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***Original Research Article***

# Frequency of Hypocalcemia in Neonates with Hypoxic Ischemic Encephalopathy Presenting Nursery Unit of Saidu Group of Teaching Hospital

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**Abstract:** *Hypoxic-ischemic encephalopathy (HIE) is a major cause of neonatal morbidity and mortality. Metabolic disturbances, including hypocalcaemia, are frequently observed in neonates with HIE and may worsen neurological outcomes if not promptly identified and managed. Early detection of hypocalcaemia is therefore essential in neonatal intensive care settings.* ***Objective:*** *To determine the frequency of hypocalcaemia in neonates with hypoxic-ischemic encephalopathy presenting to the nursery unit of Saidu Group of Teaching Hospital.* ***Methods:*** *This cross-sectional study was conducted in the Paediatric Unit of Saidu Group of Teaching Hospital from 12-01-2025 to 12-04-2025 and included 134 neonates aged 1–25 days diagnosed with hypoxic-ischemic encephalopathy. HIE was defined based on Apgar scores below 5 at 1 and 5 minutes, need for resuscitation at birth, presence of seizures, altered level of consciousness, and neuroimaging findings consistent with encephalopathy. Hypocalcaemia was defined as ionized calcium levels <4.4 mg/dL. Data were analyzed using SPSS version 21. Associations between hypocalcaemia and demographic or clinical variables were assessed, with a p-value <0.05 considered statistically significant.* ***Results:*** *Among 134 neonates, 86 (64.2%) were male and 48 (35.8%) were female. The mean age was 6.76 ± 6.48 days. The mean ionized calcium level was 4.55 ± 0.48 mg/dL. Hypocalcaemia was observed in 42 neonates (31.3%). A statistically significant association was found between hypocalcaemia and younger age (1–5 days) (p = 0.001). No significant associations were observed with gender, socioeconomic status, place of residence, or birth weight categories (all p > 0.05).* ***Conclusion:*** *The frequency of hypocalcaemia among neonates with hypoxic-ischemic encephalopathy was 31.3%. Neonates aged 1–5 days were at significantly higher risk. Routine monitoring of serum calcium levels in the early neonatal period is recommended to detect and manage hypocalcaemia in infants with HIE.*

**Keywords:** Hypocalcaemia, Hypoxic Ischaemic Encephalopathy, Neonate, Birth Asphyxia, Calcium

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## Introduction

Neonatal hypoxic ischaemic encephalopathy (HIE) is a complex neurological condition caused by the perinatal asphyxia that deprives the neonate's brain of oxygen as well as blood flow from birth. It manifests as decreased respiratory effort and unusual muscle tone, along with seizures, in the first days of life. HIE is known as the prominent cause of neonatal long-term neurodevelopmental disability across the world in low-income countries where perinatal care resources are scarce, and the incidence of asphyxiated births is higher. Physiological nadirs in calcium levels are reported among newborns. Hypoxic insults worsen this deterioration by disrupting parathyroid hormone secretion and compromising cellular calcium regulation in organs. Hypocalcaemia can lead to neuromuscular irritability, poor feeding, and seizures if untreated in time (1-4). Cellular ATP depletion, along with the failure of ion pumps, precipitates an influx of calcium ions into cells and a sustained decrease in extracellular calcium concentration. Such irregularities not merely reflect the metabolic imbalance but also indicate the underlying asphyxia severity and reperfusion injury. Such instabilities highlight the complex relationship between metabolic homeostasis and neurological insult in infants (5).

A study found that over one-third of term neonates with HIE showed noteworthy hypocalcaemia in the first 3 days of life, with ionized calcium levels sometimes considerably below the normative range. Hypocalcaemia and associated electrolyte imbalances are frequent in infants with birth asphyxia, underlining the requirement for initial biochemical supervision in this high-risk population. Approximately 22% of asphyxiated neonates had hypocalcaemia, further strengthening the occurrence of this metabolic complication in Pakistan (6, 7).

Pathophysiology of hypocalcaemia in HIE also crosses with other electrolyte abnormalities, which may additionally disrupt the calcium equilibrium and hypoglycaemia, which independently deteriorates the neurological injury. Such metabolic disturbances, which frequently coexist with HIE in newborns, reflect the systemic effects of perinatal hypoxia on organs beyond the central nervous system (8-10).

As no such study has been conducted locally on this subject, this study aims to determine the frequency of hypocalcemia in neonates with HIE presenting to the nursery unit of Saidu Group of Teaching Hospital. Exploring the mechanisms behind hypocalcemia in such neonates is essential, as low calcium levels can result in neuromuscular irritability and raise the seizure risk, further complicating clinical management. The findings of this study will elucidate the clinical implications of hypocalcemia in neonates with HIE, providing valuable insights for developing targeted therapeutic strategies that could improve neurological recovery and overall neonatal care.

## Methodology

The present cross-sectional study was conducted from 12-01-2025 to 12-04-2025 in the Pediatric Unit of Saidu Group of Teaching Hospital, Swat, following ethical approval from the institutional ethics committee. The sample size was 134 patients, calculated using the WHO sample size calculator, based on a previous frequency of hypocalcaemia of 33.6% in neonates with hypoxic-ischemic encephalopathy (11), a 95% confidence interval, and a margin of error of 8%. A consecutive nonprobability sampling technique was used for patient enrollment.

Neonates of either gender aged between 1 and 25 days presented with hypoxic ischemic encephalopathy were included in the study, which was defined as neonates with all of the following indications: Apgar scores < 5 at 1 and 5 minutes, need for resuscitation at birth, seizures, and altered consciousness. Neuroimaging, i.e., ultrasound examination, showed all of the following features: encephalopathy, basal ganglia injury, and

watershed-area infarctions. Neonates with trachea-esophageal atresia, micro or macrocephaly, prematurity, and meningitis were excluded.

Informed written consent was acquired from all participating patients. Baseline demographics, including age, gender, weight, socioeconomic status, and place of residence, were recorded. Neonates confirmed with hypoxic ischemic encephalopathy were evaluated for hypocalcaemia, i.e., defined in neonates with all of the following symptoms: muscle twitching/spasms, seizures, irritability/agitation. Laboratory tests were used to measure serum calcium levels; ionized calcium levels were < 4.4 mg/dl (1.1 mmol/L). For ionized calcium measurement l-2 mL of blood was taken through vein puncture using a needle and collected in an air-tight tube for laboratory assessment. The whole assessment was performed under the guidance of a consultant with at least 5 years of post-fellowship experience. A pre-designed, structured pro forma was used to record each patient's details. The researcher himself took all the data.

IBM SPSS 21 software was used to analyze the data. Mean ± SD were calculated for numerical data such as age and ionized calcium levels. Frequencies and percentages were calculated for categorical data such as gender, hypocalcaemia, birth weight categories (overweight/normal weight/underweight), socioeconomic status, and place of living. Effect modifiers such as age, gender, birth weight categories, socioeconomic status, and place of living were controlled through stratification. Post-stratification, Chi-square/Fisher's exact test was applied, with p-values ≤ 0.05 considered significant.

## Results

This study was conducted on 134 neonates with hypoxic ischemic encephalopathy. The mean age of the patients at presentation was 6.76±6.476 days. Their mean ionized calcium level was 4.5484±0.48051 mg/dL. Regarding gender distribution, 86 (64.2%) were male, and 48 (35.8%) were female. Socioeconomic status showed that 47 (35.1%) belonged to the lower class and 62 (46.3%) to the middle class (Table 1). The majority of the children had a normal weight, 64 (47.8%) (Figure 1). Hypocalcaemia was observed in 42 (31.3%) neonates, while 92 (68.7%) did not have this condition (Table 2).

Subgroup analysis showed that younger neonates, 1 to 5 days old, had a higher frequency of hypocalcemia compared to children who were aged 6 to 10 and more than 10 days (P = 0.001). Hypocalcemia was not associated with gender, residence, socioeconomic status, or birth weight (Table 3).

**Table 1: Demographics**

| Demographics | | n | % |
|---|---|---|---|
| Gender | Male | 86 | 64.2% |
| | Female | 48 | 35.8% |
| Socioeconomic status | Lower class | 47 | 35.1% |
| | Middle class | 62 | 46.3% |
| | Upper class | 25 | 18.7% |
| Place of living | Rural | 54 | 40.3% |
| | Urban | 80 | 59.7% |
| Birth weight categories | Normal weight | 67 | 50% |
| | Under weight | 38 | 28.4% |
| | Over weight | 29 | 21.6% |

**Table 2: Frequency of hypocalcaemia**

| Hypocalcaemia | n | % |
|---|---|---|
| Yes | 42 | 31.3% |
| No | 92 | 68.7% |

**Table 3: Association of hypocalcaemia with demographics**

| Variables | | Hypocalcaemia | | | | P value |
|---|---|---|---|---|---|---|
| | | Yes | | No | | |
| | | n | % | n | % | |
| Age distribution (days) | 1 to 5 | 20 | 47.6% | 56 | 60.9% | 0.001 |
| | 6 to 10 | 10 | 23.8% | 21 | 22.8% | |
| | > 10 | 12 | 28.6% | 15 | 16.3% | |
| Gender | Male | 27 | 64.3% | 59 | 64.1% | 0.98 |
| | Female | 15 | 35.7% | 33 | 35.9% | |
| Socioeconomic status | Lower class | 14 | 33.3% | 33 | 35.9% | 0.85 |
| | Middle class | 19 | 45.2% | 43 | 46.7% | |
| | Upper class | 9 | 21.4% | 16 | 17.4% | |
| Place of living | Rural | 14 | 33.3% | 40 | 43.5% | 0.26 |
| | Urban | 28 | 66.7% | 52 | 56.5% | |
| Birth weight categories | Normal weight | 10 | 23.8% | 54 | 58.7% | 0.001 |
| | Under weight | 15 | 35.7% | 28 | 30.4% | |
| | Over weight | 17 | 40.5% | 10 | 10.9% | |

## Discussion

Hypoxic ischemic encephalopathy is considered a significant contributor to neonatal morbidity and mortality, with metabolic disturbances frequently complicating the clinical course of affected newborns (11, 12). Among these imbalances, hypocalcaemia has gained specific attention due to its potential to worsen neurological injury and precipitate seizures (13). The association between perinatal asphyxia and alterations in serum calcium homeostasis has been explored across various studies, though the exact mechanisms remain incompletely understood (14). Several hypotheses have been proposed to explain this phenomenon, including impaired parathyroid hormone secretion, increased calcitonin release, and cellular calcium influx during the reperfusion phase following hypoxic injury (15).

The existing studies provide compelling evidence for a strong association between hypoxic ischemic encephalopathy and hypocalcemia. Hussain et al. documented a hypocalcemia frequency of 33.6% among their cohort of 116 neonates with hypoxic ischemic encephalopathy (11). Khattak et al. in their study reported that 34.1% of term neonates with hypoxic ischemic encephalopathy had hypocalcemia (12). Their findings highlighted the multifactorial nature of this metabolic disturbance, suggesting that both biological and socioeconomic factors may contribute to its Development.

Jahan et al., in their Bangladeshi study, showed not only a high frequency of hypocalcemia but also a clear relationship with disease severity, with mean serum calcium levels progressively declining from 9.17±1.04 mg/dL in stage I hypoxic-ischemic encephalopathy to 7.73±0.86 mg/dL in stage III disease (13). This dose-response relationship strengthens the argument for a causal link between the severity of hypoxic insult and the

degree of calcium disturbance. Bhat et al. similarly observed that electrolyte abnormalities such as hypocalcemia, hyponatremia, and hyperkalemia worsened with increasing severity of encephalopathy. Their finding that 92.3% of neonates with stage III encephalopathy had hypocalcemia underscores the nature of this disturbance in the most severely affected infants (14). Another study from Pakistan by Aikta et al. reported a lower frequency of 22.2% for hypocalcemia, also documented hypomagnesemia in 17.4% of asphyxiated neonates, highlighting the complex relation of multiple electrolyte derangements in this population (16).

Regarding the demographics of the current study, the mean age of the neonates was 6.76±6.476 days, which is higher than the reported age of 1.0±0.7 days by Khattak et al., while Aikta et al. included neonates with a mean postnatal age of 16.6±8.4 hours. This variation in age at assessment is clinically relevant as neonatal calcium levels undergo physiological changes during the first days of life. The gender distribution in the present study showed a male predominance, which aligns with the findings of Khattak et al., who reported 66.6% males, and Jahan et al., who reported 61.7% males. This consistent male majority across studies from different centers raises questions about potential biological vulnerability that merit further investigation.

The frequency of hypocalcemia observed in this study was 31.3%, which aligns with the figures reported by Hussain et al. (33.6%) and Khattak et al. (34.1%) (11, 12). This consistency across studies conducted in different Pakistani centers strengthens the external validity of these findings. It suggests that approximately one in three neonates with hypoxic ischemic encephalopathy in this region may develop hypocalcemia. The lower figure reported by Aikta et al. at 22.2% may reflect differences in the study population, as they included all neonates with birth asphyxia rather than restricting to those with established encephalopathy. The significantly higher frequencies reported in the Indian and Bangladeshi studies, especially among those with severe encephalopathy, highlight the influence of disease severity on calcium status.

The novelty of the present study lies in the confirmation of a consistent hypocalcemia frequency across multiple Pakistani centers, highlighting the need for routine screening in this vulnerable population. The observation that hypocalcemia was most frequent in the youngest neonates suggests that the first few days of life represent a critical window for monitoring and intervention.

## Conclusion

In conclusion, the present study demonstrated that the frequency of hypocalcaemia in neonates with ischemic encephalopathy presenting to the nursery unit was 31.3%. It was observed that neonates aged 1 to 5 days were at a higher risk of developing hypocalcaemia. Routine screening for hypocalcaemia should be considered in all neonates admitted with hypoxic ischaemic encephalopathy, particularly during the first week of life.

## Declarations

**Data Availability statement**

All data generated or analysed during the study are included in the manuscript.

**Ethics approval and consent to participate**

Approved by the department concerned. (215-ERB/024)

**Consent for publication**

Approved

**Funding**

Not applicable

## Conflict of interest

The authors declared no conflicts of interest.

## Author Contribution

***IU (Postgraduate Resident), SK (Associate Professor)***

*Contributed to study design, data collection, and initial manuscript drafting*

*Assisted in data acquisition, literature review, and manuscript editing*

*Performed statistical analysis and contributed to the interpretation of results*

*Contributed to patient recruitment, data entry, and results compilation*

***MW (Postgraduate Resident), SA (Postgraduate Resident)***

*Assisted in referencing, proofreading, and final revisions of the manuscript. Guided study execution and critically reviewed the manuscript.*

*Supervised the research, coordinated among authors, finalized the manuscript, and approved the final version*

*All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.*

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