

## Case Report

# Restless Leg Syndrome in a Child and an Adolescent with Excellent Responses to Iron Replacement Therapy

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### Abstract

We report symptomatic Restless Leg Syndrome (RLS) in an adolescent with normal intelligence, and a young autistic child who suffered from stroke. Both were found to have low serum ferritin levels. In both cases, iron replacement therapy resulted in complete remission of symptoms. The findings substantiate the hypothesis that brain iron deficiency is implicated in the pathophysiology of RLS. Ferritin level below 112 pmol/L (50 ng/ml) serves as a useful threshold to aid diagnosis and treatment in symptomatic young children who cannot tell their discomfort.

### Key words

Iron deficiency; Iron supplementation; Restless leg syndrome; Serum ferritin

### Case One

An 18-year-old girl presented with lower back injury during volleyball practice. She complained of low back pain, lower limb weakness and numbness. X-ray and Magnetic Resonance Image (MRI) of lumbosacral spine were unremarkable. After a course of physiotherapy, she still complained of persistent lower limb numbness despite improvement in weakness and pain. She described the feeling as "a sense of insufficient blood flow" to lower limbs and therefore an urge to move in order to relieve such discomfort. The discomfort was more obvious during nighttime that made her difficult to initiate sleep. Examination showed decrease in touch sensation over right lower limb below knee level, but no definite gloves and

stockings distribution of numbness. No focal neurological signs were elicited. Complete blood count, liver, renal and thyroid function, muscle enzymes (CK and LDH), fasting glucose, vitamin B12 and folate level were normal. Nerve conduction studies (NCV), visual evoked potentials (VEP) and somatosensory evoked potentials (SSEP) did not reveal any evidence of neuropathy. However, she was found to have low serum ferritin level 18 pmol/L (reference 24-675 pmol/L) and iron saturation 8% (reference 15-50%); notably serum iron, total iron binding capacity (TIBC), haemoglobin level and mean corpuscular volume (MCV) were normal. Ferrous sulphate 300 mg twice daily (equivalent to elemental iron 195 mg daily, or 4 mg/kg/day) was given. Ferritin level raised to 51 pmol/L 9 weeks after supplementation at which time she has partial improvement in symptoms, while she declined further blood taking thereafter. Total 3 months of iron supplementation was given. Sustained remission with improved sleep six months after iron therapy was taken off was noted in subsequent follow-up.

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### Case Two

A 3-year-old right hemiplegic autistic boy with idiopathic acute ischemic stroke was admitted for neuro-rehabilitation. Mother reported and video-recorded marked

irritability, repetitive non-stereotyped left lower limb movement at nighttime which disturbed sleep. The child remained fully conscious but was difficult to be consoled. Family history was negative for RLS. Investigations revealed low serum ferritin 48 pmol/L (reference 53-739 pmol/L); serum iron, TIBC, haemoglobin level and MCV were normal. He was empirically started on elemental iron 90 mg per day (6.2 mg/kg/day). Two months later the symptoms persisted and rechecked serum ferritin varied from 42 to 90 pmol/L. Iron supplement was increased to 120 mg per day (8.3 mg/kg/day). Serum ferritin level subsequently raised to 132 pmol/L at four months after treatment, associated with total resolution of symptoms. He was given six months of iron supplement, and mother reported sustained remission of leg movement with improved sleep five months after cessation of treatment.

## Discussion

RLS is a common, complex while treatable neurological condition affecting the central nervous system sensorimotor network. Paediatric population-based studies reveal a prevalence ranging from 2-6%, with 25% children and 50% adolescents experiencing moderate to severe

symptoms.<sup>1</sup> Intriguingly, the condition is not commonly reported in local literature. Zhang et al conducted a local population-based family study using a single question to screen for RLS symptoms in 1549 adolescents, revealing a prevalence of 2.8%.<sup>2</sup> Prevalence in children was not studied. A thorough search through the Hospital Authority Clinical Data Analysis and Reporting System (CDARS) from 1st January 2014 to 31st December 2018 retrieved two in-patients with the diagnosis of RLS among 431,322 Paediatric admissions, yielding an estimated incidence of 4.6 per 100,000 admissions. While the exceptionally low incidence is likely due to low hospitalisation rate for RLS, this also reflects under-diagnosis of this treatable condition, particularly in young children who cannot tell their symptoms.

Table 1 summarises the National Institute of Health (NIH) diagnostic criteria for definite RLS in children and adolescents.<sup>3</sup> As illustrated in case one, in most adult and adolescent cases aged 13-18, the diagnosis of RLS is entirely based on clinical history which can be summarised as the acronym "URGE":

- Urge to move legs, usually associated with unpleasant sensation
- Rest induces symptoms
- Getting active brings relief
- Evening and night make symptoms worse

**Table 1** NIH workshop diagnostic criteria for RLS in children and adolescents

Diagnostic criteria for definite RLS in children 2-12 years old:

*"Definite 1" RLS*

A. All four adult essential criteria are met:

1. An urge to move the legs;
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 is worse in the evening or night than during the day or only occurs in the evening or night; and

B. The child uses his/her own words to describe leg discomfort.

**or**

*"Definite 2" RLS*

A. All four adult essential criteria are met, and

B. 2-3 supportive criteria are met:

1. Sleep disturbance inappropriate for age
2. Biological parent or sibling has definite RLS
3. The child has a sleep study documenting a periodic limb movement index  $\geq 5$ h of sleep

Diagnostic criteria for definite RLS in adolescents 13-18 years old:

All four adult essential criteria are met.

For all ages: The leg sensations are not solely accounted for as symptoms of another medical or a behavioural disorder

Definitive diagnosis is more difficult in children aged 2-12 years, who often have difficulty to describe the leg discomfort in his/her own words. Diagnosis in the latter requires supportive criteria including first degree family history, polysomnographic evidence of periodic limb movement or significant sleep disturbance (Table 1). As illustrated in case 2 who had limited speech and negative family history, definitive diagnosis is challenging for the family paediatrician who does not readily have access to polysomnography. Moreover, mimics such as orthopaedic problems, myalgia, dermatitis, polyneuropathy, cramps or arthritis will need to be excluded.<sup>3</sup> RLS may also be overlooked in children who present as impaired cognition and daytime functioning secondary to sleep disturbance. Co-morbid conditions such as attention deficit/hyperactive disorder (ADHD) and mood disorders may also be the chief complaints shrouding underlying RLS in young kids.<sup>4</sup>

Brain iron deficiency has been implicated in the pathophysiology of RLS. Paediatric studies identified low ferritin levels below 112 pmol/L in over 80% of RLS cases.<sup>5</sup> Iron is a co-factor for tyrosine hydroxylase, an important enzyme in the synthesis of dopamine. Iron deficiency below 112 pmol/L is hypothesised to disrupt dopamine production in norepinephrine and serotonin neurotransmitter systems.<sup>4</sup> Physicians should be aware this cut-off level is higher than the lower-limit-of-normal for diagnosis of iron deficiency anaemia, as hemoglobin synthesis is only affected with ferritin level below 22.5-27.0 pmol/L.<sup>6</sup> In symptomatic young children with probable RLS (i.e. first degree family history, together with urge to move legs, rest induces symptoms, getting active brings relief, but symptoms may not be worse toward evenings), the finding of low ferritin level below 112 pmol/L is a useful guide to initiate iron replacement. A favorable therapeutic response, in retrospect, may help confirm the diagnosis in young children. Sleep study may be reserved for those probable RLS with normal ferritin levels, or non-responders to iron replacement therapy.<sup>1</sup>

Dye et al evaluated 105 children with RLS and serum ferritin below 112 pmol/L.<sup>7</sup> Clinical improvement of periodic limb movement coincided with serum ferritin increases. The latest clinical practice guidelines by the International Restless Legs Syndrome Study Group (IRLSSG) in 2017 also supports setting a therapeutic target for serum ferritin  $\geq 112$  pmol/L for oral iron in RLS. The usual recommended dose is 3-6 mg/kg/day of elemental iron for three months, with repeat serum ferritin levels to assess response and avoid iron overload.<sup>7</sup> As illustrated in

case 2, refractory symptoms with suboptimal ferritin level after initial iron replacement may warrant augmentation of supplement to attain ultimate therapeutic threshold. If ferritin levels are very low or levels fail to improve after treatment with iron, further evaluation is required to exclude occult blood loss and malabsorption.<sup>4,7</sup> Intravenous iron therapy is effective in refractory adult RLS cases with severe iron deficiency or malabsorption. The IRLSSG recommended that intravenous iron is used if following occur: a prior iron treatment of at least 3 months has not produced an adequate benefit or was discontinued because of adverse effects and there has been no appreciable rise in serum ferritin levels with 3 months of oral iron treatment.<sup>8</sup> Non-pharmacological treatment includes maintaining good sleep hygiene, avoid medications, nicotine and caffeine that may aggravate RLS symptoms. Pharmacological treatment is used in cases with ongoing significant symptoms despite iron supplementation. Dopaminergic agents including ropinirole and pramipexole are considered first-line agents in adult RLS. Clonidine and gabapentin have also been shown to improve symptoms in children with prominent sleep disturbance.<sup>4,7</sup>

## Conclusion

RLS is a complex but treatable condition; yet it is likely to be under-diagnosed in local paediatric population. Careful history taking, physical examination and relevant investigations are mandatory to detect the condition and look for comorbid conditions. Ferritin level below 112 pmol/L is a useful diagnostic as well as therapeutic threshold to guide initiation of iron replacement in symptomatic children.

## Declaration of Interest

All authors do not have any financial and personal relationships with other people or organisations that could inappropriately influence their work.

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