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ORIGINAL ARTICLE

Frequency of hypomagnemsemia in neonate with hypocalcemic seizures presenting to a Tertiary Care Hospital.

Waqar Ahmed[1], Aisha Kiran[2], Fareeda[3], Mahesh Kumar[4], Moomal Imdad[5], Sajid Ali[6]

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ABSTRACT… Objective: To determine the frequency of hypomagnesemia in neonate with hypocalcemic seizures presenting to a tertiary care hospital. **Study Design:** Cross-sectional Descriptive Study. **Setting:** Ghulam Muhammad Mahar Medical College Hospital in Sukkur. **Period:** 1st May 2022 to 31st October 2022. **Methods:** The research involved a group of 157 infants who had experienced seizures due to low calcium levels. A proficient phlebotomist with over two years of experience drew a 3cc venous blood sample from each participant, which was subsequently sent to the hospital laboratory for analysis. The serum magnesium levels were determined, and hypomagnesemia was defined as a magnesium level below 1.7mg/dl. These findings were meticulously documented in the attached annexure proforma. **Results:** A total of 157 infants presented with hypocalcemic seizures were included in this study. The average age of the infants was 6.31±4.62 days. Frequency of hypomagnesemia in neonate with hypocalcemic seizures was 28.9% (44/157) infants. The data indicates that exclusively breastfed neonates have the highest prevalence of hypomagnesaemia at 41%, while those exclusively formula fed have the lowest at 22.2%. However, the p-value of 0.110 suggests that these differences are not statistically significant, indicating that feeding status may not be a major contributor to hypomagnesaemia in neonates. The prevalence of hypomagnesaemia is higher in the 6.6-7 mg/dl range (31.7%) compared to the 5-6.5 mg/dl range (25.5%). **Conclusion:** In our research, the occurrence of low magnesium levels in newborns experiencing seizures due to low calcium levels is more prevalent among infants. This typically indicates the presence of both vitamin D deficiency and hypomagnesemia simultaneously, and can be effectively addressed with short-term therapy. Newborns who have seizures and are diagnosed with low calcium levels are unlikely to gain any advantages from neuroimaging assessments.

Key words: Hypocalcemia, Hypocalcemic Seizures, Infants, Neonate.

INTRODUCTION

Low calcium levels in newborns can pose a serious risk as they can lead to seizures, irregular heart rhythms, and potentially even breathing cessation.[1]

From a physiological perspective, magnesium serves as a natural intracellular calcium antagonist, exerting its regulatory influence at the motor end-plate of neurons and across various muscle fiber types.[2] Magnesium sulfate competes with calcium, leading to the suppression of NMDA receptors in the brain.[2,3] These receptors get triggered by oxygen-deprived pressure and enable calcium to flow into the nerve cells, resulting in irreversible cellular harm.[4]

Abnormalities in magnesium concentrations, such as hypomagnesemia, can lead to disruptions in nearly all bodily systems and potentially give rise to life-threatening issues like ventricular arrhythmia, coronary artery vasospasm, and sudden death. Despite the widely acknowledged significance of magnesium, both deficient and excessive levels have been observed in sick patients[5], leading to occasional references to magnesium as the "overlooked ion".[6,7]

Hypocalcemia occurring later in neonates is frequently an indication of concomitant hypomagnesemia and can be effectively treated with short-term therapy. Neonates who exhibit tetany or seizures because of low calcium

1. MBBS, FCPS (Pediatric Medicine), Assistant Professor Pediatric Medicine, Sindh Institute of Child Health and Neonatology Sukkur, Pakistan.
2. MBBS, FCPS Resident Pediatric Medicine, Ghulam Mohammad Mahar Medical College Sukkur (GMC Sukkur), Pakistan.
3. MBBS, Registrar Pediatric Medicine, Sindh Institute of Child Health & Neonatology (SICHN) Sukkur, Pakistan.
4. MBBS, FCPS Resident Pediatric Medicine, Ghulam Mohammad Mahar Medical College Sukkur (GMC Sukkur), Pakistan.
5. MBBS, Admin Registrar Pediatric Medicine, Liaquat University Hospital Jamshoro, Hyderabad Pakistan.
6. MBBS, FCPS Trainee, Resident Pediatric Medicine, Ghulam Mohammad Mahar Medical College Sukkur (GMC Sukkur), Pakistan.

Correspondence Address:
Dr. Waqar Ahmed
Department of Pediatric Medicine
Sindh Institute of Child Health and Neonatology, Sukkur, Pakistan.
sahitowaqar95@gmail.com

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levels are unlikely to gain any advantage from neuroimaging examinations.[8]

While there haven't been thorough investigations that specifically examine the occurrence of hypomagnesemia categorized by age brackets, it is possible that neonates are at a higher risk of developing this condition. The precise reason behind this remains unclear, although multiple studies indicate that neonates might have an elevated demand for intracellular magnesium in their developing tissues.[9-12]

In a research investigation, it was noticed that 96.15% of the infants experiencing hypocalcemic seizures exhibited a deficiency in magnesium, referred to as hypomagnesemia.[8,13] Therefore, there is a need to estimate the frequency of hypomagnesemia in infants with hypocalcemic seizures. If found to be higher, strategies could be developed to screen such cases even if asymptomatic so that prompt treatment could avoid or minimize morbidity related to it. To determine the frequency of hypomagnesemia in neonate with hypocalcemic seizures presenting to a tertiary care hospital.

METHODS

This descriptive cross-sectional study was conducted on 157 infants at Ghulam Muhammad Mahar Medical College Hospital Sukkur, for 6 months from 1st May 2022 to 31st October 2022. We included all infants with <28 days of age (male and female) and presented with hypocalcemic seizures as defined in operational definition. While those infants who were premature; confirmed from medical record, primary management at outside facility. Any congenital heart disease/ Critical illness, other cause /Renal disease/ Neurologic disorder /Gastrointestinal disorder were excluded.

This study was conducted after getting approval from College of Physician and surgeon of Pakistan (CPSP) (CPSP/REU/PED-2015-3454). All infants with hypocalcemic seizures attending emergency department of Ghulam Muhammad Mahar Medical College Hospital, Sukkur was included on the basis of inclusion and exclusion criteria. Purpose of study was explained to parents/guardians. Moreover, signed informed consent was taken from parents/guardian. A 3cc sample of venous blood was extracted by a skilled phlebotomist with over 2 years of experience and delivered to the hospital's laboratory. The laboratory then assessed the serum magnesium concentration. Hypomagnesemia was diagnosed when the magnesium level was found to be <1.7mg/dl. This information along with age, gender and feeding status was noted in the proforma attached as annexure.

Statistical Analysis

We created a database utilizing SPSS, specifically version 16.0 designed for Windows. To provide a comprehensive overview, we conducted descriptive analyses, calculating both the mean and standard deviation for variables such as age, calcium levels, and magnesium levels in the blood. Additionally, we assessed categorical variables including gender, feeding status, and the occurrence of hypomagnesemia, presenting the results as frequencies and percentages. Stratification was done to see the effect of age, gender, Calcium Level and feeding status on the outcome. The chi-square test was utilized, and significance was determined with a p-value of ≤0.05.

RESULTS

A total of 157 infants presented with hypocalcemic seizures were included in this study. The mean age of the individuals in this population is approximately 6.31 days, with a standard deviation of 4.62, indicating a relatively wide age range within the sample. On the other hand, the calcium level has a mean value of 6.401, with a relatively low standard deviation of 0.55, suggesting that calcium levels among the individuals are relatively consistent and close to the mean value. In contrast, the magnesium level has a lower mean of 2.074, but a higher standard deviation of 0.66, indicating greater variability in magnesium levels among the individuals. (Table-I)

Hypomagnesaemia, a condition characterized by low levels of magnesium in the blood, is examined in relation to age groups, gender, feeding status,

and calcium levels.

Regarding age groups, the data indicates that there is a slight difference in the prevalence of hypomagnesaemia among neonates of different age ranges. The age group "6-10 days" shows the highest prevalence with 37.7% of neonates experiencing hypomagnesaemia, while the "1-5 days" group has a lower prevalence at 20.3%. However, the p-value of 0.114 suggests that these differences are not statistically significant, indicating that age may not be a significant factor in the occurrence of hypomagnesaemia in neonates.

Similarly, when analyzing gender, the data shows that there is no substantial difference in the prevalence of hypomagnesaemia between males (28.9%) and females (27%). The p-value of 0.793 further supports the idea that gender is not a significant factor in the occurrence of this condition.

Feeding status is another variable examined, with three categories: exclusively breastfed, both formula fed and breastfed, and exclusively formula fed. The data indicates that exclusively breastfed neonates have the highest prevalence of hypomagnesaemia at 41%, while those exclusively formula fed have the lowest at 22.2%. However, the p-value of 0.110 suggests that these differences are not statistically significant, indicating that feeding status may not be a major contributor to hypomagnesaemia in neonates.

Finally, the data looks at calcium levels, categorized into two ranges: 5-6.5 mg/dl and 6.6-7 mg/dl. The prevalence of hypomagnesaemia is higher in the 6.6-7 mg/dl range (31.7%) compared to the 5-6.5 mg/dl range (25.5%). However, the p-value of 0.395 suggests that these differences are not statistically significant, indicating that calcium levels may not be strongly associated with hypomagnesaemia in neonates.

The data does not reveal strong statistically significant associations between hypomagnesaemia in neonates and age groups, gender, feeding status, or calcium levels. This suggests that other factors not considered in this analysis may play a more significant role in the development of hypomagnesaemia in neonates. Further research and a larger dataset may be needed to better understand the factors contributing to this condition. (Table-II)

Variables	Mean	Std. Deviation
Age (Days)	6.31	4.62
Calcium Level	6.401	0.55
Magnesium Level	2.074	0.66

Table-I. Descriptive statistics of the patients (n=157)

Age Groups (Days)	Hypomagnesaemia In Neonate		Total	P-Value
	Yes	No		
1-5	16(20.3%)	63(79.7%)	79	0.114
6-10	20(37.7%)	33(62.3%)	53	
11-15	7(36.8%)	12(63.2%)	19	
>15	1(16.7%)	5(83.3%)	6	
Chi-Square				5.95
Gender				
Male	24(28.9%)	59(71.1%)	83	0.793
Female	20(27%)	54(73%)	74	
Chi-Square				0.069
Feeding Status				
Exclusively Breastfed	16(41%)	23(59%)	39	0.110
Both Formula fed and Breast fed	20(24.4%)	62(75.6%)	82	
Exclusively formula fed	8(22.2%)	28(77.8%)	36	
Chi-Square				0.069
Calcium Level				
5-6.5 mg/dl	24(25.5%)	70(74.5%)	94	0.395
6.6-7 mg/dl	20(31.7%)	43(68.3%)	63	
Chi-Square				0.722

Table-II. Frequency of hypomagnesemia in neonate with hypocalcemic seizures by age groups, gender distribution, feeding status, and calcium level (n=175)

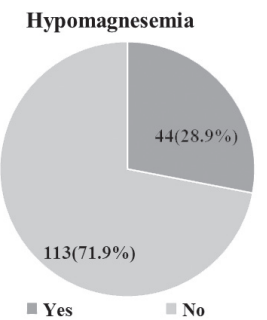

Figure-1. Frequency of hypomagnesemia in neonate with hypocalcemic seizures (n=157)

DISCUSSION

Magnesium plays a vital role in cellular metabolism, encompassing a range of phosphokinases and phosphatases that participate in storing and using energy. In the central nervous system and peripheral neuromuscular systems, a deficiency of magnesium results in heightened central neuronal excitability and improved transmission in neuromuscular pathways.[14] The equilibrium of magnesium levels within the body is meticulously controlled and relies on the interplay of magnesium absorption in the intestines and its removal through the kidneys. When there is a sudden shortage of magnesium, both the reabsorption of magnesium in the tubules and the absorption in the distal small intestine increase to uphold the overall equilibrium. Should the deficiency persist, the magnesium concentration in the bloodstream drops, and magnesium stored in the bones becomes a factor in sustaining the magnesium levels in the extracellular fluid.[14]

Hypomagnesemia is observed in pediatric patients in a variety of clinical situations, including polycythemia during infancy, malabsorption syndrome, short bowel syndrome, infants born to diabetic mothers, and the familial kidney disorder characterized by magnesium loss.[15]

The infants' average age was 6.31±4.62 days. Among them, there were 83 (52.87%) males and 74 (47.13%) females. In a research study, the middle value (with an interquartile range [IQR]) for the age when the 78 affected neonates were admitted was 8.0 (7.0–10.0) days, and the typical length of their hospital stay was 3.0 (2.0–4.0) days.[8] The occurrence of hypomagnesemia in neonates with hypocalcemic seizures was 28.03% (44 out of 157) in one study. Another study found that 75 (96.15%) of the infants with hypocalcemic seizures exhibited hypomagnesemia.[16]

There have been limited accounts of infants arriving in urgent medical settings with seizures or muscle spasms, and further investigation revealed that the underlying cause was low calcium levels.[17-19] In numerous instances within these reports, the babies underwent comprehensive examinations that encompassed blood, urine, and cerebrospinal fluid cultures; full blood cell analyses; blood chemistry assessments; EEGs; EKGs; and/or neuroimaging investigations.

Merewood and colleagues[20], discovered that among a predominantly Hispanic and African American group of 376 newborns, 58% had a deficiency in vitamin D, while 83% were deficient in the available pool. Furthermore, the median 25(OH) D levels in the healthy newborns stood at 43 nmol/L (with no reported IQR), in contrast to our patients whose levels measured 35 nmol/L (with an IQR of 29–45). In a distinct investigation involving 111 healthy neonates in South Carolina, Hollis et al.,[21] reported a mean (SD) of 25 (OH) D levels at 46 (25) nmol/L, while our population exhibited levels of 38 (17) nmol/L (resulting in a significant difference, $P < 0.03$, according to a t-test).

A study conducted in the United States involving 20 cases and another in Qatar involving 15 cases both indicated that there is a possibility of low vitamin D (hypovitaminosis D) and insufficient parathyroid hormone (relative hypoparathyroidism) occurring together in cases of symptomatic late-onset hypocalcemia. Ashraf and colleagues[22], in their research, observed that out of 23 infants with late neonatal hypocalcemia, 13 of them had 25 (OH) D levels measuring 32.5 nmol/L (equivalent to 13 ng/mL). Notably, none of the infants with hypocalcemia had a 25 (OH) D level exceeding 62 nmol/L (25 ng/mL), which implies that having higher levels of this vitamin might provide protection against hypocalcemia. This boundary varies from the guidelines proposed in the latest Institute of Medicine publication[21], where they characterized a shortage of vitamin D as having a concentration of 25(OH)D below 30 nmol/L (equivalent to 12 ng/mL) and insufficient vitamin D levels as falling within the range of 30 to 50 nmol/L (or 12–20 ng/mL).

Nevertheless, the 2011 Endocrine Society Clinical Practice Guideline recommends that adequate vitamin D levels should be characterized as 25(OH)D concentrations of 75 nmol/L (30 ng/mL).[23] At this level, it seems that the excretion of calcium in the urine has reached a balanced state,

and the absorption of calcium in the intestines seems to be at its peak efficiency.[24,25]

In summary, our recommendation for the assessment of neonates who exhibit late-onset hypocalcemia is as follows: an initial evaluation should encompass checking calcium, phosphorus, magnesium, intact parathyroid hormone (PTH), and 25-hydroxyvitamin D (25 (OH) D) levels. If there are no signs of focal neurologic issues or indications of dysmorphism or cardiac abnormalities, it is advisable to postpone neuroimaging and genetic investigations. While treatment should be tailored to the individual, it seems that administering calcium supplements, vitamin D in the form of 1, 25-dihydroxyvitamin D, either D2 or D3, magnesium (intravenous and/or oral), and a low-phosphorus formula for a brief period of 1 to 2 months is an effective approach for managing neonates who present with late-onset hypocalcemia.

CONCLUSION

In our research, the occurrence of low magnesium levels in newborns experiencing hypocalcemic seizures is more frequent among infants. This typically indicates the presence of both vitamin D deficiency and hypomagnesemia and can be effectively treated with a short-term therapy regimen. Newborns with seizures associated with low calcium levels are unlikely to gain any advantages from neuroimaging assessments.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Waqar Ahmed	Designed the research, assessed the vases, wrote the paper, Interpretation of discussion and data entry in SPSS.	
2	Aisha Kiran	Collected the data, did the literature search, drafted the manuscript assisted in writing the paper.	
3	Fareeda	Involved in data collection, analyzed the data revised the manuscript, proof reading, help in methodology.	
4	Mahesh Kumar	Revised the original manuscript, reviewed the cases, analyzed the data and assisted in writing the paper, Interpretation in results writing.	
5	Moomal Imdad	References, citation manager designing of results and charts and Graphs in manuscript.	
6	Sajid Ali	Data entry in SPSS and other technical help, help in corrections.