

# Treatment of restless legs syndrome with iron infusion therapy

This 52-year-old woman's case reaffirms the importance of a careful history and appropriate diagnostic studies in evaluating a patient with symptoms of RLS.

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## **CASE**

A 52-year-old female presented to the clinic with symptoms of daytime somnolence and nocturnal leg discomfort. She described the leg discomfort as an “urge to move” and “tingly.” The sensation disappeared with walking or activity. The patient also reported that she had leg symptoms in the daytime. The results of a physical examination, including neurologic and musculoskeletal assessments, were unremarkable. Results were normal on the CBC, the basic metabolic panel, and the test for thyroid-stimulating hormone.

On nocturnal polysomnography, decreased sleep efficiency (67%) was noted as calculated by the ratio of time spent asleep to time spent in bed. An arousal awakening index of 17.3 per hour suggested significant sleep fragmentation. The patient's sleep architecture demonstrated a predominance of stage II sleep, comprising 58.3% of the sleep; and deep delta wave sleep comprising stages III and IV was decreased to 7.9%. Sleep latency was 27 minutes. Rapid eye movement (REM) latency was 219.5 minutes, which is significantly prolonged. The patient had an increased apnea/hypopnea index of 8.5 per hour (normal, <5/hour). There were significant periodic limb movements present, with 355 total count noted during the study and an index of 70.1 per hour. Seven out of the 355 were associated with arousals. The patient was titrated on 8 cm of nasal continuous positive airway pressure (CPAP) with a C-flex of 3 for treatment of apnea/hypopneas.

At the 1-month follow-up visit, the patient reported that her daytime somnolence had diminished and she had increased energy. She was using the CPAP device and tolerating it well. Eighteen months later, however, she returned to the clinic reporting a nocturnal “urge to move” and restless sensations in her legs that were not relieved with the use of CPAP. Eventually, the leg symptoms progressed to the level where the patient took several hours to fall asleep. She stopped using the CPAP because she needed to get out of bed often to walk to relieve

her symptoms. The daytime somnolence returned. The patient was then started on pramipexole, 0.125 mg orally at bedtime titrated up to 0.5 mg. The medication and the CPAP produced only partial relief, and the patient continued to have delayed sleep onset due to the restless legs syndrome (RLS).

A physician who specializes in sleep disorders was consulted and recommended obtaining an iron and ferritin level to determine if iron deficiency was present. The patient's iron level was 16  $\mu\text{g/dL}$  (normal value 26-170  $\mu\text{g/dL}$ ), and her ferritin was 6 ng/mL (normal value, 10-200 ng/mL). The specialist recommends treating patients with a ferritin level less than 50 ng/mL with iron infusion therapy.

The patient was started on iron sucrose infusion therapy (Venofer). She received three treatments at 2-week intervals for 6 weeks. The first treatment was 500 mg IV infused over



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2 hours. The patient experienced burning and paresthesias of the feet following infusion, resulting in the dose being decreased to 250 mg IV for the 2 remaining treatments. She received a total of 1,000 mg of Venofer and was weaned off the pramipexole between the first and second doses of Venofer.

Two weeks after the last Venofer infusion, the patient reported complete resolution of the symptoms of restless legs. She had a sleep latency of only 5 to 10 minutes and now was able to sleep through the night using her CPAP. On follow-up testing, her iron level was 104 µg/dL and the ferritin level was 176 ng/mL.

### DISCUSSION

Although the pathophysiology of RLS is unknown, CNS dysregulation,<sup>1</sup> neurotransmitter systems (dopaminergic), and abnormal iron metabolism<sup>2</sup> have all been considered to play a role. RLS may be associated with decreased dopaminergic neurotransmission; RLS symptoms have been observed to increase at night, when dopamine levels fall.<sup>3</sup> Allen pointed out that “RLS improved with use of dopaminergic medications and is exacerbated with use of dopamine blockers.”<sup>2</sup>

Earley and Allen have looked at the pathophysiology of RLS in relation to CNS iron homeostatic dysregulation using MRI studies that showed reduced iron stores in the striatum and red nucleus.<sup>2,4</sup> They also found reduced iron echogenicity in the substantial nigra on CNS ultrasound in patients with RLS.<sup>2,4</sup>

Primary RLS is considered an autosomal-dominant disorder, and clinicians should ask affected patients about a family history of the condition. A significant number (up to 50%) report that other family members describe symptoms of RLS.<sup>5</sup> People who develop RLS at a young age (less than 45 years) are likely to have a genetic form.<sup>3</sup> As was true in this case, the primary etiology of RLS may include iron deficiency in as high as 25% to 30% of patients.<sup>3</sup>

Secondary RLS can be associated with a variety of conditions relating to iron status, such as iron deficiency, pregnancy, renal failure, and repetitive blood donation. Disorders such as neuropathy, radiculopathy, myelopathy, and rheumatologic conditions may result in RLS, and patients with related symptoms should be screened for these disorders. RLS symptoms may also be precipitated by medications (eg, selec-

tive serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]), caffeine, alcohol, and sleep deprivation. Patient education and behavioral modification are key components of treatment.

**Clinical features** of RLS are an overwhelming or uncontrollable urge to move, onset or exacerbation of symptoms at rest, symptom relief with movement, and onset or worsening of symptoms at night. “The core symptom of RLS is an uncontrollable urge to move the legs.”<sup>3</sup> Patients cannot keep their legs still. Some characterize the sensations as a “creepy-crawly feeling,” “electrical currents,” “worms or bugs under the skin,” or a throbbing muscular ache or pain. When reported, pain usually appears to be neuropathic. As the dis-

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ease progresses, other body areas (shoulders, arms, and trunk) may be affected.

RLS symptoms manifest when the patient is in a comfortable position. The urge to move mounts in a crescendo pattern until the patient moves the legs. The legs may jerk involuntarily. Symptoms resolve immediately or soon after initiating movement.

Other clinical features that support the diagnosis of RLS are sleep disturbance, periodic leg movements (this is a separate clinical disorder and not required for the diagnosis of RLS), response to dopaminergic therapy, a positive family history, and normal examination results.

**The diagnostic workup**<sup>5,8</sup> should include a thorough medical history (including a family history), a current list of medications, and a physical examination (including a full neurologic examination). The sleep history should involve specific questions relating to the patient’s sleep patterns: How many hours of sleep do you get at night? How long does it take you to fall asleep? Do you wake up during the night? How many times?

### TEACHING POINTS

- Restless legs syndrome (RLS) is characterized by unpleasant leg sensations or urges to move the legs. These symptoms are worse with rest, worse in the evening and at night, and relieved by movement.
- The pathophysiology is unknown, but CNS dysregulation, neurotransmitter systems (dopaminergic), and abnormal iron metabolism have all been considered to play a role.
- Ferritin deficiency has been correlated with increased symptom severity, decreased sleep efficiency, and increased periodic limb movement disorder associated with arousal and is present in 50% to 60% of all cases of primary RLS.
- RLS is a clinical diagnosis. The condition is generally underdiagnosed and undertreated. Physical and neurologic examinations usually produce normal findings. A thorough sleep history along with a medical history, current list of medications, and appropriate laboratory studies should be performed to support diagnosis.
- Heavy advertising of certain drugs used in the treatment of RLS may cause patients to request a prescription from their health care provider. Screening first for iron/ferritin deficiency may prevent subjecting patients to potential side effects of these agents.

Do you know what wakes you up? When you wake up in the morning, do you feel refreshed? Do you fall asleep inappropriately during the day? Do your legs have an urge to move at rest? Do you get relief of leg symptoms with movement? Are leg movements worse at night? Do they interfere with your ability to fall asleep? Ask also about substances or medications that can aggravate restless legs symptoms, such as nicotine, caffeine, SSRIs, TCAs, metoclopramide, prochlorperazine maleate, dopamine antagonists, diphenhydramine, alcohol, calcium channel blockers, and sleep deprivation.

Diagnostic tests may include serum iron studies, including iron, total iron binding capacity, ferritin, and a CBC. If the patient is iron deficient, investigations into possible causes should be pursued, such as menorrhagia, GI blood loss, and frequent blood donation. Measures of serum B<sub>12</sub>, folate, and magnesium levels are advised. Other tests include polysomnography with arm and leg leads (not required for diagnosis but should be used as appropriate to rule out any concurrent sleep conditions), electromyography (for neuropathy, radiculopathy, or myelopathy, if suspected), and CNS MRI (for myelopathy or stroke, if suspected).

**The differential diagnosis**<sup>5-8</sup> should include periodic limb movement disorder (PLMD)—repetitive limb movements (affecting lower more than upper extremities) that occur during sleep, with no sensory complaints or urges to move limbs for comfort during rest, associated with arousals in sleep and excessive daytime sleepiness. The patient is usually unaware of movements, but the bed partner may report limb jerking or kicking during sleep. PLMD is present in 50% to 60% of cases of primary RLS, and up to 85% of patients with RLS experience PLMD symptoms involving the legs. Other conditions in the differential include peripheral neuropathy, radiculopathy, myelopathy, or other CNS injury; anxiety and mood disorders; narcolepsy; REM behavior disorder; parasomnias (sleepwalking, confusional arousals); obstructive sleep apnea; iron deficiency; neuroleptic-induced akathisia (caused by phenothiazines), usually involving spontaneous movement of the whole body; dyskinesias while awake; and nocturnal leg cramps with or without peripheral arterial disease.

**The treatment** for patients with RLS should be individualized based on the following: iron/ferritin status, disease severity, frequency/duration of symptoms, presence of pain, and drug side-effect profile.<sup>4,8,9</sup>

Whether to give oral or IV iron therapy depends on the degree of iron deficiency. With oral iron supplementation, the patient should receive 50 to 65 mg of elemental iron per dose, 2 to 4 times a day. To improve absorption, the iron should be taken on an empty stomach with 200 mg of vitamin C. An iron panel should be ordered every 3 months, with a goal of a ferritin level that is higher than 50 to 60 ng/mL. To avoid hemochromatosis, iron repletion should not be administered to patients with an iron saturation greater than 45%. In patients who have severe iron deficiency (ferritin <10 ng/mL) or oral iron intolerance, consider prescribing IV iron.

The sleep disorder specialist consulted in this case recommended treating patients with a ferritin level of less

than 50 ng/mL with iron infusion therapy. "A low serum ferritin level (<45-50 ng/mL) has been associated with increased severity of RLS and may be associated with an increased risk for RLS."<sup>5</sup> Results of a study on IV iron sucrose in RLS demonstrated that small, multiple infusions of iron are more effective than one large dose and are less likely to cause adverse effects.<sup>4</sup> In this study, patients were given a total of 1,000 mg of iron sucrose in two separate doses.<sup>4</sup>

Patients with RLS should be counseled to avoid potential exacerbators such as caffeine, alcohol, and nicotine. A regular sleep schedule and good sleep hygiene are important. Stimulating activities close to bedtime should be avoided; massage and hot baths may be beneficial.

**Four categories of drug therapy** are available for RLS. Dopaminergic medications such as ropinirole, pramipexole, and levodopa/carbidopa are first-line agents and should be considered if the patient is experiencing daily symptoms. These drugs stimulate dopamine receptors. Common side effects include nausea and vomiting, insomnia, hallucinations, nasal congestion, fluid retention, and daytime sleepiness. All dopaminergic medications can cause augmentation or rebound, which may require discontinuation of medication or additional therapies.

Second-line therapies for RLS include antiepileptics such as gabapentin, carbamazepine, levetiracetam, and topiramate. The direct mechanism of action of these drugs is unknown. Dosing of gabapentin should be scheduled to cover the symptomatic period. Thus if symptoms occur only at bed-

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time, only a late-evening dose is recommended. If symptoms occur throughout the day, three-times-a-day dosing may be needed. Common side effects include sleepiness, dizziness, fluid retention, and increased appetite.

Opiates or opiate/analgesic combinations, which produce analgesia and sedation, are third-line agents. Tramadol, hydromorphone, propoxyphene HCl, oxycodone, and hydrocodone/acetaminophen are just a few examples.

The fourth category of pharmacologic agents used to treat symptoms of RLS are the benzodiazepines. These drugs play a viable role in treatment in selected cases. Benzodiazepines may be a good first-line choice for patients with intermittent nighttime symptoms, as they offer a quick onset of action with only a short-lived period of pharmacologic action. Clonazepam and temazepam are preferred over the short-acting benzodiazepines.<sup>1,10</sup>

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### SUMMARY

Initially, the patient in this case received CPAP for sleep apnea and pramipexole for RLS. Her symptoms failed to resolve, which led to consultation with a sleep specialist who recommended diagnostic studies that identified an underlying iron/ferritin deficiency. After receiving IV iron therapy, the patient's RLS symptoms resolved.

Only about one-quarter of patients with RLS symptoms receive an appropriate diagnosis,<sup>5</sup> and thus, many are treated less than optimally. Agents used to treat RLS have been heavily advertised, and patients may request a prescription from their health care provider. This case reaffirms the importance of the medical history and diagnostic studies when evaluating a patient with symptoms of RLS. Screening first for iron/ferritin deficiency may prevent subjecting patients to the potential side effects of unnecessary medications. [JAAPA](#)

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### DRUGS MENTIONED

Carbamazepine  
Clonazepam (Klonopin)

Diphenhydramine  
Gabapentin (Gabarone, Neurontin)  
Hydromorphone (Dilaudid)  
Hydrocodone/acetaminophen (Vicodin)  
Levetiracetam (Keppra)  
Levodopa/carbidopa (Parcopa, Sinemet)  
Metoclopramide (Reglan)  
Oxycodone (Oxycontin, Oxydose)  
Pramipexole (Mirapex)  
Prochlorperazine maleate  
Propoxyphene HCl (Darvon)  
Ropinirole (Requip)  
Temazepam (Restoril)  
Topiramate (Topamax)  
Tramadol (Ultram)

### REFERENCES

1. Durmer JS. Restless legs syndrome. Ferri's Clinical Advisor 2008 on MD Consult. 1st ed. <http://www.ferri.clinicaladvisoronline.com/>. Accessed February 5, 2009.
2. Allen RP. Controversies and challenges in defining the etiology and pathophysiology of restless legs syndrome. *Am J Med.* 2007;120(1A):S13-S21.
3. Gamaldo CE, Earley CJ. Restless legs syndrome. *Chest.* 2006;130(5):1596-1604.
4. Earley CJ, Horska A, Mohamed MA, et al. A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome. *Sleep Med.* Feb 14, 2008. ePub ahead of print.
5. Kushida CA. Clinical presentation, diagnosis, and quality of life issues in restless legs syndrome. *Am J Med.* 2007;120(1A):S4-S12.
6. Goetz CG, ed. *Textbook of Clinical Neurology*. 3rd ed. W.B. Saunders; 2007.
7. Silber MH. The investigation of sleepiness. *Sleep Medicine Clinics*. Elsevier; 2006:1-7.
8. Hogl B, Kiechl S, Willeit J, et al. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. *Neurology.* 2005;64(11):1920-1924.
9. Ryan M, Slevin JT. Restless legs syndrome. *Am J Health Syst Pharm.* 2006;63(17):1599-1612.
10. Restless legs syndrome. DynaMed Web site. <http://dynaweb.ebscohost.com/Detail.aspx?id=114812&sid=aef36c6f-2d89-4896-af7a-18eac20e881c@sessionmgr2>. Accessed February 5, 2008.