cases, multiple causes were identified. Ten patients with HIE had an associated intracranial hemorrhage, hypoglycemia was recorded in 15 children with HIE, intracranial bleed or hypocalcemia; 4 cases of HIE had associated meningitis. Hypocalcemia was associated with HIE in two babies, with hypoglycemia in two and with subarachnoid hemorrhage in one. Etiological profile and the type and frequency of seizures were comparable between the group that came for follow up (*n*=110), and those lost to follow-up (*n*=25). 60.7% (82/135) of our patients had focal clonic seizures, 14.1% (19/135) had subtle seizures, 21.5% (29/135) had tonic seizures and 3.7% (5/135) had myoclonic seizures. There was no significant association between EEG changes and, etiology and type of seizure.

EEG change: Out of 85 neonates with normal EEG, 4 (4.7%) died, and 15 (17.6%) had sequelae. Of the four who died inspite of a normal EEG, two had an inborn error of metabolism, one had severe HIE and the fourth was a preterm baby. The EEG pattern associated with highest mortality was spikes waves 2/8 (25%). Sharp waves were associated with 1/25 (4%) mortality. Initial EEG showing predominant spike waves was associated with abnormal development in 50% (4/8). Sharp waves or a normal EEG were associated with abnormal development in 48% (12/25) and 22.7% (15/66) respectively.

TABLE I ETIOLOGICAL PROFILE OF NEONATAL SEIZURES

Etiology	Number (%) (*n*=135)
Hypoxic ischemic encephalopathy*	30 (40.5%)
Hypoglycemia*	24 (32.4%)
Benign neonatal seizures*	8 (10.8%)
Meningitis*	7 (9.4%)
Intracerebral hemorrhage*	5 (6.7%)
Benign sleep myoclonus*	4 (5.4%)
Cerebral malformation*	3 (3.6%)
Neonatal stroke*	3 (3.6%)
Seizure disorder*	3 (3.6%)
Kernicterus*	2 (2.7%)
Hypocalcemia*	2 (2.7%)
Inborn error of metabolism	2 (2.7%)
Anoxic*	1 (1.3%)
Unknown	6 (8.1%)
Multiple causes	35 (47.2%)

** The sole reason identified for the seizures.*

25% (2/8) of neonates with predominant spike waves in the initial EEG, 12% (3/25) with predominant sharp waves and 3% (2/66) of those with normal EEG had post neonatal epilepsy. Five of the 100 patients who underwent a follow-up EEG had an abnormal record. Two of them had HIE at presentation; two had a neuronal migration disorder and one had hypoglycemia.

Outcome: Ten patients died during the study period. Out of 100 who came for follow up, 32 had developmental delay. Of those with developmental delay 7 of the babies followed up had post neonatal epilepsy, 24 had spasticity, 10 had abnormal vision and 5 had defective hearing at the four month follow-up. 68 babies were normal at follow up. Birthweight, gestational age, head circumference at birth, and age of first seizure could not predict adverse outcome in this cohort.

Table II provides details of risk factors for adverse outcome. Hypocalcemia (OR:21.9; 95% CI: 1.2-391.2) had a significant association with mortality. None of the variables had a significant association with post-neonatal epilepsy. Spike waves in the first EEG (OR 3.5; 95% C.I. 1.2-10.8)) had a significant relation to abnormal neurological outcome.

TABLE II RISK FACTORS FOR ADVERSE OUTCOME IN NEONATAL SEIZURES

Risk Factor	Death *n/N* (%)	OR (95% CI)	Post Neonatal Seizures *n/N* (%)	OR (95% CI) *n/N* (%)	Abnormal neuro-development	OR (95% CI)
Seizure type						
Subtle	2/16(12.5)	0.11(0.01- 3.1)	2/14(14.2)	0.28(0.02- 3.3)	5/14(35.5)	0.39 (0.04- 3.58)
Clonic	3/64(4.6)	0.37(0.02- 7.03)	3/61(4.9)	0.99(0)	17/61(27.8)	0.64 (0.05- 2.2)
Tonic	5/27(18.5)	0.62(0.03- 10.6)	2/21(9.5)	–	10/22(45.4)	1.1 (0.05- 2.2)
Myoclonic	0/3(0)	–	0/3(0)	–	0/3(0)	–
PIH	5/27(18.5)	0.19(0.01- 3.7)	4/21(19)	–	11/22(50)	1.9 (0.05- 2.2) *
Birth asphyxia	4/34(11.7)	4.1(0.34- 49)	3/29(10.3)	1.6(0.04-68.8)	12/30(40)	1.4 (0.49- 4.4)
Hypoglycemia	1/35(2.8)	0.26(0.02- 3.3)	2/34(5.8)	–	9/34(26.4)	0.77 (0.25- 2.4)
Hypocalcemia	2/6(33.33)	21.9(1.2,391.2)	0/4(0)	–	3/4 (75)	4.9 (0.39- 62.6)
Abnormal CT	5/62(8)	0.38(0.04,3.4)	5/56(8.9)	3.9 (0.11-137.8)	23/57(40.3)	2.1 (0.74- 6.2) †
EEG: Sp w	2/8 (25)	17.5(0.64-78.9)	2/8 (25)	–	4/8 (50)	3.5 (1.2-10.8) *
Sh w	1/25 (4.8)	0.21(0.01-4.8)	3/25(12.5)	–	12/25 (48)	4.3 (0.67-28.1)

**P*<0.05; †*P*=0.05; *N – Normal; PIH – Pregnancy induced hypertension; Sp w – Spike waves predominant; Sh w – Sharp waves predominant.*

DISCUSSION

Our study included both term and preterm neonates. The major seizure type was focal clonic seizures followed by tonic seizures. There was 10% mortality on follow-up; but among the survivors the majority had a normal outcome. We also found a significant association between patients with an adverse neurological outcome and the interictal EEG. No factor seemed to predict the occurrence of seizures beyond the neonatal period. The association of hypocalcemia with mortality has been previously noted in the literature not only in critically ill neonates, but also in children and adults(5,6). EEG changes were associated with abnormal development although it could not predict post neonatal epilepsy. The limitations of this study were the small sample size and short period of follow up.

Several studies have reported outcome in the form of death, neurodevelopmental delay and ongoing seizures(3,8-12). The percentage of children who died during the study period, and the proportion of children who developed post neonatal epilepsy were much less in our study than in the earlier studies. The neurodevelopmental outcome of the children in our cohort was comparable to the outcome of the children in the other studies. This could be because of the small numbers (27 babies) who were followed up. In a recent publication, Pisani, *et al*.(13) identified fifty-one preterm infants with gestational age <36 weeks with neonatal seizures and prospectively followed them up. Ten infants had a favourable outcome, 17 died, and 23 had an adverse outcome. Nine infants presented later with post-neonatal epilepsy.

Hypocalcaemia though by simple logic cannot be the immediate cause of death; the neonatologist should be on the look out for hypocalcaemia in the neonate with seizure and give priority for its correction; as it has been found to be the only significant association with mortality in our study. To prognosticate seizures beyond the neonatal period would be difficult; and you have to be judicious if you attempt to prognosticate as no factor including any particular etiology failed to show a statistically significant relation to the persistence of post neonatal seizures. Predominance of spike waves in the EEG can be probably taken as a marker of abnormal neurological outcome;

WHAT IS ALREADY KNOWN?

- Outcome of neonatal seizure is determined by its etiology.

WHAT THIS STUDY ADDS?

- The outcome of a child with neonatal seizure cannot be simply associated with the etiology of the seizures. Predominantly spike waves in the EEG seem to predict an abnormal neurological outcome.

predominantly sharp waves do not predict a bad outcome. Since the majority of neonates with seizures have a good outcome; the follow up should be meticulous to reassure the "normal" and to pick out the cases with early spasticity so that rehabilitative measures can be initiated with no delay.

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