



IRON DEFICIENCY AND RESTLESS LEGS SYNDROME: PATHOPHYSIOLOGICAL ASPECTS

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Abstract Restless legs syndrome (RLS) is a neurological disorder characterized by an irresistible urge to move the legs, especially at rest and at night. Iron deficiency is considered a key pathophysiological factor in the development of this syndrome. This article analyzes the mechanisms underlying the relationship between iron deficiency and RLS, including impaired dopaminergic transmission, changes in the central nervous system, and metabolic aspects.

Key words: iron deficiency, restless legs syndrome, dopamine, central nervous system, pathophysiology.

Аннотация Синдром беспокойных ног (СБН) — это неврологическое расстройство, характеризующееся непреодолимым желанием двигать ногами, особенно в состоянии покоя и ночью. Дефицит железа считается ключевым патофизиологическим фактором в развитии этого синдрома. В данной статье анализируются механизмы, лежащие в основе взаимосвязи между дефицитом железа и СБН, включая нарушение дофаминергической передачи, изменения в центральной нервной системе и метаболические аспекты.

Ключевые слова: дефицит железа, синдром беспокойных ног, дофамин, центральная нервная система, патофизиология.

Introduction

Restless legs syndrome (RLS), also known disease, affects approximately 5 - 10% of the adult population. It is characterized by sensory and motor symptoms that

worsen during rest and at night. Although the exact etiology remains unclear, accumulating evidence highlights the central role of iron deficiency in the development and progression of RLS. Despite its high prevalence, the pathophysiology of RLS remains incompletely understood. However, one of the most consistently identified factors is iron deficiency, particularly within the central nervous system. Studies suggest that even in the absence of systemic anemia, patients may exhibit reduced brain iron levels, indicating a localized dysregulation of iron metabolism.

Restless Legs Syndrome (RLS) is fundamentally linked to brain iron deficiency, often resulting in dopaminergic dysfunction and disrupted iron homeostasis, even when systemic iron levels appear normal. Reduced central iron, particularly in the substantia nigra, decreases tyrosine hydroxylase activity (a rate-limiting step in dopamine synthesis), leading to decreased dopamine transmission. This deficiency acts as a key, actionable driver of symptoms, often corrected with iron supplementation

Physiological Role of Iron

Iron is an essential micronutrient involved in oxygen transport, mitochondrial function, and neurotransmitter synthesis. In the central nervous system, iron plays a critical role in myelination and dopamine metabolism. Proper iron homeostasis is essential for maintaining neuronal integrity and function.

Research indicates that cerebrospinal fluid ferritin levels are often reduced in RLS patients, even when serum ferritin appears normal. This suggests that the problem lies not only in systemic iron deficiency but also in impaired iron transport across the blood - brain barrier. Recent studies (2024) further highlight **iron dysregulation at the neuronal level**, showing altered iron handling in neuron-derived extracellular vesicles, reinforcing the concept of central iron imbalance.

Brain Iron Deficiency

Patients with RLS often exhibit reduced iron levels in specific brain regions, particularly the substantia nigra. Importantly, brain iron deficiency may occur even when systemic iron levels appear normal. This discrepancy is attributed to impaired iron transport across the blood - brain barrier.

Clinical manifestations.

The main symptoms of RLS are discomfort in the legs, which worsens with rest and is temporarily relieved by movement. Symptoms most often occur in the evening and at night, disrupting sleep and reducing quality of life.

Dopaminergic Dysfunction

One of the central mechanisms in RLS pathophysiology is dysfunction of the dopaminergic system. Iron acts as a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. Reduced iron levels lead to decreased dopamine production and altered receptor activity, contributing to RLS symptoms.

Dopamine plays a central role in motor control and sensory processing. In RLS:

- Dopamine production is reduced
- Dopamine receptor activity is altered
- Circadian dopamine fluctuations are disrupted

Iron deficiency contributes to this dysfunction because it reduces the activity of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis.

Additionally, decreased D2 receptor activity in the striatum has been observed in patients with RLS. This explains why dopaminergic medications (e.g., pramipexole, ropinirole) are effective in treating symptoms.

Genetic and Molecular Factors

Recent studies suggest that genetic predisposition may influence iron metabolism and dopaminergic pathways in RLS. Variants in genes associated with iron regulation and neuronal signaling have been identified in affected individuals.

Clinical Manifestations

RLS is characterized by unpleasant sensations in the legs, often described as crawling, tingling, or burning. Symptoms are typically worse in the evening and during periods of inactivity. Movement provides temporary relief, which is a hallmark feature of the disorder.

Diagnosis

Diagnosis of RLS is primarily clinical, based on established criteria. Laboratory tests, particularly serum ferritin levels, are important for assessing iron status. Ferritin levels below 50 µg/L are commonly associated with symptom severity.

Treatment Approaches

Management of RLS includes correction of iron deficiency through oral or intravenous supplementation. Pharmacological treatments include dopaminergic agents, anticonvulsants, and opioids in severe cases. Addressing underlying iron deficiency is a cornerstone of therapy. Understanding the pathophysiological mechanisms allows for more effective diagnosis and treatment of this condition. Further research is needed to clarify the mechanisms by which iron interacts with neurotransmitter systems.

Conclusion Iron deficiency plays a crucial role in the pathophysiology of restless legs syndrome. Iron deficiency - particularly within the brain - is a fundamental factor in the pathophysiology of restless legs syndrome. It leads to dopaminergic dysfunction, impaired myelination, and altered neuronal signaling. Modern research supports a multifactorial model involving genetic, metabolic, and neurochemical pathways. Future studies should focus on targeted therapies aimed at restoring brain iron homeostasis and improving long - term outcomes. Understanding the relationship between iron metabolism and neural function provides valuable insights into diagnosis and treatment. Future research should focus on targeted therapies aimed at restoring brain iron homeostasis.

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