Case in Point

Restless Legs Syndrome Complicating Iron Deficiency

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This case examines the challenge of diagnosing restless legs syndrome.

Restless legs syndrome (RLS) is a sensorimotor disorder, characterized by unpleasant sensations in the legs, that occurs mainly at night or during periods of inactivity. The sensations are typically accompanied by a compelling urge to move, and movement provides temporary relief. Patients with moderate or severe RLS report significant symptoms, including insomnia, daytime fatigue, reduced mental acuity, decreased motivation, occupational impairment, anxiety, and even frank depression.[1]

Normally pleasurable social activities that require prolonged sitting or immobility, such as moviegoing or travel, may be avoided. In fact, the impact of RLS on various quality of life (QOL) measures in the most severely affected patients may approach or exceed that attributed to debilitating neurologic disorders, such as Parkinson disease (PD) and stroke.[2] For these reasons, it is important that primary care physicians (PCPs) have a working knowledge of the diagnosis and management of RLS. We present the case of a woman with RLS, briefly review our current understanding of pathophysiologic mechanisms, and discuss relevant diagnostic and management issues.

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CASE REPORT

A 43-year-old woman presented to her physician having experienced insomnia and daytime fatigue. She described an "irritating" feeling in her calf muscles and an urge to move her legs that made it very difficult for her to fall asleep. Vigorous massaging and rhythmic movement or walking provided immediate, albeit temporary, relief. She noted that the leg symptoms worsened in the evening and became unbearable when she retired to her bed. She did not have a current bed partner but had been previously told that she sometimes snored and "jerked" as she was drifting off to sleep.

Her medical history was notable for chronic nasal congestion, anxiety, and depression. Medications included an antihistamine, anxiolytic, and antidepressant. She reported regular, heavy menses. Recently retired from the military, she was employed in a sedentary administrative position by the U.S. Marine Corps. Alcohol consumption was minimal, and she did not report tobacco or illicit drug use. She had recently reduced her caffeine intake to 1 caffeinated soft drink per day. She was unaware of any family members with similar leg symptoms.

Vital signs were normal, and the physical examination revealed boggy nasal mucosa with polyps, normal cardiovascular examination and peripheral pulses, and normal neurologic survey. Basic laboratory studies, including complete blood count, chemistry panel, thyroid function tests, and an iron panel, were ordered. Except for the iron profile, all laboratory values were within normal limits. The iron profile suggested reduced total body iron stores, although the serum hemoglobin and mean corpuscular volumes were normal. The serum iron was 89 ug/dL (28-170); transferrin, 296 mg/dL (192-282); and serum ferritin, 11.4 ng/mL (10-291).

Based on the characteristic symptomatology, a diagnosis of RLS was made. The patient was advised to discontinue the sedating antihistamine and initiate therapy with a dopamine agonist medication (pramipexole). Concurrently, the patient was prescribed oral iron replacement therapy in addition to an iron-enriched diet. Although the dopamine agonist provided relief, it was poorly tolerated

due to nausea, and she discontinued it. Despite aggressive oral iron replacement, repeat ferritin levels over a 6-month period never exceeded 32 ng/mL, and she was prescribed parenteral iron replacement. After 8 infusions of sodium ferric gluconate complex (total dose 1,000 mg elemental iron), the ferritin level increased to 274.8 ng/mL, and her RLS symptoms completely abated. When she returned for follow-up 6 months later, she noted partial recurrence of symptoms that accelerated over a period of 2 months. A repeat ferritin level at that time was 59 ng/mL, and a second course of parenteral iron was prescribed, once again with complete resolution of RLS symptoms. One year later she presented with worsening leg symptoms and a ferritin level of 30.7 ng/mL.

DISCUSSION

Restless legs syndrome has been considered an obscure disorder; however, advocacy by patient support groups and aggressive drug marketing by the pharmaceutical industry in recent years have increased public awareness. The prevalence rate for RLS symptoms in the general population is reported to range between 5% and 10% of adults and is slightly higher in women than men.[3-6] Given the reliance on subjective criteria to diagnosis RLS and a wide spectrum of symptom severity (ranging from occasional and minor to daily and debilitating), some authors contend that RLS is a disorder susceptible to "disease mongering," ie, efforts by pharmaceutical companies to "convince people that they are sick and need medical intervention," thereby enlarging the treatment market.[7] Clearly, physicians and other health care providers must be meticulous in the diagnosis, impact assessment, and management of this disorder.

Patients use a wide variety of adjectives to describe the deep-seated dysesthesia that affects the lower (and much less commonly upper) extremities, including, creepy, crawly, tingly, electrical, buzzing, prickly, aching, and irritating. A powerful urge to move the legs accompanies the dysesthesia, and movement invariably brings temporary, short-lived relief.

The diagnosis of RLS is established by identifying 4 provoking or alleviating features of the dysesthesia that were standardized by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 and modified at a National Institutes of Health-sponsored workshop in 2003.[8] These primary features can be recalled using the mnemonic "URGE": (1) urge to move; (2) rest induced; (3) gets better with activity; and (4) evening and night accentuation.[9] Unfortunately, several other conditions, notably cramps, positional discomfort, neuropathy, claudication, neuroleptic-induced akathisia, and local leg pathologies may mimic RLS.[10] A recent study that used a validated and structured interview conducted by an RLS expert over the telephone reported a false positive rate of 16% even when all 4 IRLSSG criteria were met.[11] The presence of additional features, including periodic limb movements, a family history of RLS affecting a first-degree relative, and unambiguous response to dopaminergic therapy, reduces the diagnostic uncertainty. The IRLSSG also developed and validated the International Restless Legs Syndrome Scale (IRLS), which can be helpful in assessing the severity of symptoms and response to treatments.[12] The IRLS consists of 10 questions and uses a 5-point scale (0-4) to rate symptom intensity and frequency; symptom scores from 11 to 20 are considered moderate, 21 to 30 severe, and 31 to 40 very severe. Laboratory, radiographic, or nerve conduction testing are unnecessary except to rule out other disorders when the diagnosis is uncertain.

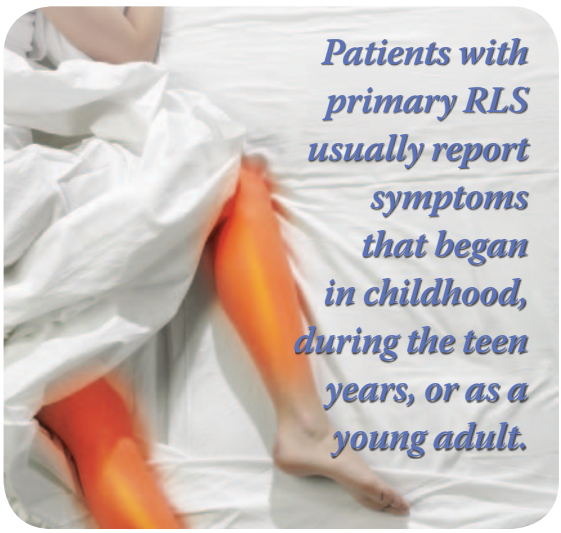
Polysomnography (sleep testing) is not needed for the diagnosis or management of RLS; however, many physicians are aware of the association between RLS and periodic limb movements of sleep (PLMS) and assume that sleep testing is required. PLMS are brief, stereotyped (often just a subtle dorsiflexion of the great toe, or movement of the foot, knee, or hip), and repetitive leg movements that recur at 20- to 50-second intervals during non-rapid eye movement sleep and are easily captured by an electromyograph electrode attached to the lower leg. Although PLMS usually accompany RLS and can be used to support the diagnosis of RLS in uncertain cases, the movements are not specific; the majority of patients with PLMS do not have RLS. The clinical significance of PLMS either associated or unassociated with RLS is unclear, even though individual leg movements may elicit a discrete electroencephalographic arousal from sleep or transient elevation in blood pressure or heart rate.[13] Attempts to provoke and quantify RLS symptoms and periodic limb movements in a monitored setting by asking patients to refrain from moving their legs has been suggested but is not in widespread clinical use and not required for diagnosis.[14] PLMS frequency has been used as an objective surrogate marker in pharmacologic trials for RLS.[15]

The pathophysiology of RLS is unclear, although dysfunction of the dopamine neurotransmitter system has long been postulated based on impressive therapeutic responses to various dopamine agonists or levodopa and worsening of symptoms by dopamine antagonists. Unlike PD, RLS does not seem to be a de-

generative brain disorder; however, structural and functional abnormalities at several levels of the central and peripheral nervous systems have been described.[16] Current data suggest dysfunction of the dopaminergic system at the level of the hypothalamus (specifically, the A11 cell group, which provides the only source of dopaminergic innervation to the spinal cord), striatum, or spinal dopamine receptors.[17] Dopaminergic dysfunction seems to reduce inhibition of spinal motor neurons and increase random firing, resulting in PLMS or periodic limb movements of wakefulness (PLMW) that almost always accompany RLS symptoms. Increased excitability of spinal neurons may, in turn, affect processing of sensory afferents in various brain stem structures.[18] The profound exacerbation of RLS by centrally active dopamine antagonists and soothing of RLS symptoms by dopamine agonists strongly support the dopamine hypothesis for RLS.

Given the well-established association between iron deficiency and RLS symptoms, inadequate brain stores, maldistribution, or dysregulation of iron metabolism have been implicated in the pathophysiology of RLS.[19] Reduced brain iron stores have been demonstrated by 3 separate lines of inquiry—cerebral spinal fluid analysis, brain imaging, and direct tissue examination using autopsy material from affected patients. Cerebral spinal fluid analysis was reported to show decreased ferritin levels indicating reduced central nervous system iron stores in early-onset—but not late-onset—RLS patients.[20] Studies using magnetic resonance imaging (MRI) found regional differences in "iron concentration" in patients with RLS compared with controls with a clear reduction in the normally iron-rich substantia nigra that correlated with RLS severity, but once again only in patients with early-onset RLS.[21]

Finally, initial autopsy data comparing patients with RLS with controls showed a marked decrease in iron and ferritin staining in the substantia nigra of 7 patients with RLS.[22] A more recent neuropathology study reported an imbalance of mitochondrial ferritin (increased) relative to cytosolic ferritin (decreased) in a subset of substantia nigra cells, suggesting an increased metabolic demand of these neuromelanin-containing neurons, perhaps leading to relative cytosolic/cellular iron deficiency that could play a pathophysiologic role.[23] Central nervous system iron deficiency or dysregulation may be linked to RLS pathophysiologically through its effects on dopamine transporter activity. Iron is a critical cofactor for the enzyme tyrosine hydroxylase, the rate-limiting step in dopamine production.



Primary (idiopathic) RLS may be clinically distinguished from secondary RLS by age of symptom onset, family history, and natural history of the disease. Patients with primary RLS usually report symptoms that began in childhood, during the teen years, or as a young adult. They are more likely to be female and often have a family history of similar symptoms. Studies of monozygotic twins have found a very high genetic association of RLS, and there is a reported genomic association between a sequence variant in chromosome 6p and PLMS in Icelandic and American cohorts with RLS.[24]

Secondary RLS may be due to several medical conditions or drugs. Patients with secondary RLS generally report relatively abrupt onset of symptoms later in life, often arising after developing a condition known to contribute to the pathophysiology of RLS. The most frequently associated conditions linked to secondary RLS are known to affect iron stores or metabolism (iron deficiency anemia, pregnancy, and end-stage renal failure). Diabetes, rheumatoid arthritis, and various neurologic disorders such as peripheral neuropathies may also predispose patients to RLS. Emergence or worsening of RLS symptoms may occur when patients take antidepressants, antihistamines, or dopamine receptor blockers. Finally, nicotine, alcohol, and caffeine have all been associated with RLS.

Patients who satisfy all 4 IRLSSG diagnostic criteria should be carefully evaluated for predisposing conditions, and if possible, potentially offending medications should be withdrawn. Smoking cessation and abstinence from alcohol and caffeine may be useful. Since iron deficiency is associated with RLS, all patients should have iron, ferritin, and transferrin levels measured. As this case illustrates, patients can have a clinically significant reduction in systemic iron stores

without affecting erythropoiesis and a normal complete blood count should not preclude further evaluation of iron status. The patient's failure to respond to prolonged oral replacement therapy prompted a trial of intravenous iron administration, and a clear correlation between symptoms and ferritin level became apparent when ferritin levels dropped over 6 to 9 months on 2 subsequent occasions following iron replacement. The literature, in fact, suggests that a serum ferritin level below 50 ng/mL may be a risk factor for RLS and is a reasonable threshold for a therapeutic trial of iron replacement.[19] Although the response to iron replacement can be impressive, it should be recognized that the majority of patients with RLS seem to have normal body iron stores.

TREATMENTS FOR RLS

A variety of nonpharmacologic and pharmacologic treatments have been recommended for RLS.[25] Behavioral measures that may alleviate symptoms include massage, deep heat therapy, and cognitive distraction activities, such as working a crossword puzzle.

Medications from several major drug classes, including dopaminergic, opioid, anticonvulsant, and sedative/hypnotic, may provide relief from RLS symptoms; however, only 4 medications are currently approved for use in the U.S.

Dopamine Agonists

Three of the 4 approved agents for RLS are dopamine agonists and were approved by the FDA in 2005 (ropinirole), 2006 (pramipexole), and 2012 (rotigotine transdermal) for treatment of moderate-to-severe primary RLS. All 3 are nonergot derivatives with D2-receptor activity that reduces prolactin secretion and may cause nausea and orthostatic hypotension. Ergot-derived dopamine agonists previously used off-label for RLS have been associated with valvular fibrosis and other fibrotic complications; one of these agents, pergolide, was voluntarily withdrawn from the market in 2007.

Dosing. Unlike the dosing of dopaminergic medications used for PD, all the RLS trials for the dopamine agonists used a single nightly dose that targeted the strongly circadian-influenced spike in RLS symptoms that occurs around bedtime.

The mean effective dose of ropinirole in these trials was 2 mg; the drug manufacturer recommends beginning with 0.25 mg given 1 to 3 hours before bedtime and then increasing to 0.5 mg after 2 days, to 1 mg after 7 days, and then by 0.5-mg increments/week until an efficacious dose is achieved (maximum 4 mg). The mean effective dose in clinical trials of pramipexole was in the range of 0.25 mg to 1 mg; the drug manufacturer recommends beginning with 0.125 mg given 2 to 3 hours before bedtime and doubling the dose every 4 to 7 days until symptoms are controlled (maximum recommended dose by the manufacturer is 0.5 mg, although this is below the mean effective dose in some clinical trials as noted earlier). Rotigotine transdermal is a new FDA-approved 24-hour patch with a starting dose of 1 mg/24 h, which can be increased by 1 mg a week to a maximum dose of 3 mg/24 h. Rotigotine and ropinirole undergo hepatic metabolism, while pramipexole is 90% eliminated unchanged from the kidneys. Although dopamine agonists may cause somnolence, they have not yet been reported to cause the sudden "sleep attacks" in patients with RLS that may accompany the multiple dose regimens used in the treatment of PD.

Adverse Events. Perhaps the most important adverse event (AE) associated with dopaminergic medications is "augmentation," or paradoxical worsening of symptoms, which may include an increase in symptom intensity, earlier appearance of symptoms, and even symptoms that spread to the upper extremities.[26] Augmentation was initially reported as a common AE of levodopa but seems to be infrequently associated with the dopamine agonists. Nevertheless, it is very important to recognize augmentation in order to avoid inappropriate dose escalation when, in fact, the appropriate response would be medication withdrawal and a switch to another drug. Rotigotine contains a sulfite metabolite that can result in severe allergic reactions in people sensitive to sulfites.

Anticonvulsants

The only other approved medication for RLS treatment is the anticonvulsant gabapentin enacarbil, which received formal FDA approval in 2011 and has the same indications as the dopamine agonists, ie, moderate-to-severe primary RLS. Gabapentin enacarbil is a prodrug of gabapentin and undergoes conversion to gabapentin in intestinal epithelial cells.[27] Administration of the prodrug provides more predictable and sustained serum levels of its active metabolite and allows for once-daily dosing.

Dosing and AEs. The recommended initial dose is one 600-mg tablet taken with food at about 5 PM, which may be increased to 1,200 mg if needed. The most commonly reported AEs of gabapentin enacarbil are daytime sleepiness (20%) and dizziness. As with the other approved RLS medications, patients should be cautioned not to drive or operate dangerous equipment after taking gabapentin enacarbil until its effect on daytime function is clear.

CONCLUSION

RLS is a disorder typically character-

ized by unpleasant sensations in the lower legs, which are aggravated by immobility and are transiently alleviated by movement. Symptoms are most prominent in the evening hours and may interfere with sleep onset or trigger recurrent arousals or awakenings. Disturbed sleep likely contributes to the reduced QOL experienced by some patients with RLS. The diagnosis is most reliably established when all 4 key historical criteria are met, although recent data have cast some doubt on the specificity of these features, and careful assessment for other pathology is recommended. PLMS are usually present in patients with RLS; however, their detection by polysomnography is not needed for the diagnosis or management of RLS. Other laboratory, radiographic, and nerve conduction studies are best used to evaluate for other disorders when the diagnosis is in doubt.

Because of the association between low iron stores and RLS, screening for peripheral iron deficiency is recommended, and aggressive replacement should be considered when the ferritin level is below 50 ng/mL. In addition, medications such as antihistamines, antidepressants, and dopamine receptor blockers suspected to exacerbate RLS symptoms should be withdrawn if possible. Nonpharmacologic measures, such as massage and heat application, are sometimes useful; however, moderate or severe RLS may require pharmacologic treatment. Three dopamine agonists, ropinirole, pramipexole, and rotigotine transdermal, and 1 anticonvulsant, gabapentin enacarbil, are currently the only FDA-approved drugs for RLS. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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