Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Association of Biochemical Abnormalities in Different Type of Neonatal Seizures

R Malai Arasu[1], P Jagadeesan[2]

[1]Chief Civil Surgeon, Department of Pediatrics, Government Headquaters Hospital, Ramanathapuram, Tamil Nadu, India, [2]Senior Civil Surgeon, Department of Pediatrics, Government Headquaters Hospital, Ramanathapuram, Tamil Nadu, India

Abstract

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 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 Department of Pediatrics, Government Headquaters Hospital, Ramanathapuram. Details of history, examination and investigations were recorded on predesigned proforma.

Results: Out of total 100 cases, 82(82%) cases had seizures during the first 3 days of life and hypoxic ischemic encephalopathy remains the main etiological factor in 32 (32%) cases. More than one metabolic abnormality was present in five cases. Hypoglycemia and hypomagnesemia were the most common abnormality in neonates having seizures.

Conclusion: A biochemical workup 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.

Key words: Biochemical abnormalities, Etiology, Hypoglycemia, Neonatal seizure

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.[2,3] The other common etiologies of neonatal seizures are intraventricular hemorrhage or intraparenchymal hemorrhage, meningitis, sepsis, or metabolic disorders. 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.[4] 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.[5] The neonate is at particular risk for the development of seizures because of metabolic, anoxic, structural, and infectious causes, although no causes can be identified in one-fourth cases. Clinical presentation of seizure, etiology, management, and diagnosis of seizure differ markedly to convulsions occurring in older children.[6]

Access this article online

www.ijss-sn.com

Month of Submission : 09-2021
Month of Peer Review : 10-2021
Month of Acceptance : 11-2021
Month of Publishing : 11-2021

METHODS

This study was conducted in the neonatology unit, Department of Pediatrics, Government Headquaters Hospital, Ramanathapuram from February 2018 to January 2020. All neonates (1–28 days) with neonatal seizures admitted to onsite hospitals were included in the study. A detailed history was recorded in each case on a pretested

Corresponding Author: P Jagadeesan, Senior Civil Surgeon, Department of Pediatrics, Government Headquaters Hospital, Ramanathapuram, Tamil Nadu, India

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 myoclonic.[7] 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 hypocalcemia, hypomagnesemia if $Mg^{+2}$was <1.5 mg/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 Statistical Presentation System Software (SPSS) for Windows, version 10.0 (SPSS, 1999. SPSS Inc.: New York).

RESULTS

During the study period, total number of deliveries was 1634, out of which 63 neonates developed seizures. Among the 628 neonates referred from outside, 37 of them developed seizures. Table 1 depicts the age-wise distribution of onset of neonatal seizures. Out of total 100 cases, 82 (82%) cases had seizures during the first 3 days of life. In the present study, 8 (8%) cases had seizures after 7 days of life which were mainly due to infections and metabolic causes. Fifty-two (82.53%) inborn neonates had day 1 seizures.

Table 2 shows the distribution of cases according to gender. Among outborn, out of 37 neonates, 25 (67.56%) were male and among inborn babies, 51 (80.95%) were male.

Table 3 shows the distribution of cases in relation to gestational age. Among outborn 31 (83.78%) were term and 6 (16.21%) were preterm. Among inborn babies 55 (87.31%) were term and 8 (12.69%) were preterm. Out of 86, term neonates 26 had hypoglycemia (30.23%) and among 14 preterm neonates, 6(42.85%) had hypoglycemia. Out of 86 term neonates, 15 (17.44%) had hyponatremia, two preterm inborn neonates with infection had hyponatremia. Four neonates had hyponatremia with primary metabolic disorders with no other associated comorbid states.

Table 1: Onset of seizures in neonates as per age

Onset of seizure	Neonates
Day 1	82
2–3 Days	4
4–7 Days	6
8–28 Days	8
Total	100

CC: 0.228; P<0.4

Table 2: Distribution of patients as per gender

Gender	Neonates (%)		Total (%)
	Out born	In born	
Male	25 (67.56)	51 (80.95)	76 (76)
Female	12 (32.43)	12 (19.04)	24 (24)
Total	37 (100)	63 (100)	100

CC=0.81; P<0.553

Table 3: Distribution of patients in relation to gestational age

Gestational age	Neonates (%)		Total (%)
	Out born	In born	
Term (≥37 weeks)	31 (83.78)	55 (87.31)	86 (86)
Pre term (<37 weeks)	6 (16.21)	8 (12.69)	14 (14)
Total	37 (100)	63 (100)	100 (100)

Out of 86 term neonates, 10 (11.62%) had hypocalcemia, among 14 preterm neonates 1 (7.14%) had hypocalcemia. Two term neonates had hypocalcemia as direct metabolic abnormality; whereas no preterm neonate had hypocalcemia in the primary metabolic group. Of 86 term neonates 27 (31.39%) had hypomagnesemia, among 14 preterm neonates two (14.28%) had hypomagnesemia. Among 86 term neonates 4 (4.65%) had Hypermagnesemia. Three neonates with Primary metabolic disorder had hypomagnesemia of these two neonates had hypocalcemia with hypomagnesemia. 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 five cases. Hypoglycemia and hypomagnesemia were the most common abnormality in neonates having seizures. Four neonates had only hypocalcemia and these four neonates had late-onset hypocalcemia. Three neonates had hypocalcemia with hypomagnesemia. Table 5 highlights the concomitant metabolic abnormalities in cases of neonatal seizures with established etiologies such as hypoxic-ischemic encephalopathy (HIE), meningitis, IC bleed, and sepsis.

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 depicts the distribution of cases with different types of seizure activity. The most common type of seizure noted in this study was subtle seizure seen in 25% of cases.

DISCUSSION

In the present study, out of 1634 babies born in the hospital during the study period, 63 (3.85%) had seizures. Of 628 neonates referred to this institution during the study period, 37 (5.89%) had neonatal seizures. The incidence of neonatal seizures as reported by various authors ranges from 0.2% to 1.4%. Keen[8] from Manchester and Brown *et al*.,[9] from Edinburgh, reported an incidence of 0.9% and 1.4%, respectively, which is slightly less than our study findings. Studies done by Brown[10] from Nigeria showed the same as being 1.2% and 0.8%, respectively, Goldberg and Sheely in 1983 from Melbourne,[11] reported an overall increase in the incidence of neonatal seizures from 2.6/1000 to 8.6/1000 live births from 1971 to 1980. 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 g and more.[6,12] The present study observations are in contradiction to the findings of most of the investigations such as Bergman (0.6), Goldberg (0.6), Airede (0.8), Garg (0.2-0.8), and Keen (0.9).[1,8,13-15]

In the present study out of 100 neonates, 92 (92%) cases presented with seizures during the 1st week of life and 8 (8%) of the neonates had seizures after 7 days of life. Rose and Lombraso[6] from Boston reported incidence of 115 (77.66%) cases during the 1st week of life, 21 (14.09%) cases during 2nd week, and 13 (8.72%) after the 2nd week.

In the present study out of total 100 cases, 82 (82%) cases had seizures during the first 3 days of life and HIE remains the main etiological factor in 26 (26%) cases. In the present study 8 (8%) cases had seizures after 7 days of life which were mainly due to infections and metabolic causes. Calciolari *et al*.,[16] reported that 73.30% of cases had seizures during the first 2 days of life and Hypoxic-Ischemic-encephalopathy remains the main etiological factor in 87 (79.09%). A study by Kumar *et al*., from Varanasi, reported 16 cases of birth asphyxia and al, (100%) had seizures during the first 2 days of life.[1,15,17] In a similar study of 59 neonatal seizures by Sood *et al*., 32 (54.23%) cases had seizures during the first 3 days of life and Hypoxic-Ischemic-Encephalopathy remains the main etiological factor.[18]

In the present study, an overall male to female ratio of 3.16:1 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 100 neonates, 60% of cases had single seizure type. Focal clonic in 8 (8%) cases, multifocal clonic in 4% cases, generalized tonic in 6%, and myoclonic in 11% of the cases. Combined type of seizures was observed in 34% of cases. Calciolari *et al*.[16] 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%,

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

Gestational age	No of neonates	Hypoglycemia	Hyponatrema	Hypocalcemia	Hypo-magnesemia	Hyper-magnesemia
Preterm	11	6	2	1	2	-
Term	82	26	15	10	27	4
Total	93	32	17	11	29	4

Table 5: Biochemical disturbances in neonates with seizures.

Etiology (*n*=100)	Neonates with metabolic abnormality	Hypo-glycemia	Hypo-calcemia	Hypo-magnesemia	Hyper-magnesemia	Hypo-natremia
Hypoxic ischemic encephalopathy (*n*=37)	26	13	7	11	2	3
IC Bleed (*n*=6)	6	0	1	3	0	2
Meningitis (*n*=4)	2	1	1	0	0	0
Metabolic (*n*=24)	24	9	7	9	2	2
Infection (*n*=25)	20	10	0	9	0	2

Table 6: Distribution of patients with different types of seizure activity

Type of seizure	Observation No (%)
Subtle	25 (25%)
Focal clonic	14
Multi focal clonic	8
Multi focal tonic	6
Focal myoclonic	6
General myoclonic	4
Subtle with focal clonic	14
Subtle with multi focal clonic	23
Total	100 00%)

7% had focal and 2% had myoclonic seizure activity. In another study done by Arvind *et al*., out of 59 neonates, 69.49% of cases had a single seizure type with subtle seizures being the most common in 27.11% of cases. 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.[18] Combined type of seizures were 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 types. However, these findings are in contrast to those observed by Airede[1] 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, overall biochemical disturbances were observed in 78 cases which constituted 78% of all the subjects. Of these 78 cases hypoglycemia was observed in 33 (33%) cases, hypomagnesemia 32 (32%), hyponatremia in 9 (9%) cases, hypocalcemia in 16 (16%) cases while hypermagnesemia, and hypokalemia were observed in 4% and 4% of the cases, respectively. Kumar *et al*.[17] 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, overall 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.[18] In the present study, 33% of cases showed hypoglycemia which is comparable with the studies done by Calciolari *et al*.,[16] (38%), Kumar *et al*.,[17] (50%), and Arvind *et al*.,[18] (41.37%). 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, intracranial bleed, infections, and metabolic disorders.[17,18] 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.[6,16] In a study done by Kumar *et al*., on 35 neonates to determine the various biochemical abnormalities in neonatal seizures, primary metabolic disorders (nine cases) accounted for one-fourth of the cases of neonatal seizures, the most common being hypoglycemia, hypoglycemia with hypocalcemia, and hypocalcemia with hyperphosphatemia.[17] 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 100 neonatal seizures, 22 (22%) neonates showed primary metabolic abnormalities. Hypoglycemia 32 (32%) and hypomagnesemia 29 (29%) were the most common in neonates having primary metabolic seizures while hypocalcemia 11 (11%) as metabolic abnormality was detected, of which two neonates had late-onset hypocalcemia. Isolated hypoglycemia was observed in four cases of metabolic seizures; out of these one was preterm. More than one metabolic abnormality was observed in five 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 23%. Hypoglycemia and hypomagnesemia are the most common biochemical abnormalities accounting for seizures in this group. 51 (51%) 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 workup is necessary for all cases of neonatal seizures.

The onset of seizures was most common during the first 3 days of life, 86 (86%) of which 37 (43.02%) was due to HIE, 25 (29.06%) due to infection, 24 (27.90%) due to metabolic causes. Hence, babies with a 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. HIE is associated with significant mortality and morbidity. Hence, neonates with seizures in the first 3 days of life, with normal biochemical parameters and no evidence of sepsis; etiology is most likely to be HIE.

Subtle seizures were the most common 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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How to cite this article: Arasu RM, Jagadeesan P. Association of Biochemical Abnormalities in Different Type of Neonatal Seizures. Int J Sci Stud 2021;9(8):107-111.

Source of Support: Nil, **Conflicts of Interest:** None declared.