Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v6i4.1713
*Biol. Clin. Sci. Res. J., Volume 6(4), **2025**: 1713*
Original Research Article

Evaluation of Iron Levels in Newborns with HIE

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(Received, 24th January 2025, Accepted 22nd April 2025, Published 30th April 2025)

Abstract: *Neonatal hypoxic-ischemic encephalopathy (HIE) is a major cause of mortality and neurodevelopmental disability, particularly in low-resource settings. Iron metabolism may be disrupted in HIE due to oxidative stress and inflammation, potentially affecting neurological outcomes.* ***Objective:*** *To evaluate serum iron levels in newborns with HIE and investigate their association with disease severity and clinical outcomes.* ***Methods****: This descriptive cross-sectional study was conducted at Department of Neonatal Medicine, Sindh institute of Child Health and Neonatology Korangi-5, Karachi, July, 2024 to December, 2024. Eighty term neonates with HIE (Sarnat staging) were enrolled within 72 hours of life. Serum iron, ferritin, and total iron-binding capacity (TIBC) were measured, and their relationship with HIE severity and Apgar scores was analyzed using SPSS version 25.* ***Results:*** *Neonates with severe HIE (Stage III) had significantly lower serum iron (59.1 ± 11.4 µg/dL) and ferritin levels, and higher TIBC compared to milder stages ($p < 0.01$). Lower Apgar scores correlated with reduced iron levels.* ***Conclusion:*** *Severe HIE is associated with altered iron metabolism, suggesting a potential role for iron as a biomarker. Cautious iron management may improve outcomes, warranting further research.*

Keywords: HIE, neonates, iron metabolism, serum iron, ferritin, TIBC

[***How to Cite:*** Ali I. Evaluation of iron levels in newborns with hie. *Biol. Clin. Sci. Res. J.*, **2025;** 6(4): 205-208. doi: https://doi.org/10.54112/bcsrj.v6i4.1713

Introduction

Hypoxic ischemic encephalopathy (HIE) in the newborn remains a major cause of mortality and long-term neurodevelopmental disability and is a leading cause of neonatal mortality and morbidity in low and middle-income countries. This is a serious condition that occurs from diminished brain blood flow and oxygen content to the brain, usually during labor and delivery. Therapeutic hypothermia has become the standard of care to mitigate HIE-induced biochemical and cellular cascades leading to brain injury (1). However, although treatment strategies for HIE have improved, there is an unmet need to identify reliable biomarkers to allow accurate assessment of disease severity and progression to guide better treatment. Iron is one potential biomarker that's been drawing attention lately. Iron is important to neurodevelopment and normal cellular function and is a part of hemoglobin (iron compounds bound to the protein that transports oxygen around the body). Altered iron homeostasis in neonates, especially neonates with HIE, may primarily be due to oxidative stress, inflammation, and erythropoietic dysregulation.

Additionally, conditions including vitamin B12 deficiency, which are more generally discussed in older infants, also emphasize the interplay between micronutrient deficiencies and neurological outcomes and emphasize the importance of assessments of nutritional and hematological status in neonates with HIE (2). These raise important questions regarding whether iron metabolism is disrupted in newborns with HIE and whether these changes are of clinical or prognostic significance. Systemic changes in the critically ill neonate with HIE have recently been investigated in terms of organ function and biochemical markers. For example, urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule–1 (KIM–1) are being considered to test renal injury in these infants, as renal function can be a surrogate marker of systemic hypoxia and stress (3). However, little data are available concerning iron status in this population.

Hypothermia has been established as a neuroprotective strategy, but usually erythropoietin, magnesium sulfate, and antioxidants are given as adjuvant therapies and may affect iron metabolism directly or indirectly (4). Consequently, knowing iron levels in neonates with HIE can give insight into the more widespread metabolic derangements going on with the hypoxic-ischemic insult and recovery. However, it is already known that iron deficiency and iron deficiency anemia (IDA) are common among children living in resource-limited settings due to conditions such as poor maternal diet, low birth weight, and inadequate breastfeeding practices (5). These factors are then compounded in neonates with HIE since they frequently require intensive care and can be subjected to repeated blood sampling, transfusions, or nutritional delays. Cerebral perfusion may be compromised in other disorders as well, such as HIE, which can also affect the distribution and use of iron in the brain (6).

Assessment of iron status may prove critical to optimize recovery of neurodevelopment in the presence of treatment advances such as stem cell therapy and neuroprotective agents (7). Diagnostic information about HIE in infants is obtained through the use of neuroimaging tools, such as magnetic resonance imaging (MRI), to assess patterns and extent of brain injury (8). Nevertheless, most of these imaging modes are expensive and unavailable in many healthcare facilities in Pakistan. Because serum iron is an accessible and low-cost biomarker, it can be used by clinicians to prognosticate and tailor care plans for neonates at risk.

Additionally, systemic inflammatory indices that have some potential as diagnostic tools in neonates with moderate to severe HIE may interact with iron metabolism because inflammation influences hepcidin, a hormone that controls iron uptake and distribution (9). Neonatal neurological function is also evaluated using electroencephalographic (EEG) monitoring, which is also subject to limited availability and expertise (10). Iron status could be a good biochemical indicator combined with other already available diagnostic tools. Animal and human studies have associated iron deficiency with a range of neuropsychiatric outcomes, including mood disorders and cognitive deficits, and early life deficiencies may be harmful to brain structures such as the hippocampus and corpus striatum (11). Therefore, any early breakdown of your iron levels because of HIE could amount to a lifetime setback, emphasizing the importance of early diagnosis and address.

The mortality rates for neonates with HIE range from very low, if the neonatal care is good and interventions such as hypothermia therapy are available, to very high, depending on the severity of the HIE. Mortality

predictors are low Apgar scores, severe acidosis, multi-organ dysfunction, and delayed treatment initiation (12). Iron levels are not yet established as definitive prognostic markers of the animals, but their possibility of modulating iron's effects in contributing to and mitigating systemic effects of hypoxia should be investigated further. Iron deficiency can also be caused by other reasons like protein-losing enteropathy or excessive consumption of cow's milk, which only increases the risks of anemia and malnutrition. Although these conditions are more appropriate to settings in older infants, their mechanisms draw attention to the delicate balance of iron metabolism early in life and the consequences of nutritional insufficiency (13). Well-documented maternal and fetal risk factors for producing neonatal HIE include maternal anemia, hypertension, intrauterine growth restriction (IUGR), and prolonged labor (14).

Objective: The purpose was to evaluate iron levels in newborns diagnosed with hypoxic-ischemic encephalopathy (HIE) and to explore a potential relationship between altered iron status and severity or outcomes of HIE.

Methodology

The study was conducted at Department of Neonatal Medicine, Sindh institute of Child Health and Neonatology Korangi-5, Karachi.

The data collection was carried out over a period of six months, from July 2024 to December 2024.

Patients included were all-term newborns (gestational age ≥ 37 weeks) admitted to the NICU with a clinical diagnosis of HIE based on Sarnat staging. The only neonates enrolled were those less than 72 hours of age. Prior to inclusion, parental consent was obtained.

Newborns with congenital anomalies, intrauterine infections, or with blood transfusion before the iron level assessment were excluded. The study was also restricted to infants of mothers with known hematological disorders.

The inclusion criteria were neonates assessed within the first 72 hours of life. A detailed clinical examination was done, with HIE severity classification according to the Sarnat and Sarnat staging system. Venipuncture blood samples were collected for laboratory analysis of serum iron level, total iron binding capacity (TIBC), and ferritin. Each sample was run in the hospital's central laboratory using standardized techniques. The data obtained were gestational age, birth weight, Apgar scores, mode of delivery, and maternal history. Moreover, therapeutic interventions, including therapeutic hypothermia, were documented. Potential correlations were identified by comparing the iron parameters across different HIE severity groups. Statistical analysis was done using SPSS version 25. Continuous variables were summarised in the form of a mean or standard deviation and categorical data as frequency and percentages. Appropriate chi-square and ANOVA tests were performed, and a $p < 0.05$ was considered statistically significant.

Results

The study included 80 term neonates diagnosed with hypoxic-ischemic encephalopathy (HIE). Of these, 52 were male and 28 female. The mean birth weight was 3.1 ± 0.4 kg, and the mean gestational age was 38.5 ± 1.2 weeks. In 45 cases (56.3%), delivery was vaginal, and in 35 cases (43.7%), by cesarean. Sarnat staging was based on 30 (37.5%) neonates with Stage I HIE, 34 (42.5%) neonates with Stage II, and 16 (20%) neonates with Stage III.

Table 1 presents the distribution of serum iron levels across the different HIE stages. Neonates with Stage III HIE had significantly lower mean serum iron levels compared to those with Stage I and II.

Serum iron levels were significantly inversely related to the severity of HIE ($p < 0.01$). Additionally, neonates with Stage III HIE had lower ferritin levels and higher TIBC values, indicating altered iron metabolism. Table 2 highlights the ferritin and TIBC values about the severity of HIE. Lower ferritin and higher TIBC values were observed in more severe HIE stages, consistent with a functional iron deficiency pattern.

The study also included an evaluation of iron levels in relation to Apgar scores and a look at changes in iron profile. Lower serum iron levels were also found in neonates with lower Apgar scores at 1 and 5 min. This suggests a correlation that may depend on the degree of perinatal asphyxia with iron homeostasis.

Collectively, these findings suggest that infants with more severe HIE and lower Apgar scores have reduced iron levels and altered iron related parameters consistent with iron dysregulation that could be implicated in hypoxic injury.

Table 1: Serum Iron Levels Across HIE Stages

HIE Stage	Number of Neonates	Mean Serum Iron (µg/dL)	Standard Deviation
Stage I	30	84.2	±12.5
Stage II	34	72.6	±10.3
Stage III	16	59.1	±11.4

Table 2: Ferritin and TIBC Values in HIE

HIE Stage	Mean Ferritin (ng/mL)	Mean TIBC (µg/dL)
Stage I	165.7	305.3
Stage II	123.4	328.1
Stage III	89.6	352.7

Table 3: Correlation between Apgar score and Serum Iron Levels

Apgar Score (5 min)	Number of Neonates	Mean Serum Iron (µg/dL)
0–3	22	58.7
4–6	36	69.5
7–10	22	83.4

Discussion

This study examines levels of iron in neonates with a diagnosis of hypoxic-ischemic encephalopathy (HIE), showing a positive association between the severity of HIE and low serum iron and ferritin levels with increased total iron binding capacity (TIBC). These findings build on previous work in the literature relating to the systemic and metabolic effects of HIE in neonates on physiology, particularly iron metabolism, and its relationship to neurologic outcomes from HIE. Neonatal mortality and long-term neurodevelopmental sequelae, especially in low and middle-income countries such as Pakistan, are both induced primarily by HIE. HIE is underlain by a cascade of ischemic and reperfusion injury mechanisms that result in neuronal death and inflammation (1).

Iron is especially interesting in neonatal encephalopathy because iron is a critical cofactor in many enzymatic processes in the brain. However, paradoxically, iron's role is iron during oxidative stress, where free iron may catalyze the production of reactive oxygen species and further propagate neuronal injury (1, 6). It showed that neonates with more severe forms of HIE have significantly lower serum iron levels. Either this represents an acute phase response, or iron redistribution to tissues is observed after hypoxic insult. During systemic inflammation, the liver produces the peptide hepcidin, which downregulates intestinal iron absorption and sequesters iron in macrophages, causing serum iron to drop (5). Additionally, this mechanism may even be more pronounced in HIE due to the activation of inflammatory pathways in this condition when systemic inflammatory markers are increased in these neonates (9). Furthermore, the higher TIBC reported in neonates with more severe HIE stages suggests the presence of functional iron deficiency. If iron becomes sequestered and unavailable for erythropoiesis, the body compensates by increasing transferrin, which also increases TIBC (5). These findings are consistent with previous literature that has shown perturbed iron metabolism in critically ill neonates with neurological complications (10). In addition to hematopoiesis, iron is required for brain development and particularly for myelination, neurotransmitter synthesis, and mitochondrial function (11). Long-term cognitive, motor and behavioral

impairments have been associated with early-life iron deficiency, even in the absence of anemia (11). Neonates with HIE are given to neurodevelopmental deficits, and early recognition and correction of iron imbalance is potentially therapeutic.

However, seriously raising the already excessive iron in the blood of an already iron-overloaded population poses a danger of promoting oxidative damage. Management of HIE in term neonates remains anchored on therapeutic hypothermia, which can modify both metabolic demands as well as inflammatory responses (3, 4). Its effects on iron metabolism are not well characterized. It has been postulated that hypothermia could affect iron kinetics and thereby lead to changes in serum iron and ferritin seen in cooled infants (3). Although all neonates with moderate to severe HIE received hypothermia therapy, more work is needed to differentiate direct hypothermia effects on iron homeostasis from those related to the underlying pathology.

Another important observation was the negative correlation between Apgar score and serum iron. Serum iron concentrations in neonates were significantly lower in neonates with lower Apgar scores at 5 minutes. Low Apgar scores are reflective of poor perinatal transition and more severe hypoxic insult, which in turn strengthens the relationship between hypoxia severity and perturbed iron homeostasis (12). These results are consistent with previous studies, which showed that more severely asphyxiated neonates have elevated inflammatory cytokines and abnormal trace element profiles (9, 12). Assessing the extent of brain injury in the neonate with HIE frequently uses MRI, and previous studies have shown that iron accumulation in certain brain regions may be neurotoxic (8).

Future studies correlating serum and brain iron levels with MRI findings may shed some light on iron's double duty in neuroprotection and neurodegeneration despite the study not utilizing neuroimaging. Factors relating to maternal status must also be considered in regard to neonatal iron status. Iron imbalance predisposing to neonates may be secondary to maternal anemia, poor nutritional status, or vitamin B12 deficiency (2, 14). Maternal health conditions, including preeclampsia and gestational diabetes, can increase HIE risk in neonates, as was shown in one retrospective study (14). This highlights the need to optimize maternal health during pregnancy so as to prevent HIE and neonatal micronutrient deficiencies.

Moreover, dietary iron overload due to excessive cow's milk consumption in infancy has also been related to protein-losing enteropathy and, as a result, to iron deficiency anemia, although this is more unlikely in later infancy (13). However, it shows that it is important to balance iron levels in the small amounts needed in early life. However, several limitations of this study should be noted, followed by a short discussion of future directions. Limitations include the fact that the study was completed at a single center, thus limiting generalizability. Second, neurodevelopmental outcomes in relation to iron status were not followed longitudinally. Thirdly, maternal nutritional status and placental transfusion practices that may have confounded iron levels were not controlled.

Finally, the results show that neonates with the most severe hypoxic-ischemic encephalopathy have significant alterations in iron metabolism with decreased serum iron and ferritin levels and increased serum TIBC. These changes produce a combination of the acute inflammatory response and redistribution of iron in the tissue aftermath of hypoxic insult. Iron is important in brain development and oxidative injury, so timely monitoring and cautious correction of iron imbalance in neonates with HIE is useful. Finally, additional studies are needed to determine if tailored iron management might be a component of HIE adjunctive therapies in addition to current interventions (i.e., therapeutic hypothermia) (7).

Conclusion

This is a large association study of the iron metabolism changes in neonates and HIE severity. Those neonates with more severe HIE had markedly lower serum iron and ferritin and higher total iron binding capacity (TIBC), consistent with a functional iron deficiency from both inflammation and tissue redistribution. These results underscore the complexity of iron and its dual role as a friend and foe to neurons during oxidant stress, which results from ischemic hypoxic injury. Iron is important to brain development, and its dysregulation in HIE could help explain poor neurodevelopmental outcomes. Early recognition and management of affected neonates might potentially improve outcomes. However, iron supplementation in these individuals should be done carefully as high free blood iron can worsen neural damage. These findings require further validation in further multicenter studies and long-term follow-up, and future studies should explore therapeutic targeting of iron homeostasis in neonates with HIE.

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. (IRBEC-MTSD-78-24)

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

IA (Fellow NICU)
Manuscript drafting, Study Design,
Review of Literature, Data entry, Data analysis, and drafting article.
Study Design, manuscript review, critical input.

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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