SLEEP, 2025, **48**, 1–3
https://doi.org/10.1093/sleep/zsaf128
Advance access publication 13 May 2025
Editorial

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Bringing iron to the brain for restless legs

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A relationship between iron deficiency and restless legs syndrome (RLS) was first reported in 1953 [1], and iron dysregulation in the brain is today thought to play a fundamental role in the pathophysiology of the disorder. For many years, iron administration has been an important component of RLS therapy, reinforced by a recent American Academy of Sleep Medicine (AASM) clinical practice guideline that gave a strong affirmative recommendation to the use of intravenous ferric carboxymaltose (FCM) [2]. But there are many critical diagnostic and therapeutic factors that need to be considered for iron therapy to be successfully implemented.

Serum ferritin concentration is often used as a measure of whether iron replacement is needed in RLS. While there is no question that a serum ferritin concentration below the lower limit of normal for age and sex should prompt iron replacement in the setting of RLS, its use when values are in the ostensibly normal range is more nuanced. First, serum ferritin does not correlate well with measures of intracranial iron content, such as CSF ferritin concentration [3] or substantia nigra iron measured by MRI scans [4] or transcranial ultrasound [5]. Second, serum ferritin is an acute-phase reactant, and levels may be raised in the setting of inflammation or malignancy. Third, serum ferritin concentration is measured by immunoassay, and values vary considerably between different laboratories, depending on the reagents used [6]. Fourth, the upper limit of 100 µg/L for initial intravenous iron administration in the setting of RLS suggested by an international task force in 2018 was determined empirically by the distribution of serum ferritin concentrations found in those participating in the major clinical trials rather than by biologic considerations [7]. More recent studies have shown that RLS in patients with serum ferritin concentrations in the range of 100–300 µg/L respond equally well to intravenous iron compared to those with concentrations <100 µg/L [8, 9], and that the risk of hepatic iron overload appears to be extremely low as long as transferrin saturation is <45% [8].

Based on the considerations discussed above, it seems reasonable that patients with moderate or severe RLS should be considered for iron replacement if serum ferritin concentration is ≤300 µg/L. For patients with serum ferritin concentration ≥75 µg/L, iron should be given intravenously as absorption of oral iron is minimal above this level. If serum ferritin concentration is <75 µg/L, oral iron once every second night, together with vitamin C, may be a reasonable initial approach [10] if the patient does not have iron malabsorption because of gastrointestinal disease or prior surgery. However, oral iron may cause unpleasant side effects, and it may take several months before an increase in systemic iron levels occurs. Therefore, especially if a more rapid response is needed due to the severity of symptoms, intravenous iron may be the most appropriate therapy even in this subgroup.

Only those preparations in which dissociation of the iron–carbohydrate moiety occurs slowly should be used for RLS, as this allows iron to better penetrate the brain. Preparations include FCM, low-molecular-weight iron dextran, ferumoxytal, and ferric derisomaltose. The choice of a specific preparation is a balance between evidence of effectiveness, potential side effects, and cost and availability. Only FCM has been tested in placebo-controlled trials of primary RLS, with a recent meta-analysis of seven studies showing success [11]. Case series of low-molecular-weight iron dextran therapy suggest effectiveness [12, 13] and a trial of ferumoxytal versus oral iron showed both to be equally beneficial [14].

Intravenous iron is generally safe with the risk of anaphylaxis estimated at 1 in 200 000 [15]. FCM results in hypophosphatemia in approximately 40%–70 % of adults [16], but this is usually asymptomatic unless the patient has iron deficiency anemia or very low serum ferritin concentration, usually in the setting of ongoing gastrointestinal or uterine blood loss, and especially if repeated infusions are administered. In these circumstances, other preparations should be preferentially used to prevent osteomalacia. Hypophosphatemia may occasionally occur with the use of ferric derisomaltose, but at a frequency of less than 10% [17]. FCM is the most expensive preparation and iron dextran the cheapest.

For children and adolescents with RLS, considering iron status is even more important than in adults. Systemic iron stores are lower due to growth and expansion of red cell mass, often in the setting of a diet low in iron and exacerbated by blood loss in women after the onset of menstruation [18]. Prior small studies have shown the benefits of intravenous iron therapy in children with RLS [19, 20] with fewer side effects than with oral iron. In this edition of SLEEP, DelRosso and colleagues expand on their previous work to describe their experiences with ferric carboxymaltose in a unique intravenous iron clinic for children with sleep-related

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movement disorders in an academic hospital [21]. Their analysis of 118 patients, the majority with RLS, yields several important findings. First, it provides evidence that in an appropriate setting, intravenous iron can be safely administered to children. Second, 55% of patients required repeat infusions, more commonly in preschool children, most likely related to baseline low serum ferritin concentration and rapid growth. Third, the investigators measured serum phosphate concentration in 98 patients 8 weeks after infusion and detected no hypophosphatemia. Prior studies have suggested that about a fifth to a quarter of children receiving intravenous FCM have transient hypophosphatemia [22, 23], lower figures than reported in adults. Thus, the data from the current study indicate that any hypophosphatemia, if it were present, has remitted by 8 weeks after infusion is very reassuring.

There are several limitations in the current study. First, the authors do not discuss how they determined the efficacy of intravenous iron in their patients. This can be difficult, especially in younger patients when clinicians must rely on the reports of parents or caregivers. In a previous retrospective study by DelRosso and collaborators, information was obtained from the patients' charts regarding improvement, no change, or worsening of factors such as restless sleep, sleep maintenance, urge to move, and sleep latency [24]. Future studies would be enhanced by the use of prospective standardized global assessment tools such as the Clinical Global Impression of Change and, in older children and adolescents, the International Restless Legs Scale. Second, inclusion criteria included serum ferritin concentration <50 μg/L, thus limiting the study population to patients with suboptimal systemic iron stores. Future investigations of patients with higher ferritin concentrations would provide information regarding the applicability of using intravenous iron for children with RLS without systemic iron deficiency. Third, conclusions about efficacy are always limited in uncontrolled case series. Consideration should be given to a prospective placebo-controlled study of FCM in children with RLS to reduce or eliminate any placebo effect. Ethical concerns about equipoise could perhaps be addressed by providing FCM infusions to the participants receiving a placebo at the end of a 6- to 12-week study.

RLS management remains challenging. Available non-opioid drugs are not always effective and have side effects, especially augmentation with dopamine agonists [10]. While low-dose opioid therapy is often successful and well tolerated [25], many patients and physicians are understandably reluctant to introduce these drugs unless other options have been exhausted. Thus, bringing iron to the brain is an important first-line management tool to be considered for adults and children with troublesome chronic RLS.

Disclosure Statement

Financial disclosure: M.H.S. receives compensation from UpToDate for contributing to the section on Restless Legs Syndrome.

Non-financial disclosure: M.H.S. serves on the Scientific and Medical Advisory Board of the Restless Legs Syndrome Foundation.

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