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Review

Clinical Manifestations of Low Ferritin in Children Without Anemia

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Abstract

Iron deficiency remains one of the most prevalent nutritional deficiencies affecting children worldwide. Although anemia is commonly regarded as the primary consequence of iron deficiency, depletion of iron stores may occur long before hemoglobin concentrations decline below normal reference ranges. Low serum ferritin is recognized as an early indicator of reduced iron reserves and may be associated with a variety of clinical manifestations despite the absence of anemia. Increasing evidence suggests that iron deficiency without anemia is not merely a laboratory finding but a condition with potential implications for multiple physiological systems during critical stages of growth and development. Iron plays a central role in numerous biological processes, including oxygen transport, cellular energy metabolism, neurotransmitter synthesis, myelination, immune function, and muscle activity. Consequently, inadequate iron availability may affect tissues with high metabolic demands even when erythropoiesis remains preserved. Children with low ferritin levels may present with neurocognitive and behavioral symptoms such as impaired attention, reduced concentration, learning difficulties, irritability, and hyperactivity. Associations between low ferritin concentrations and attention-deficit/hyperactivity disorder have also been reported. Physical manifestations may include fatigue, decreased exercise tolerance, reduced endurance, and diminished overall well-being. Sleep-related disturbances, particularly restless legs syndrome, periodic limb movements during sleep, and poor sleep quality, have likewise been linked to depleted iron stores. Recognition of low ferritin without anemia presents important diagnostic challenges because symptoms are often nonspecific and may overlap with other pediatric conditions. Serum ferritin remains the most widely used marker of iron stores; however, interpretation requires consideration of factors such as inflammation and infection that can influence ferritin concentrations. Current evidence highlights the importance of evaluating iron status beyond hemoglobin measurements alone, particularly in symptomatic children and those with recognized risk factors for iron deficiency. Improved awareness of the clinical significance of low ferritin may support earlier identification of affected children, facilitate appropriate management, and help prevent progression to overt iron deficiency anemia while minimizing potential impacts on health, development, and quality of life.

Keywords: *Low ferritin, Iron deficiency without anemia, Children, Neurocognitive symptoms, Sleep disturbances*

Introduction

Iron deficiency is the most common micronutrient deficiency worldwide and remains a major public health concern in childhood. Although anemia is traditionally regarded as the hallmark consequence of iron deficiency, depletion of iron stores can occur long before hemoglobin concentrations fall below age-specific reference ranges. Serum ferritin is widely recognized as the most useful indicator of body iron stores, and low ferritin concentrations often represent the earliest laboratory evidence of iron deficiency (1). Consequently, a substantial proportion of children may have iron deficiency without anemia, a condition that can remain unrecognized because routine clinical attention is frequently focused on hemoglobin levels rather than iron stores.

Iron plays a fundamental role in numerous physiological processes beyond erythropoiesis. It is essential for cellular energy production, neurotransmitter synthesis, myelination, immune function, and normal growth and development. During infancy, childhood, and adolescence, periods characterized by rapid growth and increased iron requirements, inadequate iron intake or increased iron demand can readily lead to depletion of iron reserves. When iron stores become insufficient, tissues with high metabolic demands may be affected even in the absence of anemia, giving rise to a spectrum of clinical manifestations that are often subtle and nonspecific (2).

Emerging evidence suggests that low ferritin levels in children may be associated with neurocognitive, behavioral, and functional disturbances. Iron deficiency has been linked to alterations in attention, learning, memory, executive function, and psychomotor development. Associations have also been reported between low ferritin concentrations and conditions such as attention-deficit/hyperactivity disorder, sleep disturbances, restless legs syndrome, and reduced academic performance. These findings support the concept that iron deficiency should be viewed as a systemic disorder rather than solely a hematologic condition (2, 3).

The recognition of low ferritin without anemia presents several clinical challenges. Symptoms such as fatigue, irritability, poor concentration, decreased physical endurance, and sleep-related complaints are common in childhood and may have multiple causes. As a result, iron deficiency may not be considered in the differential diagnosis when hemoglobin values remain within normal limits. Furthermore, interpretation of ferritin levels can be complicated by inflammation, infection, and chronic disease because ferritin functions as an acute-phase reactant. Nevertheless, low ferritin concentrations remain highly specific for depleted iron stores and are valuable in identifying early iron deficiency (1, 3).

Increasing awareness of the potential consequences of iron depletion before the onset of anemia has prompted greater interest in screening, diagnosis, and management strategies. Early identification of children with low ferritin may provide opportunities to address symptoms, optimize neurodevelopment, and prevent progression to overt iron deficiency anemia. Understanding the clinical manifestations associated with low ferritin in the absence of anemia is therefore important for pediatric practice and for improving child health outcomes worldwide (2-4).

Review

Low ferritin in the absence of anemia is increasingly recognized as a clinically significant condition in children. Traditionally, the assessment of iron deficiency has focused on hemoglobin concentrations; however, growing evidence suggests that depleted iron stores may affect multiple physiological systems before anemia develops. Iron is essential for neurotransmitter synthesis, myelination, and cellular energy metabolism, which may explain why children with low ferritin can present with symptoms such as fatigue, impaired attention, behavioral disturbances, reduced academic performance, and sleep-related complaints despite having normal hemoglobin levels (5).

The relationship between low ferritin and neurobehavioral manifestations has received particular attention. Studies have reported

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associations between reduced ferritin concentrations and attention-deficit/hyperactivity disorder (ADHD), suggesting that iron deficiency may contribute to alterations in dopaminergic pathways involved in attention and executive functioning.(5) In addition, sleep disturbances, including restless legs syndrome and poor sleep quality, have been linked to low ferritin levels, with some evidence indicating symptom improvement following iron supplementation (6). These findings support the concept that iron deficiency should be identified and managed at an early stage rather than waiting for anemia to develop.

Neurocognitive and Behavioral Effects

Iron plays a fundamental role in brain development and function, making the central nervous system particularly vulnerable to depleted iron stores even before anemia becomes apparent. Low ferritin levels reflect diminished iron reserves and have been associated with alterations in neurotransmitter metabolism, myelination, and neuronal energy production. During childhood, when rapid neurodevelopmental processes are ongoing, inadequate iron availability may interfere with cognitive performance and behavioral regulation. Evidence indicates that children with iron deficiency without anemia may experience subtle but clinically meaningful neurocognitive disturbances that are not readily explained by hematologic parameters alone (7).

Research has demonstrated that reduced iron stores can affect attention, memory, learning capacity, and executive functioning. Iron serves as a cofactor in the synthesis of dopamine, serotonin, and norepinephrine, neurotransmitters that are closely involved in attention control, motivation, and emotional regulation. Disturbances in these pathways have been proposed as mechanisms linking low ferritin concentrations to behavioral symptoms observed in pediatric populations. Children with iron deficiency may exhibit diminished concentration, slower information processing, reduced task persistence, and difficulties with problem-solving activities, all of which can negatively influence academic achievement and classroom performance (2).

Behavioral manifestations have also attracted considerable interest. Several studies have reported associations between low ferritin levels and increased rates of hyperactivity, impulsivity, irritability, and emotional dysregulation. Findings from pediatric cohorts suggest that ferritin concentrations tend to be lower among children exhibiting symptoms consistent with ADHD, supporting the hypothesis that iron status may influence neurobehavioral functioning through dopaminergic mechanisms. Although causality remains difficult to establish, these observations highlight the potential role of iron deficiency as a modifiable contributor to behavioral difficulties in susceptible individuals (8).

Neurodevelopmental concerns extend beyond school-aged children. Early-life iron deficiency has been linked to long-term effects on cognitive and psychomotor development, with some deficits persisting despite later correction of iron status. Experimental and clinical data suggest that insufficient iron availability during critical periods of brain maturation may alter neuronal connectivity and myelin formation, potentially influencing later intellectual and behavioral outcomes. Such findings underscore the importance of recognizing low ferritin as more than a laboratory abnormality and support increasing attention toward iron status assessment in children presenting with unexplained cognitive or behavioral symptoms (9).

Physical and Sleep-Related Symptoms

The clinical presentation of low ferritin without anemia frequently extends beyond neurocognitive manifestations and may involve a variety of physical and sleep-related symptoms. Because iron participates in oxygen utilization, mitochondrial energy production, muscle metabolism, and neurological signaling, depletion of iron stores can produce functional disturbances despite normal hemoglobin concentrations. Children with low ferritin often report nonspecific complaints such as fatigue, reduced stamina, weakness, decreased exercise tolerance, headaches, and poor overall well-being. These symptoms may be subtle and are easily attributed to lifestyle factors, growth-related changes, or other common pediatric conditions,

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which can delay recognition of underlying iron deficiency (10).

Physical performance appears particularly sensitive to reduced iron availability. Even in the absence of anemia, iron deficiency may impair oxidative metabolism within skeletal muscle, resulting in decreased endurance and increased perceived exertion during physical activity. School-aged children and adolescents may experience diminished participation in sports, slower recovery following exercise, and reduced capacity to sustain prolonged physical effort. Such effects have been documented in studies examining iron deficiency beyond its hematologic consequences, emphasizing that tissue iron depletion can adversely affect functional status before measurable changes in hemoglobin occur (10).

Sleep disturbances have emerged as a prominent feature associated with low ferritin levels in pediatric populations. Iron is involved in dopaminergic neurotransmission, a pathway that contributes to the regulation of movement and sleep architecture. Reduced ferritin concentrations have been linked to restless legs syndrome (RLS), periodic limb movements during sleep, difficulty initiating sleep, frequent nocturnal awakenings, and non-restorative sleep. These disturbances may contribute to excessive daytime sleepiness, irritability, impaired concentration, and reduced quality of life. Clinical observations suggest that children with sleep-related movement disorders frequently exhibit ferritin levels below accepted thresholds for adequate iron stores, supporting a biological relationship between iron deficiency and sleep dysfunction (6).

Sleep-related symptoms may also overlap with behavioral and emotional concerns, creating diagnostic complexity. Poor sleep quality can exacerbate attention difficulties, mood instability, and daytime fatigue, making it challenging to distinguish primary neurobehavioral conditions from manifestations related to depleted iron stores. Recognition of low ferritin as a potential contributor to these complaints has gained importance in pediatric practice, particularly when conventional evaluations fail to identify an alternative explanation. The growing body of literature describing physical fatigue, reduced functional capacity, restless sleep, and movement-related sleep disorders reinforces the need to consider iron status in children presenting with persistent, otherwise unexplained symptoms (11).

Diagnostic and Clinical Considerations

Identifying low ferritin in children without anemia remains a challenge because clinical evaluation often prioritizes hemoglobin concentrations, which may remain within normal limits despite significant depletion of iron stores. Iron deficiency develops progressively, beginning with the exhaustion of storage iron before abnormalities appear in erythropoiesis. As a result, children may present with symptoms related to tissue iron deficiency while standard hematologic screening fails to indicate anemia. This diagnostic gap has contributed to increasing recognition of ferritin measurement as an important component of iron status assessment, particularly in children with persistent fatigue, cognitive difficulties, behavioral concerns, sleep disturbances, or unexplained functional impairment (12).

Serum ferritin is widely regarded as the most useful laboratory marker of iron stores because low values are highly specific for iron deficiency. Nevertheless, interpretation requires careful clinical judgment. Ferritin functions as an acute-phase reactant and may rise in response to infection, inflammation, liver disease, or other chronic conditions. Under such circumstances, ferritin concentrations can appear normal despite depleted iron reserves, potentially masking underlying deficiency. Contemporary pediatric recommendations therefore emphasize the importance of considering the broader clinical context and, when appropriate, incorporating complementary biomarkers such as transferrin saturation, serum iron, soluble transferrin receptor levels, and inflammatory markers to improve diagnostic accuracy (13).

The absence of universally accepted ferritin thresholds further complicates diagnosis. Historically, cut-off values have varied among

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laboratories, professional societies, and research studies, resulting in considerable heterogeneity in reported prevalence rates. Recent investigations have questioned whether conventional thresholds adequately identify children with physiologically significant iron deficiency, suggesting that some symptomatic individuals may remain undiagnosed when higher ferritin cut-offs are not considered. Efforts to establish biologically based reference values have highlighted the need for age-specific and clinically relevant diagnostic criteria that better reflect iron requirements during growth and development (14).

Clinical management decisions frequently extend beyond laboratory findings alone. Symptoms, dietary history, growth patterns, comorbid conditions, and risk factors for iron deficiency should all contribute to the diagnostic process. Rapid growth during infancy and adolescence, restrictive dietary practices, chronic inflammatory disorders, gastrointestinal disease, and socioeconomic factors may increase susceptibility to depleted iron stores. Recognition of these factors is particularly important when ferritin concentrations are borderline or when symptoms appear disproportionate to laboratory abnormalities. Current pediatric guidance increasingly supports early identification and treatment of iron deficiency with or without anemia, reflecting growing awareness that tissue-level consequences may emerge before hematologic changes become evident (15).

Conclusion

Low ferritin without anemia is increasingly recognized as a clinically relevant form of iron deficiency in children, with potential effects on neurocognitive function, behavior, physical performance, and sleep quality. Evidence suggests that tissue iron depletion may produce significant symptoms before hematologic abnormalities become apparent. Accurate interpretation of ferritin levels and awareness of associated clinical manifestations are essential for timely diagnosis. Greater attention to early iron deficiency may facilitate appropriate intervention and improve overall pediatric health outcomes.

Disclosure

Conflict of interest

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Ethical consideration

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Data availability

All data is available within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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