The Role of Iron in Pediatric Restless Legs Syndrome and Periodic Limb Movements in Sleep

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Abstract

Restless legs syndrome (RLS) is a common and treatable neurologic condition in pediatric patients, with a prevalence as high as 2 to 3%. The diagnosis of RLS is made clinically based on an urge to move the legs accompanied by lower extremity discomfort that occurs during rest usually later in the day and is relieved by movement. Periodic limb movements in sleep (PLMS) can overlap with RLS, although PLMS also exists as a separate entity characterized by stereotyped movements of lower extremities in sleep. Both conditions may be highly debilitating and interfere with daily function notably in the areas of educational attainment and behavioral regulation. Iron deficiency has been implicated in the pathophysiology of both RLS and PLMS. Current evidence suggests that treatment of ferritin levels < 50 μg/L may be beneficial in improving pediatric RLS symptoms and comorbid conditions or daytime dysfunction associated with RLS. Areas for future research include (1) clarifying the ferritin or other iron status measure level which predicts iron treatment will provide symptom improvement in pediatric patients, and (2) randomized clinical trials using iron therapy to determine the degree and duration of treatment.

Keywords
- restless legs syndrome
- periodic limb movements in sleep
- iron deficiency
- children

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), is a treatable neurologic disorder characterized by an urge to move the legs, accompanied by unpleasant sensations in the extremities which usually occurs at rest and later in the day and is relieved by movement.[1–3] In pediatric patients, RLS may be associated with considerable morbidity due to reduced educational attainment, poor mood, behavioral dysregulation, and deficits in executive functioning. Periodic leg movements in sleep (PLMS) may be associated with RLS, but is also a separate entity, characterized by stereotyped leg movements during sleep. Low levels of iron have been linked to both RLS and PLMS.[4–9] In this review, the authors explore the evidence supporting current recommendations on iron supplementation as a treatment for RLS and PLMS in the pediatric population.

Restless Legs Syndrome

Restless legs syndrome affects at least 2% of children and adolescents[1,3,10,11] with up to 5.9% prevalence in clinical sleep populations.[12] The incidence is greater in adults, with up to 5 to 10% prevalence.[13–16] Indeed, ~ 25% of adults with RLS report symptoms of RLS when they were as young as 10 to 20 years old, suggesting that RLS occurring in the pediatric population may become a chronic condition.[10] The diagnosis is made clinically, most often using consensus criteria established by the International Restless Legs Syndrome Study Group (IRLSSG), which were recently updated in 2012. ►**Table 1** shows diagnostic criteria for RLS and special considerations for children and adults. These criteria include (1) the urge to move the lower extremities associated with abnormal and uncomfortable sensations, which is (2) alleviated by movement, (3) exacerbated during periods of rest, and (4) worse during the evening or at night.[2,3] Additionally, these symptoms cannot be accounted for by other primary conditions such as growing pains, positional discomfort, sprains, myalgia, or arthritis.[2,3] Common diagnoses that could be mistaken for RLS are included in ►**Table 2** and should be considered in the differential. The clinical significance on sleep, behavior, and functioning during the day is

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Table 1 Diagnostic criteria for restless legs syndrome (RLS) with considerations for pediatric and adult patients

Patient meets all five criteria:[2,3,57] 1. An urge to move the legs usually accompanied by uncomfortable and unpleasant sensations in the lower extremities 2. The urge to move begins or worsens when sitting or lying down 3. The urge to move is partially or totally relieved by movement 4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day. 5. The symptoms are not accounted for by another primary medical or behavioral condition.	
Important considerations	
Children	Adults
The description of these symptoms should be in the child's own words.[3,57]	Specifiers for clinical course of RLS:[2] – Chronic-persistent RLS[2] – Intermittent RLS[2]
The symptoms have a significant impact on sleep, mood, cognition, and daytime function.[3,57]	Specifier for clinical significance of RLS:[2] The symptoms of RLS cause significant distress or impairment in social, occupational, educational, or other important areas of functioning.

Table 2 Differential diagnosis of Restless legs syndrome (RLS) in pediatric and adult patients

Differential diagnosis of RLS in children[1,3]	Differential diagnosis of RLS in adults[2]
Common	Common
Bruise	Anxiety
Dermatitis	Arthritis
Muscle soreness/myalgia	Habitual foot tapping
Orthopedic problems	Leg cramps
Positional discomfort	Leg edema
Transient nerve compression	Myalgia
	Peripheral neuropathy
	Positional discomfort
	Radiculopathy
	Varicose veins
	Venous stasis
Uncommon	Uncommon
Myopathy	Myelopathy
Radiculopathy	Myopathy
Sickle cell disease	Orthostatic tremor
	Vascular or neurogenic claudication

assessed.[1–3,17] In adults, RLS can be further classified with specifiers for the clinical course and clinical significance.[2] To make the diagnosis in a pediatric patient, children should report these symptoms in their own words.[3] Because children may not be developmentally capable of describing an urge to move the legs, the diagnosis may be more challenging to make in this age group.[2,3] Clinicians should be aware of typical terms children use to describe these uncomfortable sensations.[3,12] Studies suggest the following examples: "creepy," "crawly," "tingling," and "want or need to move."[3,12] These symptoms are often associated with significant impairments in children's quality of life and daily function, typically in the areas of behavioral regulation and educational achievement, through its impact on sleep.[3,11,18] Indeed, patients with RLS have significant comorbidities in the areas of attention deficit hyperactivity disorder (ADHD), mood disorders, migraine headaches, and other sleep disorders.[19–22]

Periodic Limb Movements in Sleep

Periodic leg movements are common in RLS. Periodic leg movements can occur during wakefulness or during sleep, known as periodic limb movements in sleep (PLMS). Restless legs syndrome severity can be associated with the amount of PLMS; notably early-onset RLS is often associated with greater symptom severity and frequency of PLMS.[23] Periodic limb movements in sleep are captured on polysomnography and are characterized by repetitive, stereotyped limb jerks of 8 μV or greater amplitude on electromyography. These limb movements last between 0.5 to 10 seconds in duration and are separated by 5- to 90-second intervals.[12] A diagnosis of periodic limb movement disorder (PLMD) is made when pediatric patients experience five or more PLMS per hour (PLMS index > 5) and when they experience a clinical sleep disturbance. Periodic limb movements in sleep can exist outside of RLS as a distinct entity, though the two entities share significant overlap. Genetic factors may contribute to this overlap, as RLS and PLMS are also both highly heritable, especially in early-onset cases.[24] In one retrospective study of 204 pediatric patients with RLS and PLMD, 52% of patients with RLS had parents with RLS and 53% of patients with PLMD had parents with an RLS diagnosis.[25] Indeed, a gene sequence variant of chromosome 6p is associated with both PLMS and RLS in Icelandic, American, German, and Canadian cohorts.[26,27] It should also be noted that diagnosis of RLS supersedes a diagnosis of PLMD. It is possible to have diagnosis of RLS with PLMS, but not RLS and PLMD.[25]

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Iron Deficiency and the Role of Iron in RLS/PLMS

Iron deficiency with or without anemia has been implicated in the pathophysiology of RLS and PLMS in both pediatric and adult populations. Iron deficiency anemia is a very common nutritional disorder. An estimated 1.6 billion people are anemic (25% of the world's population), and for about half, the anemia is due to iron deficiency.[28] Women who are pregnant and young children are at greatest risk for iron deficiency with or without anemia. About 25% of preschool children have iron deficiency with or without anemia worldwide and children in the United States are also affected. Overall, ~7% of U.S. children under 5 years of age have iron deficiency, as do 14% of infants 1 to 2 years of age, despite programs to combat this problem.[29,30]

Lack of iron affects many bodily processes as iron is a cofactor for enzymes that support cell division, oxygen transport, mitochondrial function, myelination, and neurotransmitter regulation. The demand for iron is particularly great during periods of growth and may also be greater due to blood loss related to trauma or chronic disease states. The demand may not be met by dietary intake due to poor iron absorption by the divalent metal iron transporter (DMT-1) at the gut.[31,32] After uptake into the enterocyte, iron transport into the blood is mediated by transport and oxidase proteins. Circulating iron is then primarily bound to transferrin, the main iron transporter protein in the body. Iron may then be transferred to the liver for storage as ferritin, used for red cell synthesis in the marrow or other cellular purposes.[31]

Standard hematologic evaluation for iron status includes a complete blood cell count (CBC) and iron status measures. Age-appropriate cutoffs for anemia are a hemoglobin level < 110 to118 g/L[33–35] and for iron deficiency, typically ≥ 2 abnormal standard iron measures.[33–35] Standard iron status measures include mean corpuscular volume (MCV; iron deficiency [ID] < 76 fl),[36] red cell distribution width (RDW; ID $> 14.5\%$), serum iron, serum ferritin (ID < 12 μg/L),[37] and percent transferrin saturation (ID $< 20\%$). Using serum transferrin receptor and serum ferritin, total body iron can be calculated as another method of measurement; < 0 mg/kg is an alternate way to define iron deficiency.[38,39] Serum ferritin does reflect total body iron stores, and is the first to fall with iron deficiency with or without anemia; however, as an acute phase reactant, serum ferritin may not be specific in cases with co-occurring inflammation or infection, hyperthyroidism, hepatocellular disease, and malignancies. In addition, the normal range for serum ferritin levels varies with age and is lower for children. In a review of National Health and Nutrition Examination Survey (NHANES) data, the mean serum ferritin level in children and adolescents ranged from 22.6 to 29.4 μg/L.[29]

A relationship between iron and movement disorders is not unexpected given the role of iron as a cofactor for central nervous system dopamine processes.[40–44] Studies have demonstrated reduced brain iron content on autopsy specimens and by imaging in individuals who had RLS and/or PLMD.[7,17] Peripheral nervous system effects have also been proposed.[7,8,45] In addition, serum ferritin and other measures, such as serum iron and CSF ferritin, have been correlated with the severity of RLS symptoms or number of PLMS.[46–50] Similarly, RLS symptoms often improve after iron status improves.[49,51,52]

In adults with established normative ferritin values, RLS treatment with iron supplementation targeting ferritin > 50 μg/L has been shown to be effective for symptom relief. In children, normative ferritin values are age-dependent, with normal values often being < 50 μg/L. The serum ferritin level for response in RLS symptoms is currently unknown in pediatric patients, though some limited evidence suggests that a ferritin level > 50 μg/L may be beneficial for treating RLS in children as well.[9,53,54] In adults, iron supplementation is recommended if serum ferritin is < 75 μg/L.[55]

The recommended treatment of pediatric patients older than 6 years of age with iron deficiency and RLS is 45 to 65 mg of elemental iron once or twice per day.[47] For children younger than 6 years, 3 to 6 mg/kg/d of elemental iron divided into two or three doses is recommended.[47,55–57] Oral iron treatment in adults is typically 65 mg elemental iron 2 to 3 times daily.[55] Intravenous iron therapy is reported in adults, but generally reserved for patients with poor absorption, intolerance to oral iron.[55] Repeat ferritin levels are obtained 2 to 3 months after initiation of treatment, to monitor iron levels and to prevent the rare complication of iron overload.[1,55] Iron is best absorbed on an empty stomach, avoiding calcium-containing products near administration (reduce iron absorption), and in conjunction with vitamin C such as orange juice (improves iron absorption).[1,56] Adverse reactions of iron therapy include constipation, abdominal pain, dental discoloration, nausea, or vomiting. Treatment of constipation may include initiation of laxative such as polyethylene glycol and treatment of abdominal pain may include three times daily dosing, as opposed to twice daily dosing.[56] Contraindications to therapy include hemochromatosis, hemolytic anemia, or hypersensitivity to iron.[55] For pediatric patients whose ferritin levels are > 50 μg/L and achieve symptomatic relief, one could continue the supplement for an additional 3 months, then discontinue.[56] Symptoms should then be monitored for recurrence. The exact duration of treatment is unclear if symptomatic relief is not provided.[56]

In addition to considering treatment with iron supplementation, behavioral interventions for RLS have been shown to be effective in the pediatric and adult population.[1,57] In children, parental supervision is important to implementing these interventions.[1] The pediatric RLS NEWREST chart includes recommendations for individuals with RLS, including optimizing nutrition, modifying the environment for sleep, monitoring symptoms, encouraging regular sleep, physical activity, discontinuing substance use, and taking appropriate supplements (►**Table 3**).[1]

Method

A literature review was conducted on PubMed focused on these conditions in children using combinations of the

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Table 3 The Peds RLS NEWREST Chart: Tips for Better Sleep[1]

Nutritional needs. A healthy, age-appropriate, diet should be adopted. Any foods containing caffeine, such as chocolate, and drinks such as soda, energy drinks, iced tea, and coffee should be restricted, especially in the late afternoon and evening. Current dietary iron intake and the need for iron supplementation should be assessed.
Environment for sleeping. The bedroom should be relaxing, quiet, and only for sleeping. Find another room for studying, loud music, TV, and "timeout."
Watch for and report restlessness, uncomfortable leg sensations, and disturbed sleep, especially when these affect daytime function.
Regular sleep schedule with a routine bedtime and wakeup time even on weekends.
Exercise daily. Physical activity can reduce RLS sensations and increases deep sleep.
Stop substance use that interferes with good sleep such as tobacco, alcohol, and recreational drugs.
Take prescribed medicine and/or approved iron supplements consistently.

Source: Reproduced with permission from Picchietti et al[1]

following search terms: Restless Legs Syndrome, RLS, Willis-Ekbom disease, WED, Periodic Leg Movements in Sleep, PLMS, Periodic Leg Movement Disorder, PLMD, iron deficiency, iron, ferritin, pediatric, children.

Studies Presenting with RLS Symptoms

Most studies regarding the association of RLS and PLMS with iron deficiency start with recruitment of subjects who first present with RLS or PLMS, who are subsequently tested for iron status. Patients may then receive an oral or intravenous iron supplementation. Though the majority of these studies are retrospective chart reviews or case studies without a control arm, patients often show improvement in symptoms of RLS or improvement in the frequency of PLMS with concomitant improvement in iron levels.[4,9,53,54,58]

There are several descriptive pediatric studies establishing a link between low iron levels with RLS. Kotagal et al found in a group of 24 children with RLS, that 83% had ferritin levels < 50 µg/L.[12] Similarly, in a group of 18 patients with RLS, serum ferritin levels were < 50 µg/L in 88%.[59] This finding of low iron status measures has also been associated with PLMS in pediatric patients. In a group of 22 young children, the PLMS index was 49 in children with ferritin < 50 µg/L, compared a with PLMS index of 25 in children with ferritin > 50 µg/L.[53]

One of the first studies to show improvement in RLS symptoms in children treated with oral iron was a case report occurring in 2002. Kryger et al evaluated three adolescents who had a RLS diagnosis and insomnia. They received oral iron therapy (300 mg ferrous sulfate twice or three times daily) for 4 to 5 months, with improvement in PLMS index from a mean of 20.5 to 10.5. Patients also reported improvement in subjective RLS symptoms and sleep latency. Some limitations to this study include the nature of a case series utilizing only three subjects and inclusion of subjects with comorbid conditions such as sleep apnea or narcolepsy.[58]

In one retrospective chart review of 30 Japanese children (aged 2–14 years) diagnosed with RLS, the average ferritin level before therapy was 26.6 µg/L (standard deviation [SD] $= 12.8$). Patients were treated with an average iron dose of 3.2 mg/kg/d with improvements in mean ferritin to 83.5 (SD $= 49.3$). Most parents subjectively reported improvement in RLS symptoms and reported the treatment to be "highly effective" in 17 children, "effective" in 10 children, and "ineffective" in 3 children.[54] Although this study had promising results, limitations included subjective symptom report and lack of a control group.

In a prospective study using the outcome measure of PLMS indices, Simakajornboon et al studied a population of 28 patients with a PLMS index > 5. These patients underwent overnight polysomnographic evaluation. Interestingly, the study authors found a higher PLMS index in patients with lower serum *iron* levels, but not for patients with lower serum *ferritin* levels. Yet, patients with ferritin levels < 50 µg/L received open-label treatment with iron sulfate and 76% responded favorably as measured by a decrease in PLMS index from 27.6 (SD $= 14.9$) to 12.6 (SD $= 5.3$) in these subjects. Additionally, serum ferritin levels improved from 40.8 µg/L (SD $= 27.4$) to 74.1 µg/L (SD $= 13.0$) posttreatment.[48]

Another open-label prospective treatment trial with oral iron supplementation was completed on children with autism spectrum disorder. The mean ferritin level increased from 16 to 21 µg/L after receiving 6 mg elemental iron/kg/d for 8 weeks. Subjects had improvement in restless sleep in response to iron supplementation. Limitations to this study include a small sample size and the lack of a placebo control group.[60]

Iron supplementation has recently been shown to have lasting effects on PLMS even 2 years posttreatment. In a retrospective chart review of 105 children with RLS, PLMD, or RLS + PLMS, patients received iron supplementation with sustained improvements in iron level and PLMS index 2 years posttreatment. Baseline ferritin level was 27.4 µg/L (SD $= 27.4$), with ferritin levels increasing postiron initiation to 45.6 µg/L (SD $= 21.2$) at 3 to 6 months, 52.0 µg/L (SD $= 48.3$) at 1 to 2 years, and 54.7 µg/L (SD $= 40.5$) at > 2 years. The PLMS index decreased significantly following supplementation. Baseline PLMS index was 21 (SD $= 27$) and decreased to 7.5 (SD $= 9.5$) at 3 to 6 months, 6.9 (SD $= 8.9$) at 1 to 2 years, and 10 (SD $= 14.5$) at > 2 years.[9]

Some evidence suggests that treatment of iron deficiency can be effective for improving RLS symptoms even when

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posttreatment ferritin levels are < 50 μg/L in the pediatric population. In one study, intravenous iron sucrose at 3.6 mg/kg was administered to 16 patients with RLS symptoms. The average ferritin increased from 16 (SD = 6.6) to 45 (SD = 22.4), with self-reported improvement in sleep in 63% of patients, though there was no control group.[4]

Iron status and RLS may also have an effect on ADHD symptoms, which is frequently comorbid with RLS. Konofal et al compared ferritin levels in 12 subjects with ADHD + RLS, 10 subjects with ADHD, and 10 healthy controls. Children with ADHD + RLS had a lower average ferritin level of 16 μg/L compared with children with only ADHD who had an average ferritin level of 25 μg/L and healthy controls with an average ferritin level of 46 μg/L. Additionally, children with ADHD + RLS had a trend toward more severe ADHD symptoms compared with those with ADHD only, though this did not reach statistical significance.[20] Similarly, Oner et al evaluated 87 ADHD subjects for RLS and iron deficiency. The prevalence of iron deficiency was 20% in subjects with ADHD and RLS compared with 1.7% in subjects with only ADHD. These studies suggest that iron deficiency may be an important modifying variable in RLS and ADHD.[61]

Indeed, RLS treatment with iron may improve comorbid ADHD symptoms and other aspects of daytime dysfunction that are associated with RLS. Furudate et al completed a prospective, controlled treatment study of 25 Japanese children with RLS, diagnosed by interview and polysomnography. Outcome measures included improvement in RLS symptoms, ADHD symptoms, and quality of life. Sixteen patients with ferritin levels < 40 μg/L were treated with iron supplementation for 3 months and had significant improvements in all of these outcomes compared with a healthy sibling control group. Additionally, 50% of subjects receiving only iron treatment had 50% improvement in RLS symptoms and 25% of subjects reported 100% improvement in RLS symptoms. Those who did not respond to iron treatment alone received additive therapy with either pramipexole, clonazepam, or both, with good response to treatment. Though this study was not randomized and posttreatment ferritin levels were not available, the results are promising and suggest that RLS treatment with iron may also improve comorbid conditions and daytime dysfunction.[62]

Studies Presenting with Iron Deficiency

The aforementioned studies start with a population of patients with RLS and then subsequently measure ferritin levels. However, a ferritin level < 50 μg/L is quite common in the pediatric population and does not necessarily represent an abnormal value depending on the pediatric age.[29] Additionally, iron deficiency in the pediatric population is highly prevalent and as many as 7.1% of 1 to 5 year olds have a diagnosis of iron deficiency.[30] Studies that start with a population of patients with iron deficiency and then measure RLS symptoms may elucidate the threshold ferritin level needed for symptom improvement. Though this literature is limited, information provided by such studies is important.

Peirano et al completed a prospective, longitudinal study, following a group of 32 infants with iron deficiency anemia and 26 healthy controls without iron deficiency anemia. The infants with iron deficiency anemia received 15 mg/d of elemental iron treatment for 1 year starting at the age of 6 months. Both groups were evaluated with a polysomnography at the age of 10 years to identify patients with PLMS. Interestingly, PLMS index was higher (mean [M] = 8.8) in patients who were diagnosed with iron deficiency anemia during infancy, compared with healthy controls (M = 5.0). Additionally, sleep latency was shorter in healthy controls (M = 19 minutes) compared with those with iron deficiency anemia in infancy (M = 37 minutes). This study suggests long-term effects of iron deficiency anemia in infancy, even after treatment for iron deficiency.[63]

Halac et al completed a prospective, cross-sectional, controlled study of 200 children referred to a hospital in Turkey. In this group, 98 children were diagnosed with iron deficiency or iron deficiency anemia with ferritin levels ranging 0.01 to 12 μg/L and 102 children were healthy controls with ferritin levels ranging 12.3 to 91.8 μg/L. The International Restless Legs Syndrome Study Group criteria were used for diagnosis of RLS. The frequency of RLS was higher in the patient group (61%) compared with the control group (37%). Similarly, the frequency of RLS in children whose ferritin levels were < 50 μg/L was 55%, while the frequency of RLS in children whose ferritin levels were > 50 μg/L was 8%. Of note, the incidence of RLS in the group of children whose ferritin levels were > 50 μg/L was still higher than noted in previous studies, most likely because the subjects were a hospitalized sample.[5]

Summary

In summary, RLS and PLMS are commonly overlooked disorders, which may be highly debilitating and interfere with daily function in children.[3] Attention deficit hyperactivity disorder, mood disorders, and other sleep disturbances are frequently comorbid with these conditions.[19–22] Both RLS and PLMS are associated with iron deficiency.[46–50] Most studies show that iron supplementation has been shown to improve symptoms, with goal ferritin levels > 50 μg/L, though no randomized clinical trials have been completed in children.[12,53,59] Consideration with behavioral interventions such as optimizing sleep hygiene, the sleep environment, and implementing mild–moderate exercise routine apart from bedtime are also important for symptomatic relief.[1]

Areas for Future Research

Although adult studies have shown symptom benefit with oral iron therapy in double-blinded, placebo-controlled studies,[64,65] there is no such study in the pediatric population. Given the subjective nature of RLS and the prevalence of lower ferritin at younger ages, it would be particularly helpful to consider pediatric double-blinded, randomized clinical trials of iron supplementation. To guide clinician management, future studies could elucidate the optimal ferritin level (or other measure of iron status) for iron treatment initiation for RLS symptoms and the dose and

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duration of treatment to afford improvement of symptoms for the majority of pediatric patients. In addition, further investigation of the potential role of iron deficiency with or without anemia during early development on incidence of RLS/PLMS later in life would be helpful.[63] Another area for future research includes further investigation on behavioral interventions in improving RLS in children as well as adults. tients. lementr (ASD), Iron Deficiency (ID), Iron Deficiency Anemia (IDA).

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