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Original Research Article

Association Between Serum Iron Indices and Neurodevelopmental Delay (NDD) in Children

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Abstract:

Background: Neurodevelopmental disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and intellectual disability (ID) are commonly associated with nutritional deficiencies, including altered iron status. Iron plays a critical role in brain development, and disturbances in iron metabolism may influence neurodevelopmental outcomes. This study aimed to evaluate differences in serum iron indices among children with different neurodevelopmental disorders.

Methods: This hospital-based observational study included 186 children aged 4–12 years diagnosed with ASD, ADHD, or ID. Neurodevelopmental diagnoses were established using standardised assessment tools. Serum iron, serum ferritin, and serum transferrin levels were measured using standard laboratory methods. Iron parameters were compared across the three diagnostic groups using appropriate statistical analyses, with a p-value <0.05 considered statistically significant.

Results: Among the 186 children enrolled, 68 had ASD, 79 had ADHD, and 39 had ID. Serum ferritin levels showed a statistically significant difference among the three groups ($p = 0.003$), with higher mean ferritin levels observed in children with ASD and lower levels in children with ADHD and ID. In contrast, no statistically significant differences were observed in serum iron ($p = 0.087$) or serum transferrin levels ($p = 0.156$) among the diagnostic groups.

Conclusion: Serum ferritin levels differ significantly among children with ASD, ADHD, and ID, indicating variations in iron storage status across neurodevelopmental disorders. These findings suggest that assessment of serum ferritin may be useful in the clinical evaluation of children with neurodevelopmental disorders, even when serum iron and transferrin levels are within normal limits.

Keywords: Neurodevelopmental Delay, Iron Metabolism, Ferritin, Autism Spectrum Disorder, Intellectual Disability.

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Introduction

Neurodevelopmental delay (NDD) in children represents a significant public health concern, particularly in low- and middle-income countries, where nutritional deficiencies remain highly prevalent [1]. Neurodevelopment encompasses the progressive acquisition of cognitive, motor, language, and social skills during early childhood, a period characterised by rapid brain growth and high metabolic demand. Any disruption during this critical window may result in long-term functional impairments, emphasising the importance of identifying modifiable risk factors contributing to delayed neurodevelopment [1-3].

Iron is an essential micronutrient required for multiple neurobiological processes, including myelination, neurotransmitter synthesis, energy metabolism, and neuronal differentiation. During infancy and early childhood, adequate iron availability is crucial for optimal brain development. Iron deficiency, even in the absence of anaemia, has been associated with adverse neurocognitive outcomes such as impaired attention, delayed motor development, and reduced learning capacity [4, 5].

Serum iron, ferritin, and transferrin are commonly used biochemical markers to assess iron status. Serum iron reflects the circulating iron available for metabolic processes, while ferritin serves as an indicator of iron stores in the body [6]. Transferrin, the primary iron transport protein, reflects iron-binding capacity and is often elevated in states of

iron deficiency. Alterations in these parameters may occur before overt anaemia develops, suggesting that subclinical iron deficiency could contribute to neurodevelopmental impairment even in children with normal haemoglobin levels [7, 8].

Several studies have demonstrated an association between iron deficiency anaemia and delayed psychomotor and cognitive development in children. However, the evidence linking individual iron indices- particularly serum ferritin and transferrin levels- with neurodevelopmental delay remains inconsistent. Some studies suggest that low ferritin levels are independently associated with poorer developmental outcomes, while others report no significant correlation after adjusting for confounding factors such as socioeconomic status, nutritional intake, and comorbid illnesses [9, 10]. Furthermore, data from developing countries remain limited, despite the higher burden of both iron deficiency and neurodevelopmental disorders in these regions [11].

Early identification of iron-related risk factors for neurodevelopmental delay may facilitate timely nutritional intervention and potentially improve developmental outcomes. Evaluating the relationship between biochemical iron parameters and neurodevelopment can help clarify whether routine assessment of iron status should be incorporated into the diagnostic evaluation of children presenting with developmental delay [3, 8].

Therefore, the present study aims to assess the correlation of serum iron, ferritin, and transferrin levels with neurodevelopmental delay in children. By analysing these biochemical markers in relation to developmental status, this study seeks to contribute to the existing body of evidence and provide insights that may guide early screening and preventive strategies in pediatric practice.

Materials and Methods

Study Design and Setting: This hospital-based observational study was conducted in a tertiary care teaching hospital over a period of one year. The study was designed to evaluate the correlation between biochemical iron parameters- serum iron, serum ferritin, and serum transferrin- and neurodevelopmental delay in children.

Study Population: A total of 186 children were enrolled in the study. Children attending the pediatric outpatient department or admitted to the pediatric ward with suspected or diagnosed neurodevelopmental delay were screened for eligibility.

Inclusion Criteria

- Children aged 4-12 years
- Children diagnosed with neurodevelopmental delay based on standardised developmental assessment tools.
- Written informed consent was obtained from parents or legal guardians

Exclusion Criteria

- Children with known genetic syndromes or chromosomal abnormalities
- History of perinatal asphyxia, central nervous system infections, or major congenital anomalies
- Children with chronic systemic illnesses (e.g., chronic kidney disease, liver disease)
- Children receiving iron supplementation or blood transfusion within the past three months

Assessment of Neurodevelopment: Neurodevelopmental status was assessed using a standardised and validated developmental screening tool, such as the Swanson, Nolan and Pelham Rating Scale (SNAP-IV), Autism Diagnostic Observational Schedule, Second Edition (ADOS-2), and Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III). Developmental delay was defined as a developmental quotient (DQ) or score below the accepted cutoff for age in one or more developmental domains, including gross motor, fine motor, language, cognitive, or social domains.

Laboratory Investigations: Venous blood samples were collected under aseptic conditions for the estimation of iron parameters. The following biochemical investigations were performed:

- Serum iron levels were measured using the colourimetric method.
- Serum ferritin levels were estimated using enzyme-linked immunosorbent assay (ELISA)/ chemiluminescence immunoassay.
- Serum transferrin levels were measured using an immunoturbidimetric assay.

All samples were analysed in the central laboratory of the institution following standard operating procedures and quality control protocols.

Data Collection: Demographic and clinical data, including age, sex, nutritional status, birth history, feeding practices, and socioeconomic background, were recorded using a structured proforma. Laboratory and developmental assessment findings were documented for analysis.

Statistical Analysis: Data was entered into Microsoft Excel and analysed using Statistical Package for the Social Sciences (SPSS). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. The correlation between serum iron parameters and neurodevelopmental delay was assessed using

Pearson's or Spearman's correlation coefficient, as appropriate. A p-value of <0.05 was considered statistically significant.

Results

A total of 186 children were included in the study, comprising 68 children with autism spectrum disorder (ASD), 79 with attention deficit hyperactivity disorder (ADHD), and 39 with intellectual disability (ID).

Table 1: Comparing subscales score (mean ± SD) and CSHQ total

Outcome	ASD (n=68)	ADHD (n=79)	ID (n=39)	p-value
Sleep duration	3.9±1.8	4.5±1.78	3.5±0.67	**0.004**
Daytime sleepiness	12.6±3.4	11.8±2.54	13.1±2.75	0.064
Parasomnias	9.3±2.3	9.3±2.67	9.1±2.72	0.836
Sleep anxiety	6.3±2.6	7.1±2.67	6.6±2.01	0.163
Sleep onset delay	1.5±0.8	1.6±0.78	1.3±0.67	0.303
Bedtime resistance	11.1±3.5	10.2±5.50	10.4±3.44	0.468
Night wakings	3.3±1.6	3.5±1.72	3.2±1.54	0.624
CSHQ total score	49.2±3.8	49.0±4.53	48.0±9.70	0.575

* $p < 0.05$ considered statistically significant

The mean total CSHQ scores were comparable among the three groups, with no statistically significant difference observed ($p = 0.575$) (Table 1). Similarly, no significant intergroup differences were noted for bedtime resistance, sleep onset delay, sleep anxiety, night wakings, daytime sleepiness, or parasomnias ($p > 0.05$ for all). However, sleep duration differed significantly among the three groups ($p = 0.004$), with post-hoc analysis showing significantly higher scores in children with ADHD compared to ASD and ID. Children with ADHD demonstrated higher mean sleep duration scores compared to those with ASD and ID. This finding suggests variation in sleep duration–related disturbances across different neurodevelopmental disorders. No other CSHQ subdomains showed statistically significant differences between the groups.

Table 2: Comparing mean values of iron, ferritin and transferrin

Outcome	ASD (n=68)	ADHD (n=79)	ID (n=39)	p-value
Ferritin (mean ± SD)	60.7±28.9	46.6±39.9	37.2±29.9	**0.003**
Iron (mean ± SD)	71.0±28.5	84.0±35.3	79.5±42.6	0.087
Transferrin (mean ± SD)	271.0±48.5	284.0±35.3	276.0±32.9	0.156

*p-value of **< 0.05** was considered statistically significant.

Serum ferritin levels differed significantly among the three groups ($p = 0.003$), with higher mean values observed in children with autism spectrum disorder compared to those with attention deficit hyperactivity disorder and intellectual disability (Table 2). In contrast, no statistically significant differences were noted in serum transferrin levels among the groups ($p = 0.156$). Similarly, serum iron levels did not show a statistically significant difference across the three groups ($p = 0.087$), although higher mean values were observed in children with attention deficit hyperactivity disorder.

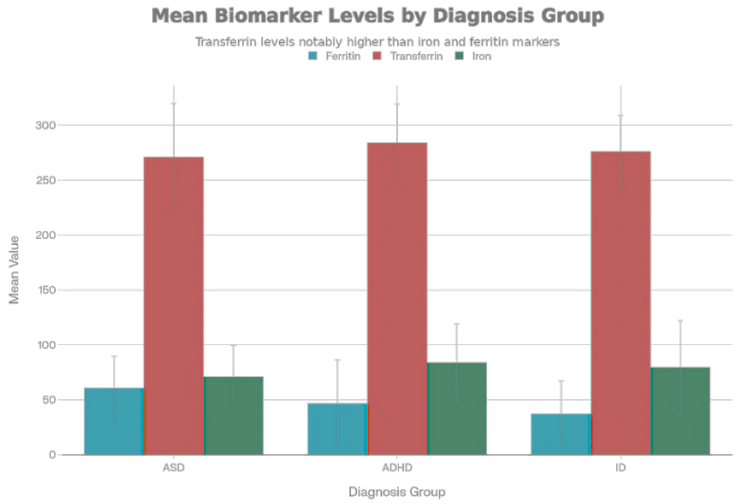

Figure 1: Mean biomarkers level

The bar graph demonstrates the distribution of mean (± SD) serum ferritin, transferrin, and iron levels across children with ASD, ADHD, and ID (Fig. 1). A clear descending trend in serum ferritin levels is observed from the ASD group to the ID group, with the intergroup difference achieving statistical significance, underscoring a differential iron storage status among the diagnostic categories. In contrast, serum transferrin concentrations were comparable across all three groups, with substantial overlap of standard deviation bars, indicating the absence of a statistically meaningful difference. Serum iron levels exhibited modest variability, with relatively higher mean values in the ADHD and ID groups compared to ASD; however, these differences did not reach statistical significance, as reflected by the overlapping dispersion. Collectively, the figure visually substantiates the analytical findings, emphasising serum ferritin as the primary biomarker exhibiting significant intergroup variation, while transferrin and serum iron appear to remain largely stable across neurodevelopmental diagnoses.

Discussion

This study examined sleep disturbances and iron profile parameters in children with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and intellectual disability (ID). Although the overall severity of sleep disturbances, as reflected by total Children's Sleep Habits Questionnaire (CSHQ) scores, was comparable across diagnostic groups, significant differences were observed in sleep duration and serum ferritin levels, suggesting diagnosis-specific variations within an otherwise shared burden of sleep problems.

Sleep disturbances were highly prevalent across all three neurodevelopmental groups, consistent with prior research demonstrating that children with ASD, ADHD, and ID are at substantially increased risk for sleep-related difficulties compared to typically developing peers [1-3]. The absence of significant intergroup differences in most CSHQ subdomains- including bedtime resistance, sleep onset delay, sleep anxiety, parasomnias, night wakings, and daytime sleepiness- supports the concept of sleep disturbance as a transdiagnostic feature of neurodevelopmental disorders rather than a disorder-specific phenomenon [8]. Neurobiological dysregulation, behavioural challenges, and environmental factors common to these conditions may collectively contribute to these shared sleep profiles.

A notable finding of the present study was the significant intergroup difference in sleep duration, with children with ADHD demonstrating higher mean sleep duration scores compared to those with ASD and ID. Reduced sleep duration in ASD has been attributed to circadian rhythm abnormalities, sensory hypersensitivity, and difficulties with sleep initiation and maintenance [12, 13]. Similarly, children with ID often experience fragmented sleep related to comorbid medical conditions, behavioural dysregulation, and limited sleep hygiene practices [14]. In contrast, children with ADHD may exhibit relatively longer sleep duration despite poor sleep quality, possibly due to increased sleep pressure, delayed circadian phase, or the effects of pharmacological and behavioural interventions [15]. This highlights the importance of domain-specific sleep assessment rather than reliance on composite sleep scores alone.

With respect to iron status, serum ferritin levels differed significantly among the groups, with the highest mean values observed in children with ASD and lower levels in children with ADHD and ID. Ferritin serves as a marker of iron stores and plays a critical role in brain development, myelination, and neurotransmitter synthesis, particularly within dopaminergic pathways implicated in attention regulation and sleep-wake control [16, 17]. Prior studies have consistently reported an association

between low ferritin levels and ADHD symptom severity, restless sleep, and periodic limb movements during sleep [18-20]. The relatively lower ferritin levels observed in the ADHD and ID groups in the present study may therefore represent a biologically relevant vulnerability, even in the absence of overt iron deficiency anaemia.

In contrast, serum iron and transferrin levels did not differ significantly among the diagnostic groups, suggesting that iron transport and circulating iron availability may remain relatively preserved, while iron storage capacity varies across conditions. This dissociation underscores serum ferritin as a more sensitive biomarker for detecting subtle alterations in iron status in children with neurodevelopmental disorders, a finding that aligns with previous pediatric and sleep medicine literature [12, 21].

Despite the observed differences in ferritin, most sleep domains did not differ significantly between groups, indicating that sleep disturbances in neurodevelopmental disorders are likely multifactorial. Iron status represents only one of several interacting biological factors, alongside genetic vulnerability, neurochemical dysregulation, behavioural characteristics, comorbid medical conditions, and environmental influences [4, 15]. The absence of a direct one-to-one relationship between ferritin levels and sleep outcomes in this study emphasises the need for a holistic approach to assessment and management.

Clinical Implications

The findings of this study carry important clinical implications. First, given the high and comparable burden of sleep disturbances across ASD, ADHD, and ID, routine screening for sleep problems should be incorporated into the standard clinical evaluation of all children with neurodevelopmental disorders, regardless of diagnostic category. Second, the significant intergroup variation in serum ferritin highlights the value of assessing iron stores, particularly in children with ADHD and ID, even when serum iron levels are within normal limits. Early identification of low ferritin levels may allow for timely nutritional counselling, dietary optimisation, or iron supplementation where clinically indicated. Finally, the lack of correspondence between ferritin levels and most sleep domains suggests that management strategies should be individualised and multimodal, integrating behavioural sleep interventions with medical and nutritional evaluation rather than relying on a single biomarker to guide treatment decisions.

Limitations and Future Directions

This study is limited by its cross-sectional design, which precludes causal inference regarding the relationship between iron status and sleep disturbances. Sleep outcomes were assessed using caregiver-reported questionnaires rather than objective measures such as actigraphy or polysomnography. Additionally, factors such as dietary iron intake, iron supplementation, medication use, and severity of neurodevelopmental symptoms were not systematically controlled and may have influenced the findings.

Future longitudinal studies incorporating objective sleep measures and comprehensive nutritional and metabolic assessments are needed to clarify the temporal and mechanistic relationships between iron metabolism and sleep disturbances in neurodevelopmental disorders. Interventional trials examining the effect of iron repletion on sleep outcomes may further inform evidence-based clinical practice.

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