The Treatment and Management of Restless Legs Syndrome

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Introduction

In 1944, Ekbom[1] described a disorder characterized by sensory symptoms and limb restlessness mainly during rest, and named this condition "restless legs" syndrome (RLS). On the basis of a multinational, large-scale study, clinically significant RLS is a common condition with a prevalence of 2.7%. It is, however, often unrecognized and misdiagnosed.

In this Expert Column, I define RLS and its clinical features; describe the etiology, pathogenesis, and diagnosis; and then focus on treatment and management.

Definition of RLS and Clinical Features

In 1995, the International RLS Study Group developed criteria for diagnosing RLS,[3] including (1) a desire to move the limbs, often with paresthesias or dysesthesias; (2) symptoms exacerbated by rest and relieved by activity; (3) motor restlessness; and (4) nocturnal increase in severity of symptoms. A National Institutes of Health (NIH) consensus panel modified these criteria in 2003 to include (1) an urge to move the limbs with or without sensations, (2) worsening at rest, (3) improvement with activity, and (4) worsening in the evening or night.[4]

Patients may describe an unpleasant sensation (paresthesias or dysesthesias) in the calves, and occasionally in the thighs, feet, or upper limbs. Most patients, however, simply relate a vague, nonpainful, indescribable discomfort in the limbs and use terms, such as crawling, creeping, jittery, tingling, burning, itching, aching, etc. The unpleasant limb sensations are precipitated by rest or inactivity, especially in bed at night or in the car, airplane, theater, etc.
Motor activity characteristically relieves the limb discomfort, and can manifest as pacing the floor, tossing and turning in bed, stretching or shaking the legs, exercising, etc. Most patients notice worsening of symptoms in the evening, usually in bed before sleep or in the middle of the night, followed by improvement early in the morning. In severe cases, patients experience symptoms both in the day and night.

About 80% of patients with RLS have unilateral or bilateral periodic limb movements in sleep (PLMS).\(^5\) Insomnia due to disturbed sleep onset or sleep maintenance is experienced by most RLS patients due largely to limb discomfort and limb jerking. This can lead to excessive daytime sleepiness and fatigue.

RLS may begin at any age, even as early as infancy, childhood, or adolescence. The majority of severely affected patients are middle-aged or older. Peripheral neuropathy and iron-deficiency anemia need to be ruled out before RLS is labeled primary or idiopathic.\(^6\) Idiopathic RLS can be familial (25% to 50% of cases), and is transmitted in an autosomal-dominant fashion. Loci with positive linkage have been identified on chromosomes 9p, 12q, and 14q.\(^7-9\) Anticipation (progressive decrease in age of onset with subsequent generations) has been described. Patients with familial RLS tend to have an earlier age of onset and slower progression.

**Etiology of RLS**

Although RLS is idiopathic in most cases, it can be associated with several conditions, particularly iron deficiency and peripheral neuropathy.\(^10-17\) The possible secondary causes of RLS include:

1. Deficiency of iron, folate, B12, or magnesium;

2. Polyneuropathy due to uremia, diabetes, alcohol abuse, rheumatoid arthritis, amyloidosis, Sjögren's syndrome, radiculopathy, monoclonal gammopathy of undetermined significance, Lyme disease, and idiopathic neuropathy;

3. Parkinson's disease (PD);

4. Pregnancy;

5. Drugs, such as lithium, neuroleptics, beta blockers, H\(_2\) antagonists, antidepressants (such as paroxetine, amitriptyline, mianserin, and mirtazapine), anticonvulsants (such as methsuximide, phenytoin, and zonisamide), and spinal anesthesia;
6. Alcohol;
7. Caffeine;
8. Gastric surgery;
9. Chronic obstructive pulmonary disease;
10. Carcinoma;
11. Chronic venous insufficiency or varicose veins;
12. Withdrawal from vasodilators, sedatives, imipramine, or opiates;
13. Cigarette smoking;
14. Myelopathy or myelitis;
15. Hypothyroidism or hyperthyroidism;
16. Acute intermittent porphyria;
17. Fibromyalgia syndrome;
18. Arborizing telangiectasia of the lower limbs; and
19. Peripheral cholesterol microemboli.

RLS can be the initial manifestation of iron deficiency.[16] In RLS, low serum ferritin levels may precede a drop in serum iron levels. Treatment with ferrous sulfate has been recommended for RLS patients with a serum ferritin level of 50 mcg/L or less, even if serum iron levels are normal.[19] Iron-responsive RLS has also been reported despite the presence of normal serum ferritin levels.[20]

About 5.2% of patients with sensory neuropathy (especially due to uremia, rheumatoid arthritis, and diabetes) develop RLS.[13] Treatment of the polyneuropathy can lead to improvement of the RLS symptoms.
Pathogenesis of RLS

Current thinking about the pathophysiology of RLS emphasizes the role of dopamine and iron. Functional imaging has shown normal presynaptic dopaminergic binding in RLS, suggesting that dopaminergic neurons and spinal pathways could be more involved in the pathogenesis of RLS than the nigrostriatal system.\textsuperscript{[21]} In particular, hypofunctioning of dopaminergic diencephalospinal pathways terminating in preganglionic sympathetic neurons, dorsal horn regions for afferent nerve processing, interneurons, and somatic motor neurons has been proposed.\textsuperscript{[22,23]} Iron deficiency in the brain has been demonstrated in MRI studies with RLS patients;\textsuperscript{[24]} reduced cerebrospinal fluid concentrations of ferritin and transferrin have also been found.\textsuperscript{[25]} PLMS, in particular, are thought to be caused by sleep-related disruption of the descending inhibitory reticulospinal pathways that are normally active at the brainstem or spinal cord level.\textsuperscript{[26]}

Diagnosis of RLS

The diagnosis of RLS rests largely on clinical history. If a secondary cause is suspected, a serologic work-up should be done that includes an assessment of blood urea nitrogen (BUN), creatinine, fasting blood glucose, glucose tolerance, complete blood count, ferritin, magnesium, thyroid-stimulating hormone, and folate levels. Needle electromyographic (EMG) and nerve conduction studies can be considered if polyneuropathy is suspected clinically, even in the setting of an apparently normal neurologic examination.\textsuperscript{[27]} Polysomnography is rarely necessary.

Treatment and Management of RLS

Nonpharmacologic Management

Avoidance of caffeine, alcohol, or nicotine may help improve symptoms in some patients. Offending medications (see numbered list above) should be discontinued. Physical measures that may partially or temporarily help include a hot or cold bath, rubbing the limbs before sleep, or vibratory or electrical stimulation of the distal lower limbs before bedtime.

Correction of a vitamin deficiency (eg, folate) or an electrolyte deficiency (eg, magnesium) can improve symptoms in RLS. Those with low ferritin levels or iron deficiency can benefit from oral iron supplementation, or in some cases intravenous infusion of iron.\textsuperscript{[28]} Sclerosing agents may improve RLS symptoms in individuals with prominent varicose veins in the legs.\textsuperscript{[29]} Uremic patients with RLS usually improve upon correction of anemia with erythropoietin, or after renal transplantation.\textsuperscript{[30]}
Pharmacologic Management

The goal of pharmacotherapy is symptomatic relief in primary or idiopathic RLS, given that a cure is only possible in secondary RLS. Medications are best initiated at low doses and taken 1-2 hours before bedtime to allow for sufficient absorption and action. Additional doses can be given in the middle of the night if the patient awakens. If tolerance develops to one drug, another class of drugs may be substituted. Severe cases of RLS may benefit from polypharmacy with 2 or more drugs. One strategy to help prevent tolerance is to find 2 or 3 effective medications and then rotate them every few months.

**Levodopa.** Carbidopa-levodopa can improve sensory symptoms and PLMS in RLS. For symptoms that start before sleep, one 25-mg/100-mg carbidopa-levodopa tablet can be taken 1-2 hours before bedtime. If the symptoms occur later during the night, a controlled-release (CR) carbidopa-levodopa tablet (either 25 mg/100 mg or 50 mg/200 mg CR) can be used. Even low doses of levodopa (50-200 mg/day) are effective in most patients. Only rarely do patients require more than 600 mg/day. Nausea and constipation are the most common side effects of levodopa.

The major drawback with levodopa is that about 80% of patients will develop "augmentation" as early as a few months after initiation of the drug.\[31\] Augmentation manifests as earlier onset of RLS symptoms during the evening, shorter latency to onset after assuming a restful position, increased intensity, or extension of the symptoms to the upper body. "Rebound" refers to an increase in severity of symptoms occurring in the morning. Augmentation often leads to escalating doses of levodopa. Once augmentation or rebound occurs, adjunctive therapy or substitution of levodopa with other drugs is an alternative treatment strategy.

**Dopamine Agonists.** The most commonly prescribed dopamine agonists for RLS are pramipexole and ropinirole. Both are nonergots, and have been determined to be effective in double-blind, placebo-controlled studies.\[32,33\] Doses as low as 0.125 mg of pramipexole (D2, D3 agonist) at bedtime or 0.25 mg of ropinirole (D2 agonist) can be effective in controlling nocturnal symptoms in mild-to-moderate cases of RLS. The majority of patients require less than 2 mg/day of pramipexole or 6 mg/day of ropinirole. Piribedil, a nonergot D2 and D3 dopamine agonist, is effective even at a low dose of 25 mg/day.\[34\] Cabergoline, a long-acting ergot dopamine agonist, can provide symptomatic relief of RLS symptoms (at doses of 2 mg/day or less) for the entire day despite the need for once-daily dosing due to its long half-life.\[35\] Rotigotine, the only dopamine agonist that is available as a patch, can provide relief of RLS both day and night with once-daily dosing.\[36\]
The side effects of dopamine agonists include nausea, light-headedness, drowsiness, and postural hypotension. Dopamine agonists are less likely to produce augmentation or rebound, and can be of benefit in patients treated with levodopa who develop these complications.

**Benzodiazepines.** Clonazepam can alleviate sensory symptoms and PLMS in RLS patients. The initial dose is 0.25 mg at bedtime, with a maximum dose of 3-4 mg/day in divided doses. Other benzodiazepines, such as temazepam and alprazolam, have also been used anecdotally with success. The major side effects of benzodiazepines include daytime drowsiness, confusion, unsteadiness, falls, and aggravation of sleep apnea. Benzodiazepines may be used in patients with mild or intermittent symptoms.

**Opioids.** Low-potency opioids, such as codeine and propoxyphene, can be of benefit for those with mild and intermittent symptoms, whereas higher potency agents, such as oxycodone, methadone, or levorphanol, may be useful in refractory cases. Opioids are best used in RLS patients who have painful symptoms, especially those with associated sensory neuropathy.

**Anticonvulsants.** Carbamazepine (200-400 mg daily) has been shown to be effective in reducing RLS sensory symptoms, especially among young patients with recent-onset and severe symptoms. Gabapentin (100-2400 mg/day) may be effective in relieving sensory symptoms and PLMS in RLS, even in refractory cases. Topiramate (25-150 mg/day) and sustained-release valproate (600 mg/day) have also been reported to be effective in some patients.

**Other Medications.** Clonidine (0.1-1 mg/day), a presynaptic alpha2-adrenergic agonist, is effective in idiopathic and secondary RLS. The sleeping pill zolpidem (5-10 mg per night) has also been reported to be effective in improving sleep, sensory symptoms, and PLMS in RLS patients. Amantadine (100-300 mg/day), a drug that is used to treat the flu and PD, can be effective in treating idiopathic and neuropathic RLS, even in those with severe symptoms.

**Surgical Management**

In PD patients with RLS, subthalamic deep brain stimulation has been noted to improve not only the motor symptoms of PD but also RLS. RLS in these patients improves significantly despite a drop in postoperative doses of dopaminergic drugs. Whether RLS in non-PD patients will respond to deep brain stimulation is uncertain.
Conclusion

RLS is a common disorder that is often unrecognized or misdiagnosed, but yet can be readily treated. Although RLS is most often idiopathic, it can be associated with several conditions, particularly iron deficiency and peripheral neuropathy. The mainstay of treatment is dopaminergic agents; benzodiazepines, opioids, and anticonvulsants are common alternatives.

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