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A Study on Biochemical Abnormalities in Neonatal Seizures

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Abstract:
Background: *Neonatal seizure does not constitute a diagnosis but is a manifestation of an underlying disease of the central nervous system which may be due to systemic and biochemical disturbances. A study was conducted on neonates with seizures for a period of 1 year from 1st August 2016 to 31st July, 2017*
Objective: *To determine the biochemical abnormalities in neonatal seizures*
Design: *Prospective cross-sectional hospital based study*
Setting: *NICU of Gauhati Medical College and Hospital*
Methods: *A prospective cross-sectional hospital based study was conducted on neonates with seizures admitted in NICU of Gauhati Medical College and Hospital for a period of 1 year from 1st August 2016 to 31st July, 2017. Term and preterm neonates with seizures admitted in NICU were included in the study. All necessary investigations performed were recorded*
Results:*85 neonates (63.4%) out of 134 convulsing neonates had a biochemical abnormality either alone or in association with other etiologies. 49 neonates (36.5%) did not have any biochemical abnormality coincident on their etiology. 38 neonates (28.35%) had primary metabolic seizures of which hypoglycemia was the commonest biochemical abnormality and was present in 50% neonates in this group. Hypocalcemia was the next common abnormality and was present in 31.5% neonates within this group. 47 (55.2%) neonates had metabolic abnormalities superimposed or coincident on a primary illness like hypoxic ischemic encephalopathy, ICH, meningitis, sepsis etc. Metabolic abnormalities were more commonly associated with birth asphyxia and meningitis.*
Conclusion: *Hypoglycemia (45.8%) followed by hypocalcemia (25.8%) and hyponatremia (18.8%) are the commonest overall biochemical abnormalities present in neonatal seizures. A thorough biochemical work up is necessary in all cases of neonatal seizure for early recognition and prompt management of biochemical abnormalities in neonatal seizure.*

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I. Introduction

Neonatal seizure is a common neurological condition which requires immediate attention. Neonatal seizures are abnormal electrical discharge in the central nervous system of neonates, usually manifesting as stereotyped muscular activity or automatic changes.[1] Neonatal seizures are more common in newborn period than in any other phase of life[2] and are most frequent during the first 10 days of life.[3] Their incidence varies from 0.5 to 0.8 in term babies and 6 -12 percent in babies weighing less than 1500g.[2] There are multiple causes of neonatal seizure and can be primarily related to disorders of brain eg. HIE, CNS infections, CNS bleeds and structural anomalies of brain or secondary to metabolic problems e.g. hypoglycaemia, hyponatremia and other electrolyte disturbances or cryptogenic. Early identification and treatment of underlying disorders causing neonatal seizure is important to prevent additional seizure and seizure related systemic effects and neuronal injury.[4] Biochemical disturbances occur frequently in neonatal seizures either as an underlying cause or as an associated abnormality.[5,6] Early identification of biochemical disturbances and timely correction is important for optimal management of seizure and long term satisfactory outcome. The present study was conducted to determine the biochemical abnormalities in neonatal seizures.

II. Materials and Methods

A *prospective cross-sectional hospital based* study was conducted on neonates with seizures admitted in NICU of Gauhati Medical College and Hospital for a period of 1 year from 1st August 2016 to 31st July, 2017. Term and preterm neonates with seizures admitted in NICU were included in the study. Outborn neonates and neonates with doubtful seizures and seizures due to structural anomalies of brain were excluded from the study. The study was approved by the Instituitional Ethical Committee.

Data collection was based on a predesigned proforma which included demographic and clinical findings. All necessary investigations performed were recorded. Informed consent of parents were also taken.

Detailed antenatal, natal and postnatal history was taken. Age of onset of seizures, type, duration and number of seizures were recorded. Anthropometry was recorded and gestational age was assessed according to New Ballard Scoring.[7] Thorough physical examination was done and seizures were diagnosed by clinical observation. The neonatal seizures were classified according to Volpe's classification into tonic, clonic, multifocal and myoclonic seizures.[8] Investigations included complete blood counts, sepsis screen, blood culture and neurosonogram. Random blood glucose was done using glucometer and values were confirmed by glucose oxidase method. Serum levels of sodium, potassium, calcium, phosphorus and magnesium were estimated.

The criteria for diagnosing various biochemical disturbances were as follows:

Hyponatremia: Na <130 m.eq/l
Hypernatremia: Na >150 m.eq/l
Hypoglycemia: Blood sugar <40 mg/dl,
Hypocalcemia: Calcium <7.0 mg/dl,
Hypomagnesemia: Magnesium <1.5 mg/dl,
Hypermagnesemia: Magnesium >2.5 mg/dl

Other investigations like CSF analysis, CT scan brain, MRI brain, EEG were done as per requirement on a case to case basis. Data was analysed by simple statistical analysis by using percentage calculation.

III. Results

134 neonates presented with neonatal seizure during the study period. There was a male preponderance (58%) of neonatal seizure, with a male to female ratio of 1.39:1. Seizures occurred more frequently among term infants (70.1%) as compared to preterms (29.9%).

TABLE 1: Sex Distribution:

Sex	No.	Percentage
Male	78	58.2
Female	56	41.7

Subtle seizures were the commonest (38%) while tonic, clonic, myoclonic and combined seizures constituted 30%, 19%, 2% and 11% respectively.

A total of 85 (63.4%) convulsing neonates had biochemical abnormalities out of the total 134 cases of neonatal seizure. 38 neonates out of 85 convulsing neonates had primary metabolic seizures in whom no other associated morbid condition that causes seizures could be made out. 47 (55.2%) neonates had metabolic abnormalities superimposed or coincident on a primary illness like hypoxic ischemic encephalopathy, ICH, meningitis, sepsis etc. 49 neonates (36.5%) did not have any biochemical abnormality coincident on their etiology. In two (1.4%) neonates the etiology could not be elucidated. The etiology wise distribution of cases is shown in table 2.

TABLE 2: Etiology of neonatal seizure

Etiology	Number	Percentage
Hypoxic ischaemic encephalopathy	66	49.2
Intracranial Haemorrhage	5	3.7
Meningitis	10	7.4
Septicaemia	13	9.7
Undiagnosed	2	1.4
Primary Metabolic	38	28.35
Total	134	

Out of the 85 babies, 49 (57.64%) were term, 36 (42.35%) were preterm. Hypoglycaemia was the most common biochemical abnormality in both preterm and term neonates with seizure which is then followed by hypocalcaemia and hyonatremia. Table 3 shows distribution of neonates in accordance with biochemical abnormalities and gestation.

Out of the 38 neonates with primary metabolic seizures, 16 (42.1%) were preterm and 22 (57.8%) were term.

TABLE 3: Distribution of Neonates with seizure in Accordance with Bio-chemical Profile and Gestational Age:

Gestation	Hyponatremia	Hypoglycaemia	Hypocalcaemia	Hypomagne Semia	Hyper Natremia	Hypo Mg+Ca	Total
Preterm	5	21	8	1	1		36
Term	11	18	14	1	3	2	49
Total	16	39	22	2	4	2	85

Hypoglycaemia was the commonest biochemical abnormality in primary metabolic seizures, comprising a total of 50% (n=19) of the total cases (n=38). The nineteen cases included 4 cases of infant of diabetic mother and others were preterm and low birth weight babies. Among the secondary metabolic causes, hypoglycaemia was most commonly associated with HIE.

Hypocalcemia was the next commonest abnormality comprising 31.5% (n=12) among the cases with primary metabolic seizures. 4 were preterm and 8 were term babies. Early onset hypocalcemia was seen in 6 cases while late onset hypocalcemia was seen in 3 cases and 3 cases were infants of diabetic mothers (IDM). Hypocalcemia was most commonly found in HIE among the secondary metabolic causes of neonatal seizure.
Combined hypocalcemia and hypomagnesemia were found in 2 cases (5.2%) who presented as convulsions with late onset hypocalcaemia. There was 1 cases (2.6%) of isolated hypomagnesemia of unknown origin. There were 3 cases of hypernatremia (7.8%) of the total 38 cases of primary metabolic seizures due to hypernatremic dehydration. There was 1 case (2.6%) of isolated hyponatremia whose cause could be elucidated. Among the secondary metabolic causes, hyponatremia was most commonly associated with HIE.

HIE was most commonly associated with biochemical abnormalities among the secondary metabolic causes. Table 4 shows distribution of neonatal seizure cases in relation to etiology and biochemical abnormalities.

TABLE 4: Distribution of cases in relation to etiology and biochemical abnormalities

Etiology	Neonates showing metabolic Abnormality	Hyponatremia	Hypoglycemia	Hypocalcemia	Hypomag Nesemia	Hypernat Remia	Hypo magnesemia+ hypocalcemia
HIE (n=66)	34	11	14	8	1		
Meningitis (n=10)	5	2	2	1			
Septicaemia(n=13)	6	1	3	1		1	
Undiagnosed (n=2)							
Intracranial Haemorrhage (n=5)	2	1	1				
Primary metabolic abnormality (n=38)	38	1(2.6%)	19 (50%)	12 (31.5%)	1(2.6%)	3 (7.8%)	2 (5.2%)
Total(n=134)	85	16 (18.8%)	39 (45.8%)	22(25.8 %)	2 (2.3%)	4(4.7%)	2 (2.3%)

IV. Discussion

In the present study, overall biochemical abnormalities were observed in 85 cases out of a total of 134 cases of all convulsing neonates which constituted 63.4 %. It is similar when compared to studies conducted by Kumar et al (22/35= 62.8%), Sood et al (29/59= 49.15%).[9,10] Kumar et al, in their study on 35 neonates with seizures found biochemical abnormalities in 22 (62.8 %) cases.[9] Sood A et al in a similar study of 59 neonates observed biochemical abnormalities in 29 cases (49.15%).[10]The present study showed that biochemical abnormalities can be an underlying cause of neonatal seizure or it may be present in association with cases of HIE, ICH, septicemia and meningitis, and that one or more biochemical abnormalities can coexist within an individual case of neonatal seizure which is in agreement with other studies.[9,10]

In this study, perinatal asphyxia (49.2%) was the most common cause of neonatal seizure followed by acute metabolic disturbances (28.35%) which is similar to studies done by Roshith et al., Ajay et al, Prasad et al, Sudia et al and Aziz Wani et al.[11,12,13,14,15]

Out of the 134 neonates with seizure, primary biochemical abnormalities were observed in 38 neonates (28.35%) in our study which is similar to studies by Sood et al, Kumar et al.[9,10] Sood et al reported primary metabolic abnormalities in 10 (16.94%) cases out of 59 neonatal seizures and Kumar et al reported primary metabolic abnormalities in 9 (25.7%) out of 35 neonates.[9,10] Sudia et al reported metabolic abnormality in 16 % cases.[14]

Hypoglycemia was present in 39 cases (45.8%) out of 85 cases of neonatal seizure with biochemical abnormality which is similar with the findings published by Kumar et al (50%), Sood et al (48.27%) and Arunkumar et al (53.65%).[9,10,16] As a primary biochemical abnormality, hypoglycaemia was the commonest cause constituiting 50% (n=19) which is similar to studies by Madhusudhan et al (52.1%) and Arun kumar et al (62.5%).[16,17] The remaining 20 cases were associated with birth asphyxia, meningitis, sepsis etc. which were possibly attributed to poor intake, increased metabolic rate coupled with increased glucose utilisation and impaired ability to mobilise glucose found in cases with sepsis and meningitis.[18]

Hypocalcemia affected 25.8% (n=22) of neonates with seizures in this study which is similar to that of studies reported by Kumar et al (31.8%), Arun kumar et al (31.7%).[9] Hypocalcaemia was the second most common cause accounting for 31.5% of cases of primary metabolic abnormalities which is similar to studies by Arun kumar et al (37.5%).[16] However Sood et al reported a higher incidence (70%).[10]

Hyponatremia (18.8%) was the third most common abnormality in the present study. Birth asphyxia accounted for 68.7% cases with hyponatremia while meningitis, ICH and sepsis accounted for the remaining cases. The most probable explanation for occurrence of hyponatremia might be due to fluid overload as a result of renal compromise or due to syndrome of inappropriate secretion of anti diuretic hormone.[19] Kumar et al reported hyponatremia in 10 out of 22 (45.45%) cases which is higher compared to our study, while Sood et al have reported a similar incidence (17.24%).[9,10] There was 1 case (2.6%) of hyponatremia presenting as a primay metabolic abnormality which is similar to studies by Kumar et al, Madhusudan et al.[9,17]

Hypernatremia was found in 4.7% cases of neonatal seizure with biochemical abnormalities. As a primary metabolic abnormality, it was present 3 cases (7.8%).This finding is similar to Madhusudan et al.[17] There were 2 cases of combined hypomagnesemia and hypocalcemia which presented as a primary metabolic abnormality similar to Madusudan et al and Yadav et al.[17,20] Hypomagnesemia was found in 2 cases (2.3%), 1 of which was associated with birth asphyxia and the other one presented as a primary metabolic abnormality, which is similar to studies by Kumar et al, Madhusudan et al and Arunkumar et al.[9,16,17] No case of hypermagnesemia, hypokalemia or hyperkalemia were encountered in this study. Table 5 shows comparison of biochemical abnormalities in neonatal seizure as reported by various authors.

TABLE 5: Comparison of biochemical abnormalities in neonatal seizure as reported by various authors:

Biochemical parameter	Kumar n =35	Madhusudhan n=52	Arunkumar n=100	Present study n= 85
Hyponatremia	10	19	24	15
Hypoglycaemia	11	17	44	39
Hypocalcemia	7	11	26	22
Hypomagnesemia	3	1	3	3
HypoCa+ HypoMg	0	1	0	1
Hypernatremia	0	3	0	5
Hypermagnesemia	1	0	2	0
Hyperphosphatemia	3	0	0	0

Madhusudhan et al found hypocalcemia in 21.73% cases, hyponatremia in 4.3% cases, hypernatremia in 13.04 % cases and hypomagnesemia in 4.3% cases which is similar to this study.[17] In a study by Calciolari et al, 8 cases of neonatal seizures with primary metabolic abnormalities were found, out of which 38 % had hypoglycemia, 50 % had hypocalcemia and 12.5 % had hyponatremia.[21] Rose et al from Boston reported hypocalcemia in 28 (20.4%) cases, followed by hypoglycemia in 7 (5.1%) case.[22]

In a study by Yadav et al, primary metabolic abnormality was found in 16% babies with neonatal convulsions, of which 41.6% had hypocalcaemia, 33.3% had hypoglycaemia, 16.6% had combined hypomagnesemia and hypocalcaemia and 8.3% had hyponatremia.[20]

Aziz Wani et al reported 31% cases with primary metabolic seizure of which hypocalcaemia was the commonest (70%) followed by hypoglycaemia (41%), hypomagnesemia and hyperphosphatemia each accounted for 29.4% and 11.8% respectively.[15]

Hypoglycaemia and hypocalcaemia were most common metabolic abnormality in neonatal seizure in this study which is in concordance with all above studies. Table 6 shows comparison of biochemical abnormalities in primary metabolic seizure as reported by various authors.

TABLE 6: Comparison of biochemical abnormalities in primary metabolic seizure as reported by various authors:

Biochemical Parameter	Kumar n=9	Madhusudhan n=23	Arunkumar n=16	Present study n=38
Hyponatremia	1	1	0	1
Hypoglycaemia	5	12	10	19
Hypocalcemia	5	5	6	12
Hypomagnesemia	1	1	1	1
HypoCa+ HypoMg	0	1	0	2
Hypernatremia	0	3	0	3

V. Conclusion

Hypoglycemia and hypocalcemia are the most common metabolic disturbances present not only as primary disorders but also associated with specific etiology. A thorough biochemical work up is necessary in all cases of neonatal seizure because early recognition and prompt management of biochemical abnormalities would help in preventing occurrence of seizures and also help in avoiding over use of anticonvulsants in the management of seizures resulting in favourable neurological outcome with less long term morbidity.

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