Iron's role in paediatric restless legs syndrome – a review

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Paediatric restless legs syndrome (RLS) treatment is important because RLS's associated sleep disturbance causes significant developmental-behavioural morbidity and impacts family well-being. RLS is associated with brain iron insufficiency and dopaminergic dysfunction. Diagnosis requires fulfillment of diagnostic criteria, which for children are currently in evolution, and have limitations, especially in preschoolers. The community physician needs to recognize the possibility of RLS to refer to a sleep specialist for diagnostic confirmation and management recommendations, which include oral iron therapy, even though there is currently no definitive research evidence for iron efficacy in most children with RLS. A 3 mg to 6 mg elemental iron/kg/day dose for three months could be tried if the ferritin level is <50 ug/L. Sleep hygiene and behavioural strategies are also recommended. Iron supplementation should be safe in the absence of iron metabolism disorders, provided that transferrin saturation and ferritin levels are monitored pre-and post-treatment.

Key Words: *Child psychology; Iron; Iron-deficiency anemia; Restless legs syndrome; Therapeutics*

Le rôle du fer dans le syndrome des jambes sans repos en pédiatrie : une analyse

Il est important de traiter le syndrome des jambes sans repos en pédiatrie (SJSR) parce que les troubles du sommeil qui s'y associent entraînent une morbidité comportementale et développementale marquée et nuisent au bien-être familial. Le SJSR est lié à une carence en fer dans le cerveau et à une dysfonction dopaminergique. Pour poser le diagnostic, il faut respecter les critères diagnostiques qui, chez les enfants, sont actuellement en évolution et comportent des limites, notamment chez ceux d'âge préscolaire. Le médecin communautaire doit convenir de la possibilité de SJSR afin d'aiguiller l'enfant vers un spécialiste du sommeil qui confirmera le diagnostic et fera des recommandations de prise en charge. Ces recommandations incluent un traitement martial par voie orale, même s'il n'existe pas de recherche irréfutable démontrant l'efficacité du fer chez la plupart des enfants ayant un SJSR. On peut expérimenter une dose de fer élémentaire de 3 mg/kg/jour à 6 mg/kg/jour pendant trois mois si le taux de ferritine est inférieur à 50 ug/L. Des stratégies reliées à l'hygiène du sommeil et au comportement sont également recommandées. Les suppléments de fer ne devraient pas poser de danger en l'absence de troubles du métabolisme du fer, pourvu qu'une surveillance de la saturation en transferrine et du taux de ferritine soit assurée depuis le diagnostic jusqu'après le traitement.

An eight-year-old boy with attention deficit hyperactivity disorder (ADHD) presents with a one-year history of intermittent 'tingling' in his legs, when sitting in school, which is relieved by walking but is now interfering with his ability to fall asleep and stay asleep. His mother's symptoms meet adult criteria for restless legs syndrome (RLS), and his, for 'probable RLS'. He eats little red meat. His ferritin level is 15 µg/L, transferrin saturation 0.13, and his total iron-binding capacity (TIBC) and complete blood count (CBC) are normal. Will iron therapy help his sleep?

Iron deficiency is linked to impaired cognitive development and academic achievement, febrile seizures, breath-holding spells, stroke and RLS. RLS is a neurological disorder characterized by an urge to move the legs (1) to relieve sensory discomfort, which causes delayed sleep onset (>30 min) and night wakings, some of which are due to periodic limb movements during sleep (PLMS) (2,3). PLMS, often rhythmic extension of the big toe and ankle dorsiflexion, occur at intervals of 20 s to 40 s and may be associated with arousal. Not all children with RLS have PLMS. RLS is diagnosed by history and PLMS by overnight sleep study (polysomnography [PSG]). One-third of adults with RLS are affected in childhood (4).

RLS is a genetic disorder involving several chromosomes, but is also associated with environmental factors. A variant of the *BTBD9* gene on chromosome 6 in adults increases the risk of PLMS and low serum ferritin (4). Risk factors for RLS include family history of RLS (positive in 53% to 77%, mother:father 3:1) (5,6), poor nutritional iron intake (below normal ferritin levels in 33% of children measured with RLS [7]), chronic renal disease, type 1 diabetes mellitus, juvenile rheumatoid arthritis, pregnancy and ADHD (8), exacerbating ADHD and its comorbidity effects. Differential diagnosis includes muscle overuse, pruritius and conditions that may require additional work-up such as those that could present with leg symptoms (eg, Osgood-Schlatter disease, chondromalacia patellae, peripheral neuropathy, leukemia, osteogenic sarcoma) and conditions that could present with restless sleep (eg, obstructive sleep apnea, seizures) (9). RLS may lead to significant morbidity because associated sleep disturbance causes deficits in attention, working memory, higher order cognitive functions, academic achievement, mood, behaviour, quality of life and family well-being (2,3,10).

The prevalence rate remains uncertain despite the recent growth of paediatric RLS literature that recognizes it as common (estimated prevalence of 1.3% to 2% of school-age children and adolescents), underdiagnosed and undertreated (2,11). The reported prevalence of RLS may have been overestimated due to selection bias or lack of in-person validation when surveys or questionnaires were used. RLS constitutes a minority of sleep-specialist diagnoses in children (7). The paucity of large-scale treatment studies may imply a difficulty in recruiting sufficient paediatric sample sizes that meet diagnostic criteria. If the prevalence is truly

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TABLE 1
Diagnostic criteria for definite restless legs syndrome (RLS)

Criteria for the diagnosis of definite RLS in children
1) The child meets all four essential adult criteria for RLS (below) AND
2) The child relates a description in his or her own words that is consistent with leg discomfort. (The child may use terms such as 'owwies', tickle, spiders, 'boo-boos', want to run and a lot of energy in my legs to describe symptoms. Age-appropriate descriptors are encouraged).
OR
1) The child meets all four essential adult criteria for RLS AND
2) Two of the three following supportive criteria are present
a) Sleep disturbance for age
b) A biological parent or sibling has definite RLS
c) The child has a polysomnographically documented periodic limb movement index of 5 or more per hour of sleep
Essential adult criteria
1) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs).
2) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3) The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

Table adapted from reference 3

2%, possible causes of under-recognition include the mild and intermittent nature of the symptoms at younger ages (4) and limited knowledge translation outside subspecialty journals. The fact that the clinical presentation in children remains largely unknown (3) may contribute to prevalence uncertainty because current diagnostic criteria may not capture all children affected. Nevertheless, despite the evolving criteria and the presence of evidence gaps for iron treatment, use of current diagnostic criteria and an iron treatment trial, when appropriate, are standard practice recommendations in the paediatric sleep literature (9).

The present article offers a review of the current literature on iron's role in paediatric RLS treatment and practical clinical pearls for physicians following these children. Clinical practice concepts of screening for iron deficiency in the absence of anemia, or using RLS iron therapy in the absence of systemic iron deficiency, are traditionally less familiar to clinicians, who may hesitate to follow treatment recommendations for fear of iron overload. The community physician needs to recognize the possibility of RLS, to refer to a sleep specialist for diagnostic confirmation and management recommendations. Paediatric sleep specialists include board-certified sleep medicine specialists, some paediatricians, neurologists and psychiatrists with sleep expertise. Because sleep specialists are scarce, community physicians may need to provide the treatment recommended by the specialist. In regions with limited access to a specialist, diagnosis and treatment initiative may occur in primary care; severe or complex cases would still require guidance by a sleep specialist, even if by long-distance case-conferencing.

METHODS

The present narrative review was based on a search of PubMed and HKN/OvidSP MEDLINE databases from 1950 to the third week of March 2011 by combining the key words "restless legs syndrome, iron, children, paediatric and treatment", and related citation searching. Of the 240 English articles and abstracts found, 194 were relevant to the present review. All paediatric treatment studies were included, as well as articles written by experts in the field. Components were extracted based on clinical relevance to each section.

IRON'S ROLE IN RLS PATHOPHYSIOLOGY

Iron deficiency has been well documented from brain autopsy, magnetic resonance imaging and cerebrospinal fluid studies of adults with RLS (12,13). Evidence suggests that RLS could result from brain iron insufficiency through several mechanisms, such as systemic iron deficiency, diurnal variation in iron availability or metabolic insufficiency in the substantia nigra, even when there is adequate peripheral iron. Hepcidin levels may also play a role (12). RLS can occur despite systemic iron overload from hemochromatosis. Evidence supports the hypothesis that RLS is caused by dopaminergic dysfunction resulting from brain iron insufficiency (13); dopaminergic agents, the first-line adult therapy, lead to augmentation (ie, symptom worsening) with lower ferritin levels.

RLS DIAGNOSIS

Diagnostic criteria are based on consensus opinion as a first step toward a validated diagnostic tool (3). To have 'definite RLS 1' (3) (Table 1), children two to 12 years of age must describe their sensory symptoms and the adult essential diagnostic criteria (URGE) (14) must be met: urge to move the legs (or arms or other body parts); rest induced; gets temporarily better with activity; and evening or night accentuation (may only occur in the evening or night) (3). Uninfluenced history from children can be obtained through criterion-specific prompts (eg, 'Do your legs bother you?') and open-ended questions (eg, 'Tell me more') (1). The diagnosis is difficult to determine in active children younger than six years of age (1), who may not describe symptoms because they lack the vocabulary or are unaware of such experiences as being abnormal. Therefore, RLS history in a biological parent or sibling is important for 'definite RLS 2'. Research criteria ('probable RLS' and 'possible RLS' for zero to 18 years of age) include a potentially broader spectrum of paediatric RLS (Table 2) (3).

Diagnostic criteria might only be met in some patients later in childhood or even mid-adulthood, when severity increases or symptoms become nightly (4,15). Children as young as infants and preschoolers may present clinically with sleep disturbance before the onset of any RLS feelings, months or years later (15). Meanwhile, would iron treatment have resolved symptoms for some of them? In preschoolers, behavioural sleep problems are more common, but RLS may be queried due to insomnia with 'restless sleep' in the absence of snoring, associated with 'borderline' iron deficiency. Other descriptors may be given such as bedtime behaviours of moving legs or leaving the bed, and during sleep, leg kicks, frequent position changes or kicking covers off. Children with RLS may present with comorbid or falsely assigned behavioural, psychiatric or medical labels from leg symptoms and sleep disruption (eg, oppositional defiant disorder, hyperactivity, anxiety, learning disorders, poor attention, parasomnias, growing pains, fibromyalgia and chronic fatigue syndrome).

IRON'S ROLE IN ADULT RLS TREATMENT

To date, guidelines for paediatric RLS iron treatment have been based on limited adult data and clinical experience, which suggest that iron treatment may improve RLS when baseline serum ferritin is <100 µg/L, especially at <45 µg/L to 50 µg/L, levels associated with greater disease severity (16,17). These data led to the current

paediatric recommendations of increasing ferritin to 50 µg/L (9). Newer data might extend the ferritin level, under which adult iron therapy could be considered, to 75 µg/L (18). Recent, small, randomized double-blind placebo-controlled trials (RCTs) involving adults showed improved RLS from oral iron (18), but mixed results from intravenous iron, keeping in question the efficacy of iron treatment for all people with RLS.

IRON'S ROLE IN PAEDIATRIC RLS TREATMENT

Whether increasing peripheral iron stores increases brain iron stores has not yet been definitively determined. The efficacy and safety of oral iron treatment for RLS need to be established by well-designed placebo-controlled trials. Only a few, small, paediatric studies (Table 3) have examined the effectiveness of oral iron supplementation for treatment of RLS (19,20,21,22), PLMS (23,24), or 'restless sleep' (ie, excessive motility) (25,26). Treatment studies include anecdotal case reports (19,20,25,22), open-label trials (23,26), a prospective long-term follow-up study (24) and a double-blind placebo-controlled trial (25). Result validity is limited by lack of RCTs, small sample sizes, and variable diagnostic criteria and treatment methodology.

The only placebo-controlled trial involving children with RLS was an RCT for ADHD (21); 14 of 19 children also had RLS, for which response to treatment was a secondary analysis. An apparent response was reported for leg sensations (12 of 14); sleep impact was not reported. RLS diagnostic criteria were not defined, although presumably were consensus criteria (3). There were only two children in the placebo group, and an excess of 'possible RLS' subjects (one in placebo, 10 in treatment). RLS case studies are subject to publication bias in favour of positive effect: insomnia resolved in adolescents (four to six months treatment) (19), and in some two- to six-year-olds (five to 12 months treatment) (22). In a six-year-old, insomnia responded initially (three months), but relapsed at a ferritin level of 73 µg/L, resolving completely once ropinirole was administered (20).

In the most objective study (23), PSG-diagnosed PLMS and RLS clinical symptoms improved in 19 of 25 children (one to 13 years of age) when ferritin increased (41 µg/L to 74 µg/L), noted to support 50 µg/L as a critical value required to improve symptoms. Clinical improvement was not defined, although the main symptoms were sleep-onset or maintenance insomnia and restless sleep. Eleven children followed for one to two years all retained decreased PLMS and remained asymptomatic (24). Another open-label study showed significant improvement in 'restless sleep' (no RLS criteria) for seven of 24 children with autism (26). Diagnostic criteria were also not reported in a case study of a preschooler whose insomnia and restless sleep improved (25).

Preliminary results suggest that iron might help sleep in some children with RLS. The serum ferritin level at which symptom response could occur in children is currently unknown. Significant symptom improvement (23,21) suggests treatment response despite the absence of baseline systemic iron deficiency (ferritin levels <10 µg/L) or depleted iron stores (ferritin levels <20 µg/L) (27). Unfavourable responses raise the question of whether differences in iron treatment regimen (eg, higher dose, longer duration) could have increased brain iron levels sufficiently to impact symptoms.

Other paediatric RLS treatments

Reported paediatric studies have not examined comprehensive treatment plans. Sleep hygiene and behavioural strategies are outlined in Table 4 and can be found through <www.rls.org>. Getting more sleep decreases symptoms (1), and keeping mentally occupied diverts attention from symptoms. For moderate to severe cases, medication can be considered by sleep specialists (1), but few children require it. Dopaminergic agents cause significant side effects, but have anecdotally improved paediatric RLS.

TABLE 2
Diagnostic criteria for probable and possible restless legs syndrome (RLS) in children

Criteria for the diagnosis of probable RLS
1) The child meets all essential adult criteria for RLS, except criterion 4 (ie, the urge to move or sensations are worse in the evening or at night than during the day) AND
2) The child has a biologic parent or sibling with definite RLS
OR
1) The child is observed to have behavioural manifestations of lower extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs. The discomfort has characteristics of adult criteria 2, 3 and 4 (ie, is worse during rest and inactivity, relieved by movement, and worse during the evening and at night) AND
2) The child has a biological parent or sibling with definite RLS*
Criteria for the diagnosis of possible RLS
1) The child has periodic limb movement disorder (PLMD)
AND
2) The child has a biological parent or sibling with definite RLS, but the child does not meet definite or probable childhood RLS definitions
Criteria for the diagnosis of PLMD in children
1) Polysomnography shows a periodic limb movement index of 5 or more per hour of sleep. The leg movements are 0.5 s to 5 s in duration, occur at intervals of 5 s to 90 s, occur in groups of 4 or more, and have an amplitude of 25% or more of toe dorsiflexion during calibration AND
2) Clinical sleep disturbance for age must be evident as manifested by sleep onset problems, sleep maintenance problems or excessive sleepiness AND
3) The leg movements cannot be accounted for by sleep disordered breathing (ie, the movements are independent of any abnormal respiratory events) or medication effect (eg anti-depressant medication)

*Table adapted from reference 3. *This last probable category is intended for young children or cognitively impaired children, who do not have sufficient language skills to describe the sensory component of RLS*

Screening for paediatric iron deficiency

Screening for systemic iron deficiency includes testing ferritin levels, iron levels, transferrin saturation, TIBC and CBC. Morning fasting samples reveal peak iron and ferritin levels, without effects of recent food consumption. Ferritin level is the best indicator of early iron deficiency, but can be a challenging marker to interpret (27). Cut-off values differ across centres and literature sources, and as an acute-phase reactant, false elevations can occur from infection or inflammation. When ferritin is falsely elevated, concentrations <50 µg/L could indicate iron deficiency and multiple markers are needed (eg, low iron level and transferrin saturation, elevated TIBC) (27). Most children with iron deficiency do not have anemia. Etiology should be pursued, such as dietary iron insufficiency (most common) or celiac disease (associated with adult RLS).

Providing iron treatment for paediatric RLS

For iron deficiency, even without anemia, treatment is straightforward (6 mg elemental iron/kg/day, three months after normalized hemoglobin levels [27]), regardless of RLS presence. For RLS without systemic iron deficiency, the appropriate dose is currently unknown. One might try the dose and duration reported to benefit PLMS (3 mg elemental iron/kg/day for three months) (23) and then recheck ferritin (1); some specialists might prescribe 5 mg to 6 mg elemental iron/kg/day. To enhance absorption, iron should ideally be taken in the morning on an empty stomach with a

TABLE 3
Studies describing oral iron treatment in paediatric restless legs syndrome (RLS)

Author (reference), year	Type of study	Sample size, n	Mean age, years	Diagnosis	Criteria for treatment	Iron dose	Treatment duration, months	Outcome measures	Presence of iron deficiency at baseline	Mean serum ferritin µg/L	
										Baseline	Follow-up
Kryger et al (19), 2002	Case studies	3	15.7	RLS	RLS/PLMS (PSG) and iron deficiency	300 mg ferrous sulfate bid, 300 mg ferrous sulfate tid	4–6	Sleep onset latency, sleep efficiency, PLMS (PSG)	Yes	17	28
Simakajornboon et al (23), 2003	Open-label treatment trial	25	7.5	PLMS	PLMS (PSG)	3 mg elemental iron/kg/day	3	PLMI (PSG)	No	41	74
Konofal et al (20), 2005	Case study	1	6	RLS and ADHD	RLS criteria and iron deficiency	80 mg ferrous sulfate bid	3	Leg sensations, night waking, ADHD	Yes	10	73
Konofal et al (25), 2005	Case study	1	3	Restless sleep and ADHD	Iron deficiency	80 mg ferrous sulfate daily	8	Sleep onset latency, excessive mobility in sleep, ADHD	Yes	13	102
Simakajornboon et al (24), 2006	Prospective follow-up study	11	7.1	PLMS	PLMD (PSG)	Multivitamin with iron	12–24	PLMI (PSG)	No	63	80
Dosman et al (26), 2007	Open-label treatment trial	32	6.5	Restless sleep and ASD	Restless sleep	6 mg elemental iron/kg/day	2	Restless sleep	Yes	16	29
Konofal et al (21), 2008	DB, RCT for ADHD	14 (19 ADHD)	6	RLS and ADHD	RLS	80 mg ferrous sulfate daily	3	RLS diagnostic criteria	No	29	56
Mohri et al (22), 2008	Case studies	5	4.4	RLS	Delayed sleep onset and low ferritin	Not reported	5–37	Sleep onset latency	Yes	18	55

ADHD Attention-deficit hyperactivity disorder; ASD Autism spectrum disorder; bid Twice daily; DB Double-blind; PLMD Periodic limb movement disorder, PLMI Periodic limb movement index; PLMS Periodic limb movements during sleep; PSG Polysomnography; RCT Randomized control trial; RLS Restless legs syndrome; tid Three times daily

TABLE 4
Nonpharmacological paediatric restless legs syndrome (RLS) treatment

Sleep hygiene
Consistent and age-appropriate bedtime routine
Consistent and age-appropriate sleep schedule (weekdays and weekends)
Sufficient duration of nighttime sleep
Caffeine elimination (chocolate, carbonated beverages)
Restriction of other known RLS causes/exacerbators: selective serotonin reuptake inhibitors, selective norepinephrine-serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, antihistamines, cold/sinus preparations, antiemetics, nicotine, alcohol
Behavioural strategies
Progressive muscle relaxation, card games
Remaining out of the bed until ready to fall asleep
Regular exercise several hours before bedtime (to increase sleep)
Walking, stretching
Massage
Hot or cold packs to help pain associated with RLS

source of vitamin C such as orange juice. Food (eg, milk, cereals, fibre, eggs) may decrease iron absorption for 2 h. Gastrointestinal discomfort may result when the stomach is empty, and might be alleviated by three times daily dosing, administration with food or dosage reduction. It is not known when to discontinue treatment if there is no response, nor how long to treat if there is symptom response. In the case of apparent treatment success, one might try discontinuing iron after three months (1) while monitoring for relapse. Children need monitoring over time for symptom recurrence.

Parents must be cautioned to keep the iron out of children's reach, because iron toxicity or death can occur from an overdose. Contraindications include hypersensitivity to any component of the preparation, hemolytic anemia and hemochromatosis. Side effects, uncommon at lower doses, include gastrointestinal pain, nausea, vomiting, constipation, dark stools/urine and teeth staining. Teeth staining can be prevented by drinking through a straw and following with water or juice, mouth rinsing or brushing teeth, and can be removed by brushing teeth with baking soda or hydrogen peroxide (3%). Darkening of gum tissue will disappear gradually after discontinuation.

Monitoring for iron overload

When prescribing iron for paediatric RLS, its safety in the absence of systemic iron deficiency necessitates caution. Hereditary hemochromatosis is a disorder of iron metabolism in which excessive intestinal iron absorption leads to damaging iron deposition in multiple organs. Other genetic disorders of iron homeostasis, although rare, exist. Iron intake should not usually constitute a risk for iron overload in otherwise healthy people who are iron-replete, because at higher ferritin concentrations, iron absorption usually decreases, preventing accumulation in the body above upper physiological limits (28). Screening for iron overload includes a personal and family history of hemochromatosis or unexplained liver disease, and measuring transferrin saturation and ferritin levels at baseline and at least twice yearly while on iron. Transferrin saturation >50% and/or ferritin levels >90th percentile are highly indicative of hemochromatosis in children (29). The upper ferritin cut-off quoted by the Glenrose Rehabilitation Hospital (Edmonton, Alberta) is: six months to 14 years of age:

>140 µg/L; ≥15 years of age: male >250 µg/L, female >120 µg/L (30).

CONCLUSION

Physicians need to be aware of RLS because it may be common, and when untreated, can cause significant functional impairment. Community physicians are best placed to recognize the possibility of RLS and may be required to treat it, usually under sleep specialist guidance. RLS is a genetic disorder associated with central nervous system iron deficiency that is believed to influence symptoms through dopaminergic dysfunction. Currently, there is no definitive research evidence for iron being an effective therapy for most children with RLS. The role iron plays in treatment, indications for its initiation and treatment response rate remain questions among experts in the field. There is also a lack of paediatric evidence basis for iron dose, treatment duration and ferritin level for which to aim. Nevertheless, current paediatric standard RLS treatment recommendations suggest that a trial is worthwhile when ferritin is <50 µg/L, and paediatric reports exist, albeit limited, of RLS improvement with iron therapy. Iron supplementation should usually be safe in the absence of hemochromatosis or other rare disorders of iron metabolism, provided that bloodwork is performed before iron treatment prescription and in follow-up, to monitor for iron overload.

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