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SPECTRUM OF BIOCHEMICAL ABNORMALITIES IN NEONATAL SEIZURES AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Biochemical disturbances occur frequently in neonatal seizures either as an underlying cause or as an associated abnormality. Metabolic disturbances could be more commonly transient and rapidly correctable or less commonly inherited as persistent causes.
Objective: To determine the frequency and spectrum of biochemical abnormalities in neonatal seizures of different etiologies.
Materials and Methods: A total of 100 consecutive neonates presenting with seizures from September 2013 to August 2014 were enrolled in the study. Baseline characteristics of convulsing neonate including sex, gestational age, weight, head circumference & length were recorded at admission. Clinical details of each seizure episode reported by the mother and subsequently observed by the resident doctors on duty were recorded i.e. age at onset of seizures, duration of seizure, number and type of seizure. Venous blood was collected as soon as possible and blood glucose, total serum calcium levels, Na+, K+, Mg and P-levels were done immediately after baby had seizures and before instituting any specific treatment.
Results: Cumulative frequency of neonatal seizures was recorded as 3.9% among admitted neonates in our setup. Around 54% neonates had a biochemical abnormality either alone or in association with other etiologies like hypoxic ischemic encephalopathy (HIE), intracranial hemorrhage (ICH), meningitis and sepsis. 17 neonates (31%) had primary metabolic seizures. Hypocalcemia was the commonest biochemical abnormality in primary metabolic seizures and was present in 70% neonates in this group. Hypoglycemia was the next common abnormality and was present in 41% neonates within this group. 37 neonates (68.5%) had biochemical abnormalities superimposed on other etiologies of neonatal seizures. Metabolic abnormalities were more commonly associated with intracranial hemorrhage (53.8%) and birth asphyxia (50%). Hypoglycemia (22.7%) followed by hypocalcemia (20.5%) were the commonest biochemical abnormalities in these patients. Hyponatremia was found in 20% (n=3) cases of meningitis and in 15.4% (n=2) cases of ICH.
Conclusion: Transient metabolic disturbances occur with a higher frequency in association with other etiologies of neonatal seizures. Early recognition and treatment of these biochemical disturbances is essential for the optimal management and satisfactory outcome. Hypoglycemia and hypocalcemia occur with higher frequency in cases of birth asphyxia, the commonest cause of neonatal seizures. Hypocalcemia followed by hypoglycemia are the commonest transient metabolic disturbances in primary metabolic seizures.

INTRODUCTION

Seizures are the most common and distinct clinical manifestation of neurological dysfunction in the newborn infant.

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Neonatal seizures are a common neurological problem in neonates with a frequency of 1.5-14/1000 neonates (Airede, 1991). Biochemical disturbances occur frequently in neonatal seizures either as an underlying cause or as an associated abnormality (Brown *et al*., 1972 and Sood *et al*., 2003). Metabolic disturbances could be more commonly transient and rapidly correctable or less commonly inherited as persistent causes. Infants of diabetic mothers, small for gestational age

(SGA) infants and infants with birth asphyxia are at more risk. Infants with sepsis and meningitis frequently have hypoglycemia which can be attributed to inadequate intake, increased metabolic rate and impaired ability to metabolize glucose (Leaks *et al*., 1981). Hypocalcemia is defined as total serum levels <7mg/dl, although the exact level at which seizure occurs is debatable. Late onset hypocalcemia due to use of high phosphate infant formula has been cited as common cause of seizures (Keen, 1973; Interny *et al*., 1969 and Rose and Lombroso, 1970). However commonly hypocalcemia occurs in infants with trauma, hemolytic disease, asphyxia and IDM and usually coexist with hypoglycemia and hypomagnesemia (Mark S. Scher, 2005) and presents at 2-3 days of life. Hypomagnesaemia with serum levels <1.5mg/dl can occasionally manifest with tetany and seizures at 2-4 weeks of age and has secondary hypocalcemia associated with it. In infants of diabetic mothers, hypomagnesaemia appears to be a consequence of maternal Mg depletion.

Hyperphosphatemia may be caused by ingestion of milk formulas containing high amounts of phosphorous, excessive parenteral administration of phosphorus, impaired renal function, and hypoparathyroidism (Carole Kenner, 2007). In a study on birth asphyxia hypocalcemia with or without hyperphosphatemia occured in around 12.5% cases (Kumar *et al*., 1995). Hyponatremia as a result of fluid overload renal compromise and SIADH (syndrome of inappropriate ADH secretion) can be a frequent complication of birth asphyxia (Kumar *et al*., 1995). Similarly SIADH can be a part of ICH (Scher and Paintar, 1989).

MATERIALS AND METHODS

A hospital based prospective observational study was undertaken in the Postgraduate Department of Pediatrics, G.B. Pant Hospital, which is a referral hospital of Government Medical College, Srinagar for children. A total of 100 consecutive neonates presenting with seizures from September 2013 to August 2014 were enrolled in the study.
Following operational definitions were used during the study;

Prematurity was considered in any neonate born before 37 completed weeks, if the last date of monthly period was known or in infants whose estimated gestation by NBS (New Ballard Score) was less than 37 completed weeks (Eregie, 2000).

Term neonate was described as having gestational age between 37 to 41 completed weeks.

Primary metabolic seizures: seizures due to transient biochemical abnormalities in the absence of other etiologies for neonatal seizures (Sood *et al*., 2003).

Non metabolic seizures: For our study purposes we defined non metabolic seizures as seizures having biochemical abnormalities coincident upon other etiologies for neonatal seizures like birth asphyxia, meningitis, sepsis etc (Sood *et al*., 2003).

Sepsis: Positive blood or CSF cultures. (definite sepsis)
Possible Sepsis (WHO, 2005): Presentation with either one of the following: Abnormal temperature (>37.5^{o}C or <35.5^{o}C), respiratory distress, lethargy, feeding problems or seizures, premature rupture of membranes (PROM), foul smelling liquor, amnionitis. Positive septic screen i.e. presence of at least two out of the four parameters namely, total leucocyte count <5000/mm^3, bands to neutrophill ratio of >0.2, CRP >10ng/ml and micro-ESR of> 10mm in one hour.

Meningitis: Diagnosed on CSF examination as >20 WBC in CSF (John P. Cloherty *et al*., 2008) with predominance of polymorphonuclear leucocytes.

Neonatal Encephalopathy (Birth Asphyxia) No cry at birth, poor Apgar score 6 or <6 at 5 min (in hospital born neonates), an accompanying history of feeding problems, restlessness, agitation, hypotonia, seizures, and coma or similar symptoms and signs after excluding other possible diagnosis.

***Intracranial Haemorrhage*:** It was diagnosed on brain ultrasound or CT scan.

Criteria for diagnosing various biochemical abnormalities: (Kumar *et al*., 1995)

Hypoglycemia : blood sugar <40mg/dl
Hypocalcemia : total serum calcium <7mg/dl
and ionized serum calcium < 4.4mg/dl
Hypomagnesemia : serum magnesium <1.5mg/dl
Hypernatremia : serum sodium >150meq/dl
Hyponatremia : serum sodium <130meq/dl
Hypokalemia : serum potassium <3.5meq/dl
Hyperkalemia : serum potassium >5.5meq/dl
Hyperphosphatemia : serum phosphorus >8mg/dl

Data Collection Procedure

Detailed antenatal history, i.e. maternal age, past medical history, parity, gestational age, history of illness during pregnancy, medication during pregnancy; natal history viz. evidence of foetal distress, apgar score, type of delivery, medication given to mother during delivery were recorded. Baseline characteristics of convulsing neonate including sex, gestational age, weight, head circumference & length were recorded at admission. Clinical details of each seizure episode reported by the mother and subsequently observed by the resident doctors on duty were recorded i.e. age at onset of seizures, duration of seizure, number and type of seizure. Seizure classification was as per criteria by Volpe (Volpe, 2001). Venous blood was collected as soon as possible and blood glucose, total serum calcium levels, Na^+, K^+, Mg and P-levels were done immediately after baby had seizures and before instituting any specific treatment. Open automated discrete, random access, patient prioritized clinical chemistry autoanalyzer (ERBA XL-300 Transasia Autoanalyzer) was used for carrying out the sample analysis. Ca was determined by Arsenazo method (Farrell, 1984) (Erba Mannheim XL System Packs): Mg by calmagnite method (Gindler and Heth, 1971) (Erba Manheim XL system pack); phosphorous with UV Molybdate method (Tietz, 1986) (Erba Mannheim XL system packs) and glucose by Trinder's method (Trinder, 1969) (Erba Mannhem XL System Packs).

Na^+ and K^+ levels were done by ROCHE OMNI arterial blood gas (ABG + Electrolyte) analyzer. In addition complete blood counts, band cell count, absolute neutrophill count, micro-ESR, blood culture, USG cranium, MRI/CT, and CSF analysis were done as per the requirement in individual cases.

Statastical Analysis

Data was described as mean ± SE and %age. Parametric variables were compared by student T test & analysis of variance. P-value less than 0.05 was considered significant. SPSS 16.0 and MS Excel software were used for data analysis.

RESULTS

A total of 2550 neonates were admitted during the study period. Out of them 1450 were referred to us from peripheral institutions (outborn), while around 1100 neonates were born in our institution (inborn). Cumulative frequency of around 3.9% was hence recorded in neonatal seizures in our set up.
Mean age, sex and place or origin is given in table 1. The etiology vise distribution of cases is shown in table 2. Primary metabolic seizures except for late hypocalcemia had presentation in the first half of first week. Late hypocalcemia presented around the end of first week.

A total of 54 (54%) convulsing neonates had biochemical abnormalities. Seventeen neonates (31%) had primary metabolic seizures and 37 (69%) neonates had metabolic abnormalities superimposed or coincident on a primary illness like hypoxic ischemic encephalopathy, ICH, meningitis, sepsis etc. Forty six (46%) did not have any biochemical abnormality coincident on their etiology. In four (4%) neonates the etiology however could not be elucidated. Out of the 17 neonates with primary metabolic seizures 5 (24%) were preterm and 12 (70.6%) were term. Hypocalcemia was the commonest biochemical abnormality in primary metabolic seizures, comprising a total of 70.6% (n=12). Preterm and term each had 4 (80%) and 8 (60%) cases respectively, being individually also the commonest biochemical abnormality in preterm as well as term primary metabolic neonatal seizures. Late onset hypocalcemia was seen in 3 cases. While early onset hypocalcemia was seen in 6 cases and in addition was present in 3 cases were infants of diabetic mothers (IDM) Hypoglycemia was the next commonest abnormality comprising 41.2% (n=7) among the cases with primary metabolic seizures, 3 cases of IDM, one was large for date, one was preterm, one IUGR and one was term baby with AGA and had poor feeding. Hypomagnesemia and hyperphosphatemia each comprised 29.4% (n=5) and 11.8% (n=2) to the cases of primary metabolic seizures.

Table 1. Presenting Characteristics of the Neonates

Characteristic		N	%
Apgar Score at 5min	< 7	44	44.0
	7 to 10	56	56.0
Gestational Age (NBS)	Preterm	35	35.0
	Term	65	65.0
Weight	Appropriate for Gestation Age	68	68
	Large for Gestation Age	6	6
	Small for Gestation Age		26
Age of Onset of seizure (day)	mean ± SE	3.7 ± 0.4 (1, 25)	
Head Circumference (cm)	mean ± SE	33.8 ± 0.1 (30, 37)	
Length (cm)	mean ± SE	47.5 ± 0.3 (42, 53)	

Table 2. Etiology of the Neonatal Seizures

Etiology	N	%
Hypoxic Ischemic Encephalopathy	44	44
Intra Cranial Hemorrhage	13	13
Meningitis	15	15
Undiagnosed	4	4
Primary Metabolic	17	17
Septicemia	7	7

Table 3. Overall Biochemical Profile in Patients with Neonatal Seizures

		Number of Patients showing Metabolic Abnormality	Hypomagnesemia	Hyperphosphatemia	Hyponatremia	Hypocalcemia	Hypoglycemia
Primary Metabolic Seizures	N	17	5	2	0	12	7
	%	31.4	29.4	11.8	0.0	70.6	41.2
Non-Metabolic Seizures	N	37	4	3	10	14	20
	%	68.5	10.8	8.1	27.02	37.8	54.0
Total	N	54	9	5	10	26	27
	%	54.0	9.0	5.0	10.0	26.0	27.0

Table 4. Distribution of Neonates having Primary Metabolic Seizures in Accordance with Bio-chemical Profile and Gestational Age

Gestation Age		Number of Patients showing Metabolic Abnormality	Hypomagnesemia	Hyperphosphatemia	Hypocalcemia	Hypoglycemia
Pre-term	N	5	3	0	4	1
	%	29.4	60.0	0.0	80.0	20.0
Term	N	12	2	2	8	6
	%	70.6	16.7	16.7	66.7	50.0
Total	N	17	5	2	12	7
	%	100.0	29.4	11.8	70.6	41.2

Table 5. Distribution of Patients of "Non-Metabolic Seizures (n=37)" in accordance with Biochemical Profile

Etiology		Number of Patients showing Metabolic Abnormality	Hypoglycemia	Hypocalcemia	Hypomagnesemia	Hyperphosphatemia	Hyponatremia
Hypoxic Ischemic Encephalopathy (44)	n	22	10	9	4	3	5
	%	50.0	22.7	20.5	9.1	6.8	11.4
Intra Cranial Haemorrhage (13)	n	7	4	4	0	0	2
	%	53.8	30.8	30.8	0.0	0.0	15.4
Meningitis (15)	n	5	3	1	0	0	3
	%	33.3	20.0	6.7	0.0	0.0	20.0
Septicemia (7)	n	3	3	0	0	0	0
	%	42.9	42.9	0.0	0.0	0.0	0.0

Three preterm neonates had hypomagnesemia along with hypoglycemia; while as 1 term AGA neonate had hypomagnesemia of unknown origin as an isolated abnormality. Hypomagnesemia was present in one neonate of IDM along with other biochemical abnormalities. The overall biochemical profile of neonatal seizures is summarized in table 3. The biochemical profile and distribution of primary metabolic seizures with respect to gestational age is summarized in table 4. That of non metabolic seizures is depicted in table 5.

DISCUSSION

Frequency of neonatal seizures varies from 11-25% in an intensive care setting (Matloob Azam and Mahmoood, 1997). The incidence data in our study was close to 4%. However our incidence rate is similar to 3% shown in studies by Ment *et al*. (1982) and 4.1% by Asindi *et al*. (1995). In the present study, overall biochemical abnormalities were observed in 54 cases which constituted 54% of the all convulsing neonates. Out of these 54 cases 17 neonates had metabolic abnormalities (primary) in the absence of other etiologies for neonatal seizures. 37 cases had metabolic abnormalities in addition to a known underlying etiology of neonatal seizures. Out of the total of 54 neonates hypocalcemia was present in 26 (48.1%), hypoglycemia was observed in 27 (50%), hypomagnesaemia in 9 (16%), hyponatremia in 10 (18.5%) and hyperphosphatemia in 5 (9%). In a similar study by Arvind Sood *et al*. (2003) out of 29 cases of biochemical abnormalities hypocalcemia was present in 14 (48.27%) hypoglycemia in 14 (48.27%), hypomagnesemia in 5 (17.24%) and hyponatremia in 5 (17.24%) of cases. Kumar *et al*. (1995) studied a total of 35 neonates and 22 among them had biochemical abnormalities. Out of 22 only 9 (40%) had primary metabolic abnormalities, 10 (45.4%) cases had hyponatremia, 7 cases (31.8%) cases had hypocalcemia, 3 (13.6%) had hyperphosphatemia, hypomagnesemia in 3 (13.6%), hypermagnesemia in 1 (4.5%) and finally hypoglycemia in 11 (50%). Our study and study conducted by Arvind Sood *et al.* (2003) portrayed a similar spectrum of biochemical abnormalities and highlights the fact that hypoglycemia and hypocalcemia are the commonest biochemical abnormalities in neonatal seizures, and hence should be aggressively sought for and appropriately treated for a successful seizure control.

Our study and study by Kumar *et al*. (1995) showed one similarity that biochemical abnormalities were seen in cases of HIE, ICH, septicemia and meningitis, and that one or more biochemical abnormalities can coexist within an individual case of neonatal seizure. Hypocalcemia and hypoglycemia were the commonest metabolic abnormalities detected by Kumar *et al*. (1995) which is again in conformity with our study. Hyponatremia to the extent of 45.45% (n=10) were present in the study by Kumar *et al*. (1995). Although our study had only 10 (18.5%) cases with hyponatremia. Hyponatremia in birth asphyxia, ICH, meningitis and septicemia can be accounted for by inappropriate secretion of antidiuretic hormone and fluid overload and partly because of renal compromise in birth asphyxia. Primary metabolic abnormalities were seen in 17 (31.8%) neonates in our study.

Out of these 17, hypocalcemia was observed in 12 (41.2%), while hypomagnesemia and hyperphosphatemia each accounted for 5 (29.4%) and 2 (11.8%) of the cases respectively. Sood A *et al*[3] in a similar study had 10 (34.4%) cases with primary metabolic seizures, hypoglycemia and hypocalcemia each contributed to 4 (40%) and 7 (70%) respectively. Calciolari *et al*. (1988) reported 8 cases of neonatal seizures with primary metabolic abnormality, among them 4 (50%) were due to hypocalcemia, 3 (38%) due to hypoglycemia and 1 (12.5%) due to hyponatremia. In the study by Kumar *et al*. (1995), 9 cases contributed to primary metabolic seizure group, 5 (55.5%) cases had hypocalcemia, 2 (22.2%) cases had hyperphosphetemia and 5 (55.5%) with hypoglycemia. One or more abnormalities co-existed in our study in case of primary metabolic seizures. The following combination of abnormalities was seen in the same order of frequency hypocalcemia 4 (23%), hypocalcemia/ hypomagnesemia 4 (23%), hypoglycemia 3 (17.64%), hypoglycemia/ hypocalcemia 3 (17.64%), hypocalcemia/ hyperphosphatemia 2 (11.7%) and hypomagnesemia 1 (5.1%), hypoglycemia/ hypocalcemia /hypermagnesemia 1 (5.8%). Kumar *et al*. (1995) in their study found the combinations in the following order to frequency hypoglycemia, hypoglycemia/ hypocalcemia, hypocalcemia/ hyperphosphatemia.

Compared with the study by Kumar *et al*. (1995), our study had 70% cases of hypocalcemia in primary metabolic seizure as compared to 55.5% in the earlier. In our study hypocalcemia was present in 12 out of total 17 primary metabolic seizures. Higher rates of hypocalcemia in our study may be attributed partly to the fact that late onset hypocalcemia occurred in 3 cases who were fed with cow milk and referred to use from peripheral institutions and early onset hypocalcemia in 6 neonates (5 preterm and 1 preterm IUGR) and 3 cases of IDM. Only in 1 neonate with late onset hypocalcemia due to cow milk, hyperphosphatemia was also associated. However none of the cases was associated with hypoparathyroidism or any evidence of vitamin D deficiency in the mother or neonate. Hyperkalemia or hypokalemia was not found in any of the cases of primary metabolic or non-metabolic seizures. This is in accordance with the studies by Kumar *et al*. (1995) and Sood *et al*. (2003).

Conclusion

Transient metabolic disturbances occur with a higher frequency in association with other etiologies of neonatal seizures. Early recognition and treatment of these biochemical disturbances is essential for the optimal management and satisfactory outcome. Hypoglycemia and hypocalcemia occur with higher frequency in cases of birth asphyxia, the commonest cause of neonatal seizures. Hypocalcemia followed by hypoglycemia are the commonest transient metabolic disturbances in primary metabolic seizures.

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