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Original Article

Hypocalcemia and Hypomagnesemia in Neonates with Convulsions in A Tertiary Level NICU: A Prospective Cross-Sectional Study

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Abstract

Background: Seizures are common in the neonatal period and may be the first sign of neonatal dysfunction. The incidence of neonatal seizures has been reported to be 1.5 to 3 in 1,000 full term live births. **Aim of the Work:** To assess the levels of serum calcium and magnesium in neonates with neonatal convulsion. **Patients and Methods:** The study includes 100 full term neonates with neonatal convulsions and 100 healthy full-term neonates as controls. Serum calcium, magnesium, sodium, potassium and random blood sugar and complete blood count were estimated in all neonates. **Results:** There was significant decrease in total and ionized calcium and magnesium in convulsions group compared to control group ($p<0.001$, <0.001 & 0.015 respectively). There was a highly significant decrease in random blood sugar in convulsions group compared to control group ($p<0.001$). While there was no statistically obvious difference between the two groups regarding potassium and sodium level ($p>0.05$). Total calcium can detect convulsion at a cutoff 7.3 mg/dl with sensitivity, specificity, PPV and NPV was 31%, 100%, 100% and 59% respectively ($p< 0.001$). Also, Ionized calcium can detect convulsion at cutoff 4.1 mg/dl with sensitivity, specificity, PPV and NPV was 53%, 97%, 94.6% and 67.4% respectively ($p< 0.001$). Magnesium can detect convulsion at cutoff 1.3 mg/dl with sensitivity, specificity, PPV and NPV was 20%, 100%, 100% and 55.56% respectively ($p=0.015$). Random blood sugar can detect convulsion at cutoff 40 mg/dl with sensitivity, specificity, PPV and NPV was 41%,95%,89% and 61.7% respectively ($p<0.001$). **Conclusions:** This study showed that hypoglycemia, hypocalcemia, and hypomagnesemia were significantly associated with neonatal seizures. A thorough biochemical work up is necessary in all cases of neonatal seizure for early detection and effective treatment of biochemical abnormalities in neonatal seizure.

Key words: Hypocalcemia, hypomagnesemia, neonates, convulsions

Introduction

Neonatal hypocalcemia is a potentially life-threatening condition, with reported prevalence varying by gestational age, maternal and infant comorbidities, and perinatal factors [1].

It is defined as a total serum calcium level of less than 8 mg / dL (2 mmol/L) or ionized calcium level less than 4.8 mg/dL (1.2 mmol/L) in term infants and total calcium level less than 7 mg / dL (1.75 mmol / L) or ionized calcium less than 4 mg / dL (1 mmol / L) in premature infants [2]**.** Calcium homeostasis begins in utero. Active calcium transfer from circulation of the mother to her fetus occurs via a transplacental calcium pump controlled by parathyroid hormone (PTH)– related peptide, primarily during the third trimester of pregnancy. This process results in a higher plasma calcium concentration in the fetus compared with that of the mother and leads to fetal hypercalcemia at term, with total calcium concentrations in the blood of the umbilical cord reaching 10 to 11 mg / dL (2.5–2.75 mmol/L) [3]**.**

Placental transfer stops abruptly after birth. Within the first few hours of life, serum calcium concentrations begin to fall and reach a trough value by the second or third day of life. The calcium level then increases to normal values seen in children and adults by the tenth day of life. This homeostasis after birth depends on PTH secretion, dietary calcium intake, renal calcium reabsorption, skeletal calcium stores, and vitamin D levels [4]**.**

A constant extracellular calcium concentration is essential for cellular membrane integrity and cellular functioning. Calcium has a very important role in a multitude of biochemical processes as a second messenger, serves as a cofactor in blood coagulation, and is a significant ion in neuromuscular excitability [5]**.**

Clinical manifestations of neonatal hypocalcemia include jitteriness, tetany, muscle jerking, generalized or focal seizures stridor (secondary to

laryngospasm) [6]**.** Wheezing (secondary to bronchospasm), vomiting (secondary to pylorospasm), and prolonged QTc on electrocardiogram. Cardiac function may also be impaired because of poor muscle contractility**.** The severity of these symptoms may range from very mild to life threatening [8-10]**.**

Magnesium is a vital element for our bodies and is involved in numerous biological processes. It is the second most plentiful intracellular cation (Mg^{2+}) in our bodies and is critical for the function of over 600 enzymes and organization of the activity of several ion channels, as well as for basing of negatively charged molecules such ATP, ADP, RNA and DNA. In order to constantly suffice the body's requirements for this ion, there is a considerable storage capacity for Mg^{2+}. Blood serum only contains a fraction of this, with normal serum Mg^{2+} concentrations [Mg^{2+}] ranging from 0.70 to 1.1 mM. Even though only two thirds of this is biologically active (the ionized fraction), total serum Mg^{2+} concentrations are used in practice as a measurement of the total Mg^{2+} levels in cases. Therefore, when serum magnesium level is less than (<1.7 mg/dL) it is defined as hypomagnesemia, while if serum magnesium level is more than (>2.5 mg/dL) it is considered hypermagnesemia. A shortage of Mg^{2+} can have direct consequences, some well-established, others less clear, but it is also associated with several other diseases. Direct consequences or symptoms that might arise from hypomagnesemia are variable in severity and may correlate to the extent and duration of the Mg^{2+} shortage, ranging from leg cramps and tiredness to seizures, coma and eventually death [8-10]**.** It is an essential element having a role in neuronal excitability. It helps in slowing the electric discharge as well as its spread in the brain. Hence depletion of magnesium can lead to hyper excitability of neurons, Low Mg can reduce surface charge of neuronal membrane, thereby increasing neuronal hyperexcitability. [8-10]

Aim of the work: We aimed in this study to assess serum calcium and magnesium

levels in neonates with neonatal convulsion

Patients and Methods

A cross sectional study was done at NICU at Al-Azhar Assiut University Hospitals and Nag Hamady General Hospital during the period from October 2021 to July 2022 and included 100 full term neonates with convulsions and 100 well mature neonates as a control.

Inclusion criteria: Neonatal seizures happened in the first 28 days of life, neonates with convulsions who were born in our hospital and also babies who were born outside our hospital are included in our study , neonates presented by one of the following type of seizures ; Subtle seizures, generalized tonic seizures, multifocal clonic seizures, focal seizures and myoclonic seizures.

Exclusion criteria: Pretem neonates, cerebral palsy, hypoxic ischemic encephalopathy (HIE) and intra cranial hemorrhage (ICH) and neonatal sepsis.

Methods: All participants subjected to the following: Full history taking, clinical examination, investigation (CBC, random blood sugar and serum Calcium, Magnesium, Sodium and potassium.):

Hypocalcemia was defined when total serum calcium < 8.0 mg/dl, hypomagnesemia when serum Magnesium <1.6 mg/dl, hyponatremia when serum Sodium <135 meq/L, hypokalemia when serum potassium < 3.5 mmol/L. [8]

Assays: Serum Calcium estimation by O-Cresolphthalein Complexone (OCPC) method. The required liquid complexone is made by dissolving 10 mg o-cresolphthalein complexone in 50 mL alkaline borate, and then 50 mL of 0.05 N HCl are added to make the solution's pH 8.5 [9].

Serum Magnesium: Spectrophotometric analysis of serum magnesium levels were carried out using a commercial kit according to manufacturer’s instructions and measurements were made with a Roche Integra 800 spectrophotometer. Magnesium was quantified by high performance liquid chromatography [15].

Serum Sodium and potassium estimation by Ion Selective electrode (I.S.E) Method [16].

Statistical analysis

Data was collected, coded then entered as a spread sheet using Microsoft Excel 2016 for Windows, of the Microsoft Office bundle; 2016 of Microsoft Corporation, United States. Data was analyzed using IBM Statistical Package for Social Sciences software (SPSS), 21st edition, IBM, United States. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Continuous data was expressed as mean ± standard deviation, median & IQR while categorical data as numbers and percentage. Data was presented as tables and graphs. Results was considered statistically significant at a p-value of less than or equal 0.05 and highly statistically significant at a p-value of less than or equal 0.001. The used tests were: Chi-square test: For categorical variables, to compare between different groups. Fisher's Exact or Monte Carlo correction: Correction for chi-square when more than 20% of the cells have expected count less than 5. Student T-test: For normally distributed quantitative variables, to compare between two studied groups. Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups. Kruskal-Wallis test: It is a non-parametric equivalent to ANOVA and used when ANOVA assumptions were violated to compare between more than two groups of skewed data. Linear Correlation Coefficient [r]; used for detection of correlation between two quantitative variables in one group. The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the Sensitivity and specificity for quantitative Diagnostic measures that categorize cases into one of two groups.

Ethical consideration

This study carried out at Al-Azhar Assiut University Hospitals and Nag Hamady General Hospital with the approval of the Ethics Committee. The procedures

presented in this study protocol had been intended to ensure that the investigators abide by the principles of good clinical practice and the ethical principles laid down in the current revision of the Ethical Committee of Faculty of Medicine–Al-Azhar Assiut university and Nag Hamady hospital. Before being participating in the study, the Parents had been informed about the nature of the study using explained consent form in Arabic language

Results

This cross-sectional study was conducted on 100 full term neonates with convulsion and 100 healthy full-term neonates as control. Table (1) illustrates demographic and clinical characteristics among the two studied groups. There were 57 males and 43 females in convulsions group and there were 45 males and 55 females in control group. The mean age in convulsions group and control group was 4.47± 2.29 days and 4.74± 2.04 days respectively. The mean weight in convulsions group and control group was 3.07± 0.31 Kg and 3.09± 0.28 Kg respectively. The mean head circumference in convulsions group and control group was 33.67± 0.57 cm and 33.68± 0.48 cm respectively.

There were no statistically remarkable difference between the two groups as regards age, gender, weight and head circumference ($p>0.05$). Table (2): shows levels of serum calcium and magnesium among the two studied groups. The mean total calcium level in convulsions group and control group was 8.37± 1.09 and 9.15± 0.67 respectively. The mean ionized calcium level in convulsions group and control group was 4.50± 1.09 and 5.10± 0.20 respectively. The mean magnesium level in convulsions group and control group was 1.78± 0.38 and 1.96± 0.18 respectively.

There were significant decrease in total calcium, ionized calcium and magnesium in convulsions group compared to control group ($p<0.001$, <0.001 & 0.015 respectively). Table (3): shows levels of serum sodium, potassium and random

blood sugar among the two studied groups. The mean Na+ level in convulsions group and control group was 130.36± 2.76 mEq/L and 130.05± 2.25 mEq/L respectively. The mean K+ level in convulsions group and control group was 4.40± 0.58 mEq/L and 4.26± 0.54 mEq/L respectively. The mean random blood sugar level in convulsions group and control group was 77.91± 23.84 mg/dl and 88.56± 10.37 mg/dl respectively. There was significant decrease in random blood sugar in convulsions group compared to control group ($p<0.001$), while there was no statistically remarkable difference between the two groups concerning Na + and K+ levels ($p>0.05$). In table (4) the levels of Hb., WBCs and platelets among the two studied groups. The mean Hb level in convulsions group and control group was 16.22± 1.15 g/dl and 16.55± 0.82 g/dl respectively. The mean WBCs level in convulsions group and control group was 17.78± 7.07 and 19.37± 7.36 respectively. The mean platelets count in convulsions group and control group was 261.51± 105.80 and 288.42± 89.96 respectively.

There were no statistically remarkable difference between the two groups concerning levels of Hb., WBCs and platelets ($p>0.05$).

Receiver operating characteristic (ROC) analysis was performed to determine the value of total calcium in prediction of convulsion cases. Total calcium can detect convulsion at cutoff 7.3 mg/dl with sensitivity, specificity, PPV and NPV was 31%, 100%, 100% and 59% respectively ($p< 0.001$).

Receiver operating characteristic (ROC) analysis was performed to determine the value of ionized calcium in prediction of convulsion cases. Ionized calcium can detect convulsion at cutoff 4.1 mg/dl with sensitivity, specificity, PPV and NPV was 53%, 97%, 94.6% and 67.4% respectively ($p< 0.001$).

Receiver operating characteristic (ROC) analysis was performed to determine the value of magnesium in prediction of

convulsion cases. Magnesium can detect convulsion at cutoff 1.3 mg/dl with sensitivity, specificity, PPV and NPV was 20%, 100%, 100% and 55.56% respectively (p=0.015). Receiver operating characteristic (ROC) analysis was performed to determine the value of random blood sugar in prediction of convulsion cases. Random blood sugar can detect convulsion at cutoff 40 mg/dl with sensitivity, specificity, PPV and NPV was 41%, 95%, 89% and 61.7% respectively (p<0.001).

Table (1): Demographic and clinical characteristics among the two studied groups

Item		Convulsions group (No. = 100)		Control group (No. = 100)		Test value	P-value	Sig.
		No.	%	No.	%			
Gender	Male	57	57.0%	45	45.0%	X^2= 2.88	0.090	NS
	Female	43	43.0%	55	55.0%			
Age (days)	Mean± SD	4.47± 2.29		4.74± 2.04		Z_{MWU}= 1.306	0.192	NS
	Median (IQR)	4.0 (3.0-6.0)		4.0 (3.0-6.0)				
	Range	1.0- 14.0		1.0- 10.0				
Weight (Kg)	Mean± SD	3.07± 0.31		3.09± 0.28		Z_{MWU}= 0.566	0.572	NS
	Median (IQR)	3.0 (2.80- 3.40)		3.0 (3.0- 3.40)				
	Range	2.50- 3.90		2.50- 3.50				
HC (cm)	Mean± SD	33.67± 0.57		33.68± 0.48		Z_{MWU}= 0.239	0.811	NS
	Median (IQR)	34.0 (33.0- 34.0)		34.0 (33.0- 34.0)				
	Range	33.0- 35.0		33.0- 34.0				

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,
SD= standard deviation, HC: head circumference, comparison between groups done by Chi-Square Test and Mann- Whitney U test.

Table (2): Comparison between the two studied groups concerning serum calcium and **magnesium levels**

Item		Convulsions group (No. = 100)	Control group (No. = 100)	Test value	P-value	Sig.
Total Ca++ (mg/dl)	**Mean± SD**	8.37± 1.09	9.15± 0.67	Z_{MWU}= 4.095	**<0.001**	HS
	Median (IQR)	8.80 (7.10- 9.10)	9.0 (8.80- 9.50)			
	Range	6.0- 10.10	7.40- 10.50			
Ionized Ca++ (mg/dl)	**Mean± SD**	4.50± 1.09	5.10± 0.20	Z_{MWU}= 6.784	**<0.001**	HS
	Median (IQR)	4.90 (3.70- 5.05)	5.10 (5.0- 5.20)			
	Range	2.80- 5.40	4.0- 5.50			
Mg+ (mg/dl)	**Mean± SD**	1.78± 0.38	1.96± 0.18	Z_{MWU}= 2.436	**0.015**	S
	Median (IQR)	1.90 (1.80- 2.0)	2.0 (1.80- 2.10)			
	Range	0.80 – 2.30	1.60 – 2.30			

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, IQR: Interquartile range-comparison between groups done by Mann- Whitney U test

Table (3): Comparison between the two studied groups concerning serum sodium, potassium and random blood sugar

Item		Convulsions group (No. = 100)	Control group (No. = 100)	Test value	P-value	Sig.
K+ (mEq/L)	**Mean± SD**	4.40± 0.58	4.26± 0.54	Z_{MWU}= 1.442	0.149	NS
	Median (IQR)	4.30 (3.90- 5.0)	4.10 (3.85- 4.75)			
	Range	3.50- 5.50	3.50- 5.30			
Na+ (mEq/L)	**Mean± SD**	130.36± 2.76	130.05± 2.25	Z_{MWU}= 0.760	0.477	NS
	Median (IQR)	130.0 (129.0- 132.0)	130.0 (128.0- 132.0)			
	Range	123.0- 145.0	125.0- 135.0			
Random blood sugar (mg/dl)	**Mean± SD**	77.91± 23.84	88.56± 10.37	Z_{MWU}= 3.858	<0.001	HS
	Median (IQR)	79.5 (67.0- 94.0)	88.50 (80.0- 99.5)			
	Range	30.0 – 133.0	70.0 – 111.0			

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, IQR: Interquartile range comparison between groups done by Mann- Whitney U test

Table (4): Comparison between the two studied groups concerning CBC

Item		Convulsions group (No. = 100)	Control group (No. = 100)	Test value	P-value	Sig.
Hb. (mg/dl)	**Mean± SD**	16.22± 1.15	16.55± 0.82	$^{Z}_{MWU}$= 1.080	0.280	NS
	Median (IQR)	16.0 (15.65- 17.0)	16.70 (15.90- 17.0)			
	Range	13.30- 19.0	15.0- 18.0			
WBCs (x10^3/mm^3)	**Mean± SD**	17.78± 7.07	19.37± 7.36	$^{Z}_{MWU}$= 1.179	0.238	NS
	Median (IQR)	15.80 (13.45- 17.95)	16.85 (14.50- 26.5)			
	Range	8.0- 37.0	10.0- 35.0			
Platelets (x10^3/mm^3)	**Mean± SD**	261.51± 105.80	288.42± 89.96	$^{Z}_{MWU}$= 1.132	0.258	NS
	Median (IQR)	267.0 (183.0- 345.0)	287.0 (198.0- 378.0)			
	Range	67.0 – 565.0	133.0 – 389.0			

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, IQR: Interquartile range comparison between groups done by Mann- Whitney U test

Table (5): Validity of total calcium ionized calcium, Magnesium and random blood sugar in prediction of convulsion cases

Item	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	P value
Total calcium	≤7.3 mg/dl	0.666	31.0%	100%	100%	59.0%	**<0.001**
Ionized calcium	≤4.1 mg/dl	0.774	53.0%	97%	94.6%	67.4%	**<0.001**
Mg	≤1.3 mg/dl	0.598	20.0%	100%	100%	55.56%	**0.015**
Random blood sugar	≤ 40 mg/dl	0.658	41.0%	95%	89.0%	61.7%	**<0.001**

PPV= Positive Predictive Value, NPV= Negative Predictive Value, AUC= Area Under Curve

Discussion

Seizures, as a symptom of central nervous system disease, are common in the neonatal period and may be the first sign of neonatal dysfunction. The incidence of neonatal seizures has been reported to be at 1.5 to 3 in 1,000 live births. However, there are significant differences in the reported statistics. This can be related to the problem of diagnosis, different definitions of neonatal seizures and the choice of the population to study [11]. A higher rate of seizures has been reported in premature

neonates. It seems that the brain of the premature neonates is more susceptible to seizures, which could be due to the earlier evolution of stimulant synapses with dominant effects on the inhibitory synapses of the brain in the early stages of growth. Moreover, due to an increased risk of developing metabolic, toxic, infectious, and structural diseases in this period of life, seizures in newborns pose a serious threat [12]. The characteristics of neonatal seizures are unique. In most cases, the diagnosis of neonatal seizures and its various causes is based on history and clinical risk assessment and only a very small percentage of neonatal seizures is idiopathic [13]. Hypoxic-ischemic encephalopathy (HIE), central nervous system infection, intracranial hemorrhage, metabolic and structural disorder of the brain are the possible causes of neonatal seizures; among them, the most prevalent etiology is HIE [14].

Neonatal seizures have various effects on the baby's brain development, the process of DNA synthesis, the proliferation and differentiation of the glia, and myelination of the nerves. New studies on animals have shown that the neonatal nervous system may be partially resistant to long seizures, but short and repeated seizures may be associated with permanent damage to the central nervous system, increased risk of epilepsy and long-term cognitive impairment. Furthermore, the harmful effects of seizures should always be compared to the potentially adverse effects of anticonvulsant drugs on the behavior and learning development of neonatal brain [15].

The etiology of neonatal seizures due to a combination of abnormalities is more common in sick neonates. Neonatal seizures include various causes such as, hypoxic-ischemic-encephalopathy, asphyxia, intracranial hemorrhage, hypoglycemia, hypocalcemia, hypomagnesaemia, intracranial infections, developmental defects and drugs withdrawal [16].

During seizures, abnormal synchronous electrical discharge (depolarization) was

occurred in neuronal groups of brain. Depolarization is due to influx of sodium ions into neuronal cells, and repolarization is due to potassium ions as they are pumped out of the cells. So, the electrical potential is maintained across the cell membrane. The electrical difference across the cell membrane is maintained mainly by the sodium potassium pump. The Na/K Pump requires ATP for its action across the membrane. This excessive depolarization of cell membrane is final common pathway of all causes of seizures. In hypoxia ischemia, due to energy failure, lack of ATP, the Na/K ATPase pump fails which leads to alteration in the electrical potential across the membrane leading to excessive depolarization and seizures. The mechanism of causation of seizures in metabolic abnormalities like hypoglycemia, hypocalcemia and mainly hypomagnesemia are also by alteration in the electrical potential across the cell membrane by producing Na influx and depolarization [17].

There were 57 males and 43 females in convulsions group and there were 45 males and 55 females in control group. The mean age in convulsions group and control group was 4.47± 2.29 days and 4.74± 2.04 days, respectively. The mean weight in convulsions group and control group was 3.07± 0.31 Kg and 3.09± 0.28 Kg respectively. The mean head circumference in convulsions group and control group was 33.67± 0.57 cm and 33.68± 0.48 cm respectively.

There was no statistically significant difference between the two groups as regards age, gender, weight and head circumference ($p>0.05$).

The current study was in line with the case control study by Pisani et al. [18] aimed to evaluate the risk factors for seizures during the whole neonatal period in preterm and term neonates born. The study enrolled 22 seizures cases and 44 controls, the groups were matched by gestational age (GA), sex, hospital, and period of birth. The study found that age,

gender and weight were non significantly correlated with convulsions incidence.

However, the study by Pisani et al. [14], aimed to evaluate the incidence of electroencephalography (EEG)–confirmed seizures in neonates born in the province of Parma and the perinatal risk factors for mortality and epilepsy. The study enrolled 112 patients presented with neonatal seizures: 102 newborns had electroclinical seizures, whereas 10 presented only electrical seizures. They reported that the incidence of convulsions was not significantly associated with sex but significantly associated with birth weight.

The risk of seizures in preterm newborns seems inversely related to birth weight. In newborns with birth weight <1500 g (very low birth weight infants) neonatal seizures incidence is 1.9–5.8% in population-based studies Kohelet et al. [19] and 3.9–48% in single center studies [20, 21]. This was in disagreement with our results, this disagreement may be explained by the differences in sample size and the inclusion criteria.

As well the study by Maheshwari et al. [22] revealed that of 100 cases and 100 controls, the male and female were noted as 61 vs. 57 and 39 vs. 43 respectively (P > 0.05).

In contrast to our results Khaje et al. [23] suggested that male gender and a postnatal age < 2 weeks are associated with an increased risk of seizures in full term and preterm infants.

Regarding calcium and magnesium in the two studied groups, the mean total calcium level in convulsions group and control group was 8.37± 1.09 and 9.15± 0.67 respectively. The mean ionized calcium level in convulsions group and control group was 4.50± 1.09 and 5.10± 0.20 respectively. The mean magnesium level in convulsions group and control group was 1.78± 0.38 and 1.96± 0.18 respectively.

There was a significant decrease in total calcium, ionized calcium and magnesium in convulsions group compared to control

group (p<0.001, <0.001 & 0.015 respectively).

This was supported by the study by Khaje et al. [23], who reported that hypocalcemia was a potential risk factor for seizures.

Also, the study by Dhale et al. [24], reported that 50% of the neonates had no specific risk factors associated with hypocalcemia and hypomagnesemia. The important causes of electrolyte imbalances leading to neonatal seizures were hypocalcemia (12.86%) and hypomagnesemia (2.86%). Out of the 2 cases of hypomagnesemia, 1 case was associated with hypocalcemia (i.e. mixed electrolyte imbalance). The mean (±SD) levels of serum ionic calcium in their study population were 4.64 ± 0.94 mg/dl, while that of serum magnesium were 1.78 ± 0.13 mg/dl.

As well the study by Maheshwari et al. [22], revealed that in cases, the mean± SD Ca++ was noted as 4.17±1.58 mg/dl, while in control it was noted as 8.15± 1.05 mg/dl. Ca++ levels as low as 3.07 mg/dl were noted in the neonatal seizure cases. Normocalcaemia was noted in 81 controls vs. 11 cases and hypocalcaemia in 18 controls vs. 89 cases. The differences were statistically significant which was in agreement with our results.

The study by Masuduzzaman et al. [25], reported that the neonates with seizures had lower mean serum calcium level 7.25 ± 0.4 mg/dl which was 8.51 ± 0.72 mg/dl in case of neonates without seizure. Statistically significant difference (p < 0.001) was found in cases of serum calcium, and serum magnesium level between the two groups, that was in agreement with our results. As well they reported that significant biochemical changes were found in 43.34% of neonates with seizures, hypocalcemia (46%) was most common followed by hypoglycemia (38%).

Furthermore, the study by Kusuma et al. [10], revealed that among the biochemical abnormalities hypoglycemia is the most common cause of neonatal seizures followed by hypocalcemia.

In addition, the study by Bezboruah and Das [8], concluded that hypoglycemia (45.8%) followed by hypocalcemia (25.8%) and hyponatremia (18.8%) are the commonest overall biochemical abnormalities present in neonatal seizures. Also, the study by Dhanjal et al. [9], reported that the primary biochemical abnormalities were seen in 12 (17.1%) neonates with seizures. Among these neonates, hypoglycemia was most commonly seen in 4 (33.3%) neonates followed by hypocalcemia seen in 3 (25%) neonates.

In line with our results Vikneswari [17], reported that the prevalence of hypomagnesemia among 150 selected neonates with seizures is 4.6% and prevalence of hypocalcemia is 31.3%. Prevalence of Combined hypocalcemia with hypomagnesemia 4% and isolated hypomagnesemia is 0.6%. Association of hypomagnesemia with hypocalcemia is 83% which is statistically significant. So, they concluded that hypomagnesemia as isolated abnormality for cause of seizures, or as associated abnormality in underlying etiology is rare. But 83% of hypomagnesemia is associated with hypocalcemia implying the interrelation in pathophysiology.

In the current study we found that the mean Na+ level in convulsions group and control group was 130.36± 2.76 mEq/L and 130.05 ±2.25 mEq/L respectively. The mean K+ level in convulsions group and control group was 4.40± 0.58 mEq/L and 4.26± 0.54 mEq/L respectively. The mean random blood sugar level in convulsions group and control group was 77.91± 23.84 mg/dl and 88.56± 10.37 mg/dl respectively (P 0.477, 0.149 & <0.001 respectively).

There was significant difference between the studied groups as regard random blood sugar levels ($p<0.001$). While there was no statistically significant difference between the two groups regarding potassium and sodium level ($p>0.05$).

However, the study by Masuduzzaman et al. [25], reported that the mean serum sodium and mean blood glucose level

were significantly lower in neonates with seizures than neonates without seizure ($p < 0.001$). They also reported that serum zinc and potassium levels were normal in all group of neonates.

Also, the study by Bezboruah and Das [8], reported that Hypoglycemia was present in 39 cases (45.8%) out of 85 cases of neonatal seizure with biochemical abnormality. The remaining cases were associated with birth asphyxia, meningitis, sepsis etc. which were possibly attributed to poor intake, increased metabolic rate coupled with increased glucose utilization and impaired ability to mobilize glucose found in cases with sepsis and meningitis.

Furthermore, the study published by Kumar et al. [26] (50%), Sood et al. [27] (48.27%) and Arunkumar et al. [28] (53.65%) reported that hypoglycemia was the commonst cause of seizures which is similar to study by Madhusudhan et al. [29] (52.1%) which is correlated with our results.

Regarding the CBC of the studied groups, we found that the mean Hb level in convulsions group and control group was 16.22± 1.15 g/dl and 16.55± 0.82 g/dl respectively. The mean WBCs level in convulsions group and control group was 17.78± 7.07 and 19.37± 7.36 respectively. The mean platelets count in convulsions group and control group was 261.51± 105.80 and 288.42± 89.96 respectively.

There was no statistically significant difference between the two groups concerning levels of Hb., WBCs and platelets ($p>0.05$).

In literature we did not find any studies reported that correlation between abnormalities in CBC and the incidence of convulsions. The retrieved studies performed the routine CBC test but not reported any abnormalities, which somehow support our findings.

Receiver operating characteristic (ROC) analysis was performed to determine the value of total calcium in prediction of convulsions cases. Total calcium can

detect convulsions at cutoff 7.3 mg/dl with sensitivity, specificity, PPV and NPV was 31%, 100%, 100% and 59% respectively ($p< 0.001$).

Also, ROC analysis was performed to determine the value of ionized calcium in prediction of convulsions cases. Ionized calcium can detect convulsions at cutoff 4.1 mg/dl with sensitivity, specificity, PPV and NPV was 53%, 97%, 94.6% and 67.4% respectively ($p< 0.001$).

Furthermore, it was performed to determine the value of magnesium in prediction of convulsions cases. Magnesium can detect convulsions at cutoff 1.3 mg/dl with sensitivity, specificity, PPV and NPV was 20%, 100%, 100% and 55.56% respectively ($p=0.015$).

Receiver operating characteristic (ROC) analysis was performed to determine the value of random blood sugar in prediction of convulsions cases. Random blood sugar can detect convulsions at cutoff 40 mg/dl with sensitivity, specificity, PPV and NPV was 41%, 95%, 89% and 61.7% respectively ($p<0.001$).

Based on the area under the ROC curve we can see that ionized calcium with optimum cutoff point 4.1 mg/dl was superior than total calcium and magnesium in prediction of convulsions cases, and have the best sensitivity

Conclusions

Biochemical abnormalities are common in neonatal seizures. These abnormalities may significantly contribute to seizures activity and hence a biochemical workup is necessary for all cases of neonatal seizures. The current study showed that hypoglycemia, hypocalcemia and hypomagnesemia were significantly associated with neonatal seizures. A thorough biochemical work up is necessary in all cases of neonatal seizures for early detection and prompt treatment of biochemical abnormalities in neonatal seizures. Further studies with larger sample sizes are needed to strength the present results and to assess more risk factors associated with neonatal seizures.

Data Availability: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Author's contributions

All authors shared equally in collection of data, designing and coordinated the implementation of the study, drafting and revision of the manuscript.

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Conflict of interest

We declared no conflict of interest concerning the study.

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References

1. Thomas AK, McVie R, Levine SN. Disorders of maternal calcium metabolism implicated by abnormal calcium metabolism in the neonate. American journal of perinatology. 1999;16(10):0515-20.
2. Oden J and Bourgeois M. Neonatal endocrinology. Indian J Pediatr. 2000; 67:217–223.
3. Levy-Shraga Y, Dallalzadeh K, Stern K, Paret G, Pinhas-Hamiel O. The many etiologies of neonatal hypocalcemic seizures. Pediatric Emergency Care. 2015; 31(3):197-201.
4. Jain A, Agarwal R, Sankar MJ, Deorari A, Paul VK. Hypocalcemia in the newborn. The Indian Journal of Pediatrics. 2010; 77(10):1123-8.
5. Root AW, Diamond JR FB. Disorders of mineral homeostasis in the newborn, infant, child, and adolescent. In Pediatric endocrinology 2008; 686-769.
6. Holick MF, Lim R, Dighe AS. Case records of the Massachusetts General Hospital. Case 3-2009. A 9-month-old boy with seizures. N Engl J Med. 2009; 360:398–407.
7. Mangat JS, Till J, Bridges N. Hypocalcaemia mimicking long qt syndrome: case report. Eur J Pediatr. 2008; 167:233–235.
8. Bezboruah G, Das N. A Study on Biochemical Abnormalities in Neonatal Seizures, 2019;18(4): 53-57.
9. Dhanjal GS, Singh V, Singh G. Etiological profile of neonatal seizures with special reference to biochemical abnormalities. Sepsis (including meningitis).;24:34-.
10. Kusuma SK, Kumar AA, Metta J. A Study of Neonatal Convulsions with Special Reference to Levels of Magnesium and Incidence of Hypomagnesemia in Hypocalcemic Neonates.

11. Patil SV, Ahire NV, Reddy K, Karne T, Joshi D. Clinical Study on Etiology, Onset and Clinical Manifestations of Neonatal Seizures. MVP Journal of Medical Sciences. 2018 (1):64-8.

12. Krawiec C, Muzio MR. Neonatal seizure. In Stat Pearls [Internet] 2021 Oct 20. StatPearls Publishing.

13. Sinha P, Verma B, Ganesh S. Age-Dependent Reduction in the Expression Levels of Genes Involved in Progressive Myoclonus Epilepsy Correlates with Increased Neuroinflammation and Seizure Susceptibility in Mouse Models. Molecular Neurobiology. 2022 22:1-7.

14. Pisani F, Percesepe A, Spagnoli C. Genetic diagnosis in neonatal-onset epilepsies: back to the future. European journal of paediatric neurology. 2018;22(3):354-7.

15. Nardou R, Ferrari DC, Ben-Ari Y. Mechanisms and effects of seizures in the immature brain. Semin Fetal Neonatal Med. 2013; 18:175–184.

16. Robertson Jr WC. Calcium carbonate consumption during pregnancy: an unusual cause of neonatal hypocalcemia. Journal of child neurology. 2002;17(11):853-5.

17. Vikneswari K. Study to evaluate the prevalence of hypomagnesemia among neonatal convulsions (Doctoral dissertation, Coimbatore Medical College, Coimbatore).

18. Pisani F, Prezioso G, Spagnoli C. Neonatal seizures in preterm infants: A systematic review of mortality risk and neurological outcomes from studies in the 2000's. Seizure. 2020; 75:7-17.

19. Kohelet D, Shochat R, Lusky A, Reichman B. Risk factors for neonatal seizures in very low birthweight infants: population-based survey. Journal of child neurology. 2004;19(2):123-8.

20. Shah DK, Zempel J, Barton T, Lukas K, Inder TE. Electrographic seizures in preterm infants during the first week of life are associated with cerebral injury. Pediatric research. 2010; 67(1):102-6.

21. Vesoulis ZA, Inder TE, Woodward LJ, Buse B, Vavasseur C, Mathur AM. Early electrographic seizures, brain injury, and neurodevelopmental risk in the very preterm infant. Pediatric research. 2014;75(4):564-9.

22. Maheshwari N, Noor N, Bashir A, Hingorjo B, Ali A, Tabassum U. Serum calcium level in neonatal seizures presenting at a Tertiary Care Hospital. Professional Med J 2021; 28(2):181-186

23. Khaje A, Mousavi SH, Golmohammadi M, Tavakolikia Z, Miri-Aliabad G, Keeykha R, Keykha M, Fayyazi A, Akhlaghpasand M. Investigating and determining the risk factors of neonatal seizures in NICU patients in the South of Iran. Journal of Pediatric and Neonatal

Individualized Medicine (JPNIM). 2021;10(1): e100129.

24. Dhale S, Valinjkar S, Sadhwani N, Jhunjhunwala M. A Study of Magnesium Levels in Neonatal Convulsions 2017.
25. Masuduzzaman SM, Islam MN, Mollah MA, Hoque MA, Hossain MA, Islam MS. Clinico-Biochemical Abnormalities in Hospitalized Neonates with or without Seizure. Medicine Today. 2020;32(1):37-41.
26. Kumar AS, Gupta VE, Kachhawaha JS, Singla PN. Biochemical abnormalities in neonatal seizures. Indian pediatrics. 1995;32(4):424-8.
27. Sood A, Grover N, Sharma R. Biochemical abnormalities in neonatal seizures. The Indian Journal of Pediatrics. 2003;70(3):221-4.
28. Arunkumar AR, Reddy VR, Sumathi ME, Pushpalatha K. Biochemical abnormalities in neonatal seizures in a tertiary care rural teaching hospital of South India. Natl J Basic Med Sci. 2013; 4:47-50.
29. Madhusudhan K, Suresh NS, Babu TR, Rao JV, Kumar SB. Study of biochemical abnormalities in neonatal seizures with special reference to hyponatremia. Int. J. Contemp. Pediatr. 2016; 3:730-4.

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