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ORIGINAL ARTICLE

RISK FACTORS AND CLINICAL CHARACTERISTICS OF LATE-ONSET NEONATAL HYPOCALCEMIA

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ABSTRACT

Objective: The study aimed to investigate the clinical profile and risk factors associated with late-onset neonatal hypocalcemia, a condition affecting neonates after 72 hours of life and to assess the role of maternal factors and neonatal health conditions.

Methodology: A prospective observational study was conducted over 18 months at a children's hospital in Srinagar, including 99 neonates diagnosed with late-onset hypocalcemia. Data were collected through clinical examinations and laboratory tests, including serum calcium, magnesium, phosphorus, vitamin D3 and parathyroid hormone levels.

Statistical analysis: Data was organized in a structured Excel spreadsheet and summarized using descriptive statistics (mean and standard deviation). Continuous variable distributions were visualized with histograms. Pearson correlation analysis was conducted to examine associations between variables. Statistical significance was assessed using predefined thresholds.

Results: The cohort consisted of 52.5% females and 47.5% males, with most neonates (93%) between 3 to 7 days old. The mean serum calcium level was 6.13 ± 0.69 mg/dL and 58.8% of neonates had vitamin D3 deficiency. A strong positive correlation ($r = 0.51$, $p < 0.001$) was observed between maternal and neonatal vitamin D3 levels.

Conclusion: Late-onset hypocalcemia is associated with maternal vitamin D deficiency, cesarean section delivery and inadequate breastfeeding. Improving maternal vitamin D supplementation and promoting exclusive breastfeeding are essential strategies for reducing neonatal hypocalcemia.

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KEYWORDS

Neonatal Hypocalcemia, Late-onset hypocalcemia, Maternal vitamin-D.

Introduction

Neonatal late-onset hypocalcemia, typically occurring after the first 72 hours of life, is a significant clinical condition that can lead to seizures, irritability and feeding difficulties in neonates. This condition arises from a complex interplay of metabolic, dietary and environmental factors, often exacerbated by predisposing conditions like maternal diabetes, vitamin D deficiency and preterm birth.[1] Understanding these diverse risk factors is critical for early identification and effective management of late-onset hypocalcemia. Timely recognition and treatment of clinical manifestations are essential to prevent complications and support optimal growth and development in vulnerable neonates.

Methodology

This prospective observational study was conducted over 18 months in the Neonatal Division, Department of Pediatrics, at a 500-bedded Children's Hospital in Srinagar. The study aimed to investigate the clinical profile and risk factors associated with neonatal late-onset hypocalcemia. A total of 99 neonates with documented biochemical evidence of late-onset hypocalcemia admitted during the study period were included in this study. Neonates with early-onset hypocalcemia (presenting within 72 hours), genetic syndromes predisposing to hypocalcemia, or prior use of calcium supplements or medications affecting calcium metabolism were excluded.

After obtaining informed consent, detailed history and physical examinations were performed. Medical history, including prenatal, perinatal and postnatal factors, was documented and symptoms of hypocalcemia (e.g., jitteriness and irritability) were assessed. Biochemical parameters like ionized calcium, serum calcium, magnesium, phosphorus, alkaline phosphatase, vitamin D3, parathyroid hormone and maternal vitamin D3 levels were measured and nutritional intake was evaluated.

Ethical Clearance - The IRB of Government Medical College Srinagar granted ethical approval via

Reference no:- IRB/GMC-SGR/Pedia/869 Dated 27-0ct-2022 and informed consent was obtained from parents/ guardians. the procedures adhered to the ethical guidelines of the Declaration of Helsinki.

Operational definitions: The following values of the various laboratory investigations were taken as being within the normal range as per various guidelines.

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Table 1. Total serum calcium and ionized serum calcium cut-offs for preterm and term infants.

Gestation	Total Serum Calcium	Ionic Serum Calcium
Preterm	<7 mg/dl (7.0-10 mg/dl)	<4 mg/dl
Term	<8 mg/dl (8.0-10.8 mg/dl)	<4.8 mg/dl

Table 2. Statistical Analysis.

Parameter	Normal Range	Remarks
Serum Magnesium	1.5-2.6 mg/dL	Normal range for magnesium levels
Serum Phosphorus	2.3-4.7 mg/dL	Normal range for phosphorus levels
Serum Alkaline Phosphatase	90-273 U/L	Normal range for alkaline phosphatase
Parathyroid Hormone (PTH)	15-68.3 pg/mL	Normal range for PTH levels
Serum Vitamin D3		
- Deficient	<50 nmol/L	Vitamin D3 deficiency
- Insufficient	50-74 nmol/L	Insufficient Vitamin D3 levels
- Sufficient	75-250 nmol/L	Optimal Vitamin D3 levels
- Potential Toxification	>250 nmol/L	Risk of Vitamin D3 toxicity

Statistical analysis: Data was organized in a structured Excel spreadsheet and summarized using descriptive statistics (mean and standard deviation). Continuous variable distributions were visualized with histograms. Pearson correlation analysis was conducted to examine associations between variables. Statistical significance was assessed using predefined thresholds.

Table 3. Characteristics of the study population.

Demographic		Frequency	Percent
Gender	Male	47	47.5%
	Female	52	52.5%
Age Group	3 - Days	45	45.5%
	4-7 Days	48	48.8%
	8-21 days	6	6.1%
Weight	<2500 g	13	13.2%
	>2500 gm	86	86.8%
Area	Rural	68	69.0%
	Urban	31	31.0%
Type Of Delivery	LSCS	64	64.6%
	NVD	35	35.4%
Clinical Features			
Irritable		41	41.3%
Abnormal Body Movement		33	33.3%
Lethargy		11	11.1%
Decreased Feeding		9	9.1%
Fast Breathing		6	5.1%
Excess Cry		3	3.0%
Jittery		62	62.6%
Hypertonic		8	8.1%
Hypotonic		5	5.1%

Table 4. Biochemical parameters in the study group.

Laboratory Investigations	Groups/Levels	Frequency(n)	Percent(%)
Serum Magnesium Levels	Low	35	35.4%
	Normal	64	64.6%
Serum Phosphorus Levels	Normal	31	31.3%
	High	60	60.6%
Serum Alkaline Phosphatase	Low	9	9.1%
	Normal	90	90.9%
PTH Levels	Normal	58	58.6%
	Low	41	41.4%
Maternal Vit. D3 Levels	Deficient	41	41.3%
	Insufficient	21	21.2%
	Sufficient	37	37.5%
Neonate Vit. D3 Levels	Deficient	58	58.8%
	Insufficient	21	21.2%
	Sufficient	20	20.0%

Neonatal vitamin D3 levels were found to be deficient in 58.8% (n=58), insufficient in 21.2% (n=21) and adequate in 20% (n=20) of cases, with a mean concentration of 35.35 ± 15.73 ng/mL. Maternal vitamin D3 levels were deficient in 41.3% (n=43), insufficient in 21.2% (n=21) and sufficient in 37.5% (n=35) with a mean level of 68.92 ± 29.50 ng/mL. A moderate to strong positive correlation ($r = 0.51$, $p < 0.001$) was observed between maternal and neonatal vitamin D3 levels, with mothers with low vitamin D3 levels having neonates with lower serum vitamin D3 levels, indicating that maternal vitamin D3 levels could be a predictor for neonatal vitamin D3 status and a risk factor for late-onset hypocalcemia.

Early onset Hypocalcemia (presenting within 72 hours of life), **Late-onset Hypocalcemia** (presenting after 72 hrs).

DEFINITION;

Hypocalcemia is defined by different total serum calcium and ionized serum calcium cutoffs for preterm and term infants.

Results

In our study, 99 neonates with late-onset hypocalcemia were included. Out of these, 52.5% (n=52) were females and 47.5% (n=47) were males. Most neonates, 68.7% (n=68), hailed from rural areas of Kashmir.

Clinically, irritability was the most common symptom, observed in 41.3% (n=41) of neonates, followed by abnormal body movements in 33.3% (n=33) and lethargy in 11.1%(n=11). Jittery movements were the most frequent clinical signs 62.6% (n=62) and 7.1% (n=7) of the neonates exhibited respiratory distress. Regarding maternal health, 2% of mothers were diagnosed with gestational diabetes mellitus (GDM) and 64.6% of deliveries were by cesarean section (LSCS). (Table 3)

Among the neonates in the study, just 15.2% (n=15) received exclusive breastfeeding, whereas nearly 85% (n=85) were fed formula alone or a combination of breast milk and formula.

The biochemical analysis of the study cohort revealed a mean serum calcium level of 6.13 ± 0.69 mg/dL, with values ranging from 4.0 to 7.20 mg/dL. Serum magnesium levels averaged 1.64 ± 0.4 mg/dL, with 35.4% (n=35) of neonates presenting low levels. The mean serum phosphorus level was 6.84 ± 1.27 mg/dL, with elevated levels observed in 60.6% (n=60) of cases. Low serum alkaline phosphatase levels were detected in 9.1% (n=9) of neonates and reduced serum parathyroid hormone (PTH) levels were found in 41.4% (n=41), with an average PTH concentration of 39.09 ± 21.14 pg/mL. (Table 4).

Discussion

This study provides valuable insights into the characteristics and potential risk factors of late-onset hypocalcemia, emphasizing the role of demographic, clinical and biochemical factors in its development. In our study, the majority of cases (n=68) 68.7% were from rural areas of Kashmir. In rural regions, inadequate prenatal care, nutritional deficiencies and cultural factors significantly impact neonatal health.[2] Maternal nutrition in these areas is often poor due to limited access to diverse foods and healthcare, leading to higher rates of maternal malnutrition, which adversely affects neonates, contributing to low birth weight, poor growth and increased neonatal mortality.[3]

Our study revealed a high cesarean delivery rate (n=64) (64.6%), consistent with other studies that link cesarean births to an increased risk of neonatal hypocalcemia.[4,5] The lack of hormonal changes

associated with vaginal delivery, along with delayed breastfeeding initiation after cesarean births, may disrupt calcium homeostasis in neonates. Another significant finding was that only 15.2% (n=15) of neonates in the study were exclusively breastfed, while almost 85% (n=85) received formula alone or a mix of breast milk and formula. Previous studies have highlighted the importance of breastfeeding in enhancing calcium bioavailability and metabolic stability in neonates.[6] The association between formula feeding and neonatal hypocalcemia has been noted in earlier research.[7] Formula-fed infants tend to receive more calcium than breastfed infants because formula contains about twice the calcium of breast milk. However, fractional calcium absorption is lower in formula-fed infants.[8]

The laboratory findings from our study underscore several key factors contributing to neonatal hypocalcemia. Hypomagnesemia was observed in 35.4% of cases, consistent with existing research indicating that magnesium deficiency can complicate hypocalcemia treatment by impairing parathyroid hormone (PTH) secretion and action.[9] Elevated phosphorus levels in 60.6% of cases suggest disruptions in the calcium-phosphorus-PTH axis, potentially reducing calcium bioavailability and complicating hypocalcemia.[10] Additionally, low PTH levels in 41.4% of cases indicate functional immaturity of the parathyroid glands, highlighting the complexities of calcium regulation during the neonatal period.

Our study also found that vitamin D deficiency was prevalent in both neonates (58.8%) and mothers (41.3%). This finding aligns with previous studies linking poor vitamin D status to an increased risk of neonatal hypocalcemia.[11,12] The interdependence of maternal and neonatal vitamin D levels is evident, with a strong correlation ($p < 0.001$) between the two, underscoring the importance of maternal supplementation during pregnancy, as supported by earlier research.[13] Vitamin D deficiency during pregnancy is a growing concern, affecting up to 50% of pregnant women globally. Since the fetus relies on the mother for vitamin D, supplementation during pregnancy can enhance maternal vitamin D levels and improve availability to the fetus and neonate. Vitamin D supplementation is crucial for exclusively breastfed infants, as breast milk alone typically contains inadequate levels of vitamin D, which is essential for bone health and calcium absorption.[14]

This study emphasizes the importance of comprehensive prenatal care, particularly the routine screening and supplementation of vitamin D for pregnant women. Addressing rural healthcare disparities, promoting vaginal deliveries and supporting exclusive breastfeeding are crucial measures to reduce the risk of neonatal hypocalcemia. These efforts are essential for enhancing neonatal health and preventing complications associated with this condition.

Conclusion

Late-onset hypocalcemia is associated with maternal vitamin D deficiency, cesarean section delivery and inadequate breastfeeding. Improving maternal vitamin D supplementation and promoting exclusive breastfeeding are essential strategies for reducing neonatal hypocalcemia.

Limitation: relatively small sample size (99 neonates), which may limit the generalizability of the findings and the lack of long-term follow-up to assess the impact of late-onset hypocalcemia on neonatal development.

Compliance with Ethical Standards
Funding: None

Conflict of Interest: None

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