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Original Research Article

A study of biochemical abnormalities and manifestations of neonatal seizures

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ABSTRACT

Background: Neonatal seizure is a common neurological problem in the neonatal period with a frequency of 1.5 to 14/1000 neonates1. Neonatal seizures have always been a topic of particular interest because of their universal occurrence. A varied number of conditions are capable of causing seizures in the neonatal period. The presence of a seizure does not constitute a diagnosis but is a symptom of an underlying central nervous system disorder due to systemic or biochemical disturbances. This study aims to study the various clinical types of seizures and the biochemical abnormalities associated with them.
Methods: This prospective study was conducted in the neonatology unit, department of pediatrics, C.S.I. Holdsworth Memorial Hospital, Mysore. Details of history, examination and investigations were recorded on predesigned proforma.
Results: Out of total 54 cases, 47(87%) cases had seizures during first 3 days of life and hypoxic ischemic – encephalopathy (HIE) remains the main etiological factor in 20 (37.04%) cases. More than one metabolic abnormality was present in 6 cases. Hypoglycemia & hypomagnesemia were the commonest abnormality in neonates having seizures.
Conclusions: A biochemical work up is necessary for all cases of neonatal seizures. The type of seizure does not give much information as to whether the seizures are purely metabolic or organic or about the type of biochemical abnormality.

Keywords: Biochemical abnormalities, Etiology, Hypoglycemia, Hypomagnesemia, Mysore, Neonatal Seizures

INTRODUCTION

Neonatal seizure is a common neurological problem in the neonatal period with a frequency of 1.5 to 14/1000 neonates.[1]Neonatal seizures often indicate primary or secondary dysfunctions of the central nervous system.[2-4] The other common etiologies of neonatal seizures are intraventricular hemorrhage or intraparenchymal hemorrhage, meningitis, sepsis or metabolic disorders.[5] New animal research suggests that neonates may exhibit some neuroprotection from prolonged seizures, but brief, recurrent seizures can result in significant, permanent changes in the central nervous system, an increased risk of epilepsy, and long term cognitive disabilities.[5] It is essential to determine the etiology of seizure at the earliest because it gives an opportunity to treat the seizure actively and promptly and avoid preventable morbidity, mortality and sequelae associated with it.[1]

A seizure is the most frequent sign of neurologic dysfunction in the neonate. Since seizures may be the only sign of a central nervous system disorder, their recognition is important.[6] The neonate is at particular risk for development of seizures because of metabolic,

anoxic, structural and infectious causes, although no causes can be identified in one fourth cases.[7] Clinical presentation of seizure, etiology, management and diagnosis of seizure differ markedly to convulsions occurring in older children.[7]

METHODS

This study was conducted in the neonatology unit, Department of pediatrics, C.S.I. Holdsworth Memorial Hospital, Mysore from March 2006 to March 2008. All neonates (1-28 days) with neonatal seizures admitted to NICU, C.S.I. Holdsworth Memorial Hospital were included in the study. A detailed history was recorded in each case on a pretested proforma. Emphasis was laid on the age of occurrence of first seizure, duration of seizure, number of seizures, type of seizure, antenatal, natal and post-natal risk factors which includes maternal drug addiction / withdrawal, maternal diabetes, prolonged rupture of membranes, Perinatal asphyxia, traumatic delivery, preterm, small for date, low birth weight baby, septicemia, meningitis, intracranial bleed and hyperbilirubinemia. Seizures were classified according to Volpe's classification as subtle, multifocal clonic, focal clonic, generalized tonic and myoclonic8. Detailed examination of neonate was done as per the proforma. Anthropometry was recorded and gestational age assessed according to new Ballard scoring system. As part of evaluation of cause of neonatal seizures, following investigations were ordered. Complete blood count, CRP, blood culture, random blood sugar, serum electrolytes, serum Ca+2, serum Mg+2, renal function tests. RBS< 40 mg/dl was diagnosed as hypoglycemia; total serum calcium <8.0 mg/dl was considered hypocalcaemia, hypomagnesemia if Mg+2was less than1.5mg/dl and hyponatremia if serum Na was less than 135 meq/L, if > 150 meq/L it was considered hypernatremia. If required, CSF analysis, neurosonogram, PT/aPTT, neuroimaging was done. The statistical operations were done through SPSS (Statistical Presentation System Software) for Windows, version 10.0 (SPSS, 1999. SPSS Inc: New York).

RESULTS

During the study period, total number of deliveries was 1992, out of which 16 neonates developed seizures. Among the 520 neonates referred from outside, 38 of them developed seizures. Table 1 depicts the age wise distribution of onset of neonatal seizures. Out of total 54 cases, 47 (87%) cases had seizures during first 3 days of life. In the present study 5 (9.3%) cases had seizures after 7 days of life which were mainly due to infections and metabolic causes. 14 (87.5%) in born neonates had day 1 seizures.

Table 2 shows distribution of cases according to gender. Among out born, out of 38 neonates 28 (73.7%) were male and among inborn babies, 13 (81.3%) were male.

Table 1: Onset of seizures in neonates according to the age.

Day of onset of seizures	Neonates
Day 1	45 (83.3%)
2-3 days	2 (3.7%)
4-7 days	2 (3.7%%)
8-28 days	5 (9.3%)
Total	54 (100%)

CC = 0.228; P <0.400.

Table 2: Distribution of cases according to gender.

Sex	Neonates		Total
	Out born	In born	
Male	28 (73.7%)	13 (81.3%)	41 (75.9%)
Female	10 (26.3%)	3 (18.8%)	13 (24.1%)
Total	38 (100%)	16 (100%)	54 (100%)

CC = 0.81; P <0.553.

Table 3: Distribution of cases in relation to gestational age.

Gestational age	Neonates		Total
	Out born	In born	
Term (≥37 weeks)	33 (86.8%)	15 (93.8%)	48 (88.9%)
Preterm (<37 weeks)	5 (13.2%)	1 (6.3%)	6 (11.1%)
Total	38 (100%)	16 (100%)	54 (100%)

CC = 0.100; P <0.461

Table 3 shows the distribution of cases in relation to gestational age. Among out born 33 (86.8%) were term and 5 (13.2%) were preterm. Among inborn babies 15 (93.8%) were term and 1 (6.3%) was preterm. Out of 48 term neonates 15 had hypoglycemia (31.3%) and among 6 preterm neonates, 3(50%) had hypoglycemia. Out of 48 term neonates 9 (18.75%) had hyponatremia, 1 preterm inborn neonate with infection had hyponatremia. Three neonates had hyponatremia with primary metabolic

disorders with no other associated comorbid states. Out of 48 term neonates, 7 (12.5%) had hypocalcemia, among 6 preterm neonates 1 (16.7%) had hypocalcemia. 3 term neonates had hypocalcemia as direct metabolic abnormality; one preterm neonate also had hypocalcaemia in the primary metabolic group without any co morbid condition. Out of 48 term neonates 15 (31.3%) had hypomagnesemia, among 6 preterm neonates 1 (16.7%) had hypomagnesemia. Among 48 term neonates 2 (4.2%) had Hypermagnesemia. 3 neonates with Primary metabolic disorder had hypomagnesemia of these two neonates had hypocalcaemia with hypomagnesaemia. Table 4 depicts the distribution of neonates having metabolic seizures in accordance with biochemical profile and gestational age.

More than one metabolic abnormality was present in 6 cases. Hypoglycemia and hypomagnesemia were the commonest abnormality in neonates having seizures. 2 neonates had only hypocalcemia and these 2 neonates had late onset hypocalcemia. 2 neonates had hypocalcemia with hypomagnesemia. Table 5 highlights the concomitant metabolic abnormalities in cases of neonatal seizures with established etiologies like HIE, meningitis, IC bleed, sepsis.

Table 4: Distribution of neonates having metabolic seizures in accordance with biochemical profile and gestational age.

Gestational age	No. of neonates	Hypo glycemia	Hypo natremia	Hypo calcemia	Hypo magnesemia	Hypo kalemia
Preterm	3	2	0	1	0	0
Term	10	3	3	3	5	0
Total	13	5	3	4	5	0

Table 5: Biochemical disturbances in neonates with seizures.

Etiology (n = 54)	Neonates showing metabolic abnormality	Hypo glycemia	Hypo calcemia	Hypo magnesemia	Hyper magnesemia	Hypo natremia
HIE (n = 20)	14	7	4	6	1	2
IC bleed (n = 3)	3	0	0	2	0	2
Meningitis (n = 2)	1	1	0	0	0	0
Metabolic (n = 13)	13	5	4	5	1	3
Infection (n = 13)	10	5	0	4	0	2

No neonates had Hypercalcemia, Hypernatremia and hyperglycemia.
*some neonates had more than one metabolic abnormalities, hence will reflect in more than one row.

Table 6: Distribution of cases with different type of seizure activity (n=54).

Type of seizure	Frequency	Percent
Subtle	14	25.9%
Focal clonic	7	13.0%
Multifocal clonic	3	5.6%
Focal tonic	3	5.6%
Multifocal tonic	3	5.6%
Focal myoclonic	3	5.6%
Gen myoclonic	2	3.7%
Subtle + focal clonic	7	13.0%
Subtle + multifocal clonic	12	22.2%
Total	54	100.0%

Table 6 depicts the distribution of cases with different type of seizure activity. Commonest type of seizure noted in this study was subtle seizure seen in 25.9 % cases.

DISCUSSION

In the present study, out of 1992 babies born in the hospital during study period, 16 (0.81%) had seizures. Out of 520 neonates referred to this institution during the study period, 38 (7.31%) had neonatal seizures. The incidence of neonatal seizures as reported by various authors ranges from 0.2% to 1.4%. Keen J.H. from Manchester and Brown et al, from Edinburgh, reported an incidence of 0.9% and 1.4% respectively.[9,10] Studies done by Brown and Airede from Nigeria showed the same as being 1.2% and 0.8% respectively Goldberg H.J. in 1983 from Melbourne, reported an overall increase in incidence of neonatal seizures from 2-6/1000 to 8.6/1000 live births from 1971 to 1980.[1,11,12] The variability in the incidence of above author's observations might be due to different criteria in selection of babies that is; gestational age, weight, high risk deliveries and population based studies. Eriksson and Zetterstrom in 1977 studied all full term neonates, whereas Rose and Lombroso studied only full term babies weighing 2500 grams and more.[7,13] The present study is comparable with the studies of Bergman (0.6), Goldberg (0.6), Airede (0.8), Garg (0.2-0.8) and Keen (0.9).[1,9,14-16] In the present study out of 54 neonates, 49 (90.74%) cases presented with seizures during the first week of life and 5 (9.25%) of the neonates had seizures after 7 days of life. Rose and Lombraso C.T. from Boston reported incidence of 115 (77.66%) cases during the first week of life, 21 (14.09%) cases during 2nd week and 13 (8.72%) after the 2nd week.[7] In the present study out of total 54 cases, 47 (87%) cases had seizures during first 3 days of life and hypoxic ischemic encephalopathy (HIE) remain the main etiological factor in 20 (37.04%) cases. In the present study 5 (9.25%) cases had seizures after 7 days of life which were mainly due to infections & metabolic causes. Calciolari et al, reported that 73.30%

cases had seizures during the 1st two days of life and Hypoxic-Ischemic-encephalopathy remains the main etiological factor in 87 (79.09%).[17] A study by Kumar et al, from Varanasi, reported 16 cases of birth asphyxia and al, (100%) had seizures during the first two days of life.[l,16,18] In a similar study of 59 neonatal seizures by Arvind et al, 32 (54.23%) cases had seizures during first 3 days of life and Hypoxic-Ischemic-Encephalopathy remains the main etiological factor.[19] In the present study an overall male to female ratio of 3.15:1 was seen. Male babies usually get better care in this society and are brought for medical care more frequently than female babies; the male dominance observed in the present study may be partially because of this factor. In the present study, out of 54 neonates, 64.81% cases had single seizure type. Focal clonic in 7 (12.96%) cases, multifocal clonic in 5.56% cases, generalized tonic in 5.56% and myoclonic in 9.26% of the cases. Combined type of seizures was observed in 35.19% of cases. Calciolariet al17 from Washington, reported single seizure type in 50% of cases and combined type in 50%. Among the single type, subtle seizures were more common in 21% cases followed by multifocal clonic 15%, 7% had focal and 2% had myoclonic seizure activity. In another study done by Arvind et al, out of 59 neonates, 69.49% cases had single seizure type with subtle seizures being the most common in 27.11% of cases.[19] Focal clonic were seen in 13.55% cases, multifocal clonic in 11.86% cases, generalized tonic in 3.39% and myoclonic in 8.47% of the cases. Combined type of seizures observed in 30.51% of cases. All the three studies are quite similar in that subtle seizures were the commonest type of seizures in both single and combined type. However, these findings are in contrast to those observed by Airede from Nigeria, this study showed single type of seizures in 91% of cases and combined type in 9%.[1] Among single type seizure activity generalized tonic were seen in 51%, focal clonic 23% and subtle in 16% of the neonates. In the present study, over all biochemical disturbances were observed in 41 cases which constituted 75.93% of all the subjects. Of these 41 cases hypoglycemia was observed in 18 (43.90%) cases, hypomagnesemia 17 (41.46%), hyponatremia in 9 (21.95%) cases, hypocalcemia in 8 (19.07%) cases while Hypermagnesemia, and Hypokalemia were observed in 4.87% and 4.87% of the cases respectively. Kumar et al18 studied 35 neonates for biochemical abnormalities in neonatal seizures. In 22 (62.8%) of their cases, hypocalcemia was detected in 7 (31.8%), hypoglycemia in 11 (50%), hypomagnesemia in 3 (13.63%) cases while Hypermagnesemia, hyperphosphatemia and hyponatremia were present in 4.54%, 13.63% and 5.45% of cases respectively. In a similar study of 59 neonatal seizures, over all biochemical abnormalities were observed in 29 (49.15%). Of these 29 cases hypocalcemia was observed in 15 (51.72%) cases, hypoglycemia in 12 (41.37%) cases, and hypomagnesemia in 4 (13.79%) cases while Hypermagnesemia, hyperphosphatemia and hyponatremia were observed in 3.44%, 3.44% and 17.25% respectively.[19] In the present study, 43.90% of cases showed hypoglycemia which is comparable with the studies done by Calciolari et al, (38%), Kumar et al, (50%) and Arvind et al, (41.37%).[17-19] The present study and the studies conducted by Kumar et al, and Arvind et al, showed one similarity in that the biochemical disturbances were seen in cases of hypoxic-ischemic-encephalopathy, intra cranial bleed, infections and metabolic disorders.[18,19] Calciolari et al, reported 8 cases of neonatal seizures with primary metabolic abnormalities, out of which 38% had hypoglycemia, 50% had hypocalcemia and 12.5% had hyponatremia. Rose AL from Boston observed hypocalcemia in 28 (20.4%) cases, followed by hypoglycemia in 7 (5.1%) cases.[7,17] In a study done by Kumar et al, on 35 neonates to determine the various biochemical abnormalities in neonatal seizures, primary metabolic disorders (9 cases) accounted for one-fourth of the cases of neonatal seizures, the most common being hypoglycemia, hypoglycemia with hypocalcemia and hypocalcemia with hyperphosphatemia.[18] A similar study showed primary metabolic abnormalities in 10 (16.94%) cases out of 59 neonatal seizures the most common being hypocalcemia 7 (70%) followed by hypoglycemia 4 (40%). In the present study of 54 neonatal seizures, 13 (24.07%) neonates showed primary metabolic abnormalities. Hypoglycemia 5 (38.46%) and hypomagnesemia 5 (38.46%) were the commonest in neonates having primary metabolic seizures while hypocalcemia 4 (30.77%) as metabolic abnormality was detected, of which 2 neonates had late onset hypocalcemia. Isolated hypoglycemia was observed in 5 (38.46%) cases of metabolic seizures, out of these 2 were preterm. More than one metabolic abnormality was observed in 6 cases. Among these, two neonates had hypocalcemia with hypomagnesemia, two neonates had hypoglycemia with hypomagnesemia, and one had hypoglycemia with hypocalcemia.

CONCLUSION

Biochemical abnormalities are common in neonatal seizures. There is a male predominance in this study. However, the study showed no significant difference in the pattern of biochemical abnormalities between the sexes. Isolated biochemical abnormalities without other co morbid states which could account for the seizures are seen in 24.1% Hypoglycemia and hypomagnesemia are the commonest biochemical abnormalities accounting for seizures in this group. 28 (51.85%) of cases of neonatal seizures with identifiable etiology had biochemical abnormality. These abnormalities may significantly contribute to seizure activity and possibly correction of these abnormalities may play a significant role in seizure control. A biochemical work up is necessary for all cases of neonatal seizures.

Onset of seizures was most common during first 3 days of life, 47 (87%) of which 20 (42.6%) was due to hypoxic ischemic encephalopathy, 10 (21.3%) due to infection, 8 (17%) due to metabolic causes. Hence babies with history

of significant birth asphyxia need to be closely watched and monitored for evidence of seizure activity. This is also of prognostic importance as, metabolic causes, once identified and treated have a good short term outcome. Hypoxic Ischemic encephalopathy is associated with significant mortality and morbidity. Hence neonates with seizures in first 3 days of life, with normal biochemical parameters and no evidence of sepsis; etiology is most likely to be hypoxic ischemic encephalopathy.

Subtle seizures were the commonest type of seizure observed in term and preterm neonates. The type of seizure does not give much information as to whether the seizures are purely metabolic or organic or about the type of biochemical abnormality.

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