Concise Review for Primary-Care Physicians

Restless Legs Syndrome

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Restless legs syndrome is a common condition characterized by unpleasant limb sensations that are precipitated by rest and relieved by activity. Symptoms are worse during the evening and may result in insomnia. Most cases are idiopathic, although the condition is sometimes familial and may be associated with a range of medical illnesses, including chronic renal failure and iron deficiency anemia. Restless legs syndrome is responsive to several medications, including levodopa, dopamine agonists, benzodiazepines, opioids, and some anticonvulsants. A practical approach to management involves a stepwise plan, commencing with intermittent therapy with less potent agents for mild cases and progressing to medications with greater potency but a higher potential for side effects.

Restless legs syndrome (RLS), a common condition, may afflict up to 10 to 15% of the population.1 It is often misdiagnosed, and patients report a mean of 2 years' delay in the correct diagnosis after they have sought medical attention. Although the condition can develop in patients of any age, about 40% of patients recall symptoms before the age of 20 years.2 The symptoms tend to worsen with age but may fluctuate with periods of relative remission and exacerbation.

CLINICAL FEATURES

RLS is a clinical diagnosis based on the history of the patient. The six essential characteristics are as follows: unpleasant limb sensations, sensations precipitated by rest and relieved by activity, compelling motor restlessness, symptoms that are worse during the evening or later at night, resultant insomnia, and association with periodic limb movements of sleep (PLMS).3

Unpleasant Limb Sensations.—Unpleasant limb sensations are most commonly experienced in the lower extremities, especially in the calves, but occasionally occur in the thighs, feet, or upper extremities. They are usually (but not always) bilateral. The discomfort is often difficult to characterize, and patients often indicate that it is not a pain. It is often described as a deep-seated, creeping, crawling, jittery, tingling, burning, or aching sensation. Frequently, patients report the sensation as indescribable.

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Sensations Precipitated by Rest and Relieved by Activity.—The unpleasant sensations are exclusively present (or worsen in severity) while the person is lying or sitting and are relieved, at least temporarily, by activity. Lying in bed is the most common precipitant, but symptoms may also occur while the patient is sitting, especially for prolonged periods such as in a theater, automobile, or airplane.

Compelling Motor Restlessness.—Motor restlessness is associated with a patient's compelling desire to move the affected limbs. Forcing them to remain still may be impossible and always results in considerable worsening of the discomfort and occasionally causes an involuntary limb jerk. Voluntary activity that may be beneficial involves stretching or jiggling the legs, pacing the floor, or exercising, such as on a stationary bicycle. Massaging the legs or taking hot baths may be effective alternative measures.

Worsening of Symptoms During the Early Evening or Later at Night.—Symptoms are most troublesome while the person is in bed before sleep or during the night. When the person is sitting, symptoms are always most prominent during the evening and are least noticeable in the morning. This phenomenon is probably due to a circadian factor and does not occur only because people tend to rest later during the day.

Resultant Insomnia.—Most patients with RLS have sleep onset or sleep maintenance insomnia, which is clearly due to limb discomfort. In some patients, the symptoms are worst before sleep, whereas in others, they may be most severe later during the night.

Association With PLMS.—PLMS are stereotyped, repetitive flexion movements of the legs during sleep that last 0.5 to 5 seconds and occur semirhythmically at intervals of...
usually 20 to 40 seconds. PLMS are common, especially in elderly people, and are usually not associated with RLS or any other clinical consequence. Nevertheless, about 80% of patients with RLS will experience PLMS, and often a sleeping partner will describe the movements. PLMS associated with RLS may sometimes cause arousals that fragment sleep and result in excessive daytime sleepiness; occasionally, PLMS without RLS may produce similar effects.

ETIOLOGIC FACTORS AND PATHOGENESIS
Most cases of RLS are idiopathic, but certain associated factors have been reported. These factors include pregnancy; neurologic conditions such as peripheral neuropathy, lumbosacral radiculopathies, myelopathies, and Parkinson’s disease; hematologic conditions, of which iron deficiency anemia is the most important; chronic renal failure; folate and vitamin B12 deficiency; rheumatoid arthritis; hypothyroidism; and medications such as tricyclic antidepressants. A family history of RLS is common, and an autosomal dominant pattern of inheritance has been suggested in several families.

The pathogenesis of RLS and PLMS is uncertain. Various lines of evidence suggest that a disturbance of inhibitory subcortical pathways, such as the reticulo spinal tract, may allow expression of a normally suppressed neural generator at the spinal cord level. This process may be modulated by abnormal peripheral sensory input from, for instance, a peripheral neuropathy.

RLS may occur at any age. The condition may remain static, but about two-thirds of patients report progression of symptoms with time. At least 16% of patients describe remission of symptoms for a month or more. RLS does not seem to predict other neurologic disease that is not evident at the time of diagnosis.

DIAGNOSIS
RLS is usually diagnosed on the basis of the patient’s history, although sleep studies are occasionally undertaken to identify the presence of PLMS. In selected patients, the suggested immobilization test can be used to measure leg movements while the patient is awake during the day. The most common mimickers of RLS have different clinical features and are usually readily distinguished by elicitation of a thorough history. These mimickers include symptoms of peripheral neuropathy such as paresthesias (different from RLS as a complication of peripheral neuropathy), nocturnal leg cramps, fibromyalgia, and akathisia. In particular, in patients with neuroleptic-induced akathisia, the need to move is more often generated by an inner sense of restlessness than by limb discomfort and is often not worse at night or at rest.

A limited search for a secondary cause of RLS should be undertaken, especially if the symptoms are brief in duration or have recently worsened. Symptoms of peripheral neuropathy, radiculopathies, or blood loss should be elicited. A brief neurologic examination of the legs should be performed. Electromyography is not usually indicated if findings from the history or examination do not suggest neurologic disease. In patients in whom RLS has only recently begun or has worsened substantially, serum iron, ferritin, folate, vitamin B12, creatinine, and thyroid-stimulating hormone concentrations should be determined.

MANAGEMENT
Nonpharmacologic management includes reduction in caffeine and alcohol intake and cessation of smoking.

Medications that have been shown to be effective in RLS are as follows: carbidopa-levodopa, dopamine agonists, opioids, benzodiazepines, anticonvulsants, and clonidine hydrochloride.

Carbidopa-Levodopa.—In controlled studies, carbidopa-levodopa has been shown to diminish the symptoms of RLS and reduce the frequency of PLMS. For symptoms that are especially troublesome before onset of sleep, the usual initial dosage of carbidopa-levodopa is one-half to one 25-100 mg tablet (25 mg of carbidopa and 100 mg of levodopa) before bed. If the main problem is waking with symptoms later during the night, one 25-100 mg tablet of controlled-release carbidopa-levodopa is preferable. In some patients, a combination of the short-acting and controlled-release formulations may be needed; others may require an additional dose of medication during the early evening or later during the night. Levodopa should always be taken on an empty stomach to enhance absorption. Minor side effects such as nausea and insomnia occur occasionally, but long-term studies have shown that dyskinesias do not generally develop.

The main complication of levodopa therapy for RLS is the development of worsening symptoms during the afternoon or early evening, despite adequate control later at night. This phenomenon, which has been termed “restless legs augmentation,” may occur in 50 to 80% of patients, sometimes within months after therapy has been instituted. In the past, it was often confused with the development of tolerance to the medication, an outcome that is considerably rarer. A recent study showed that the development of restless legs augmentation correlates with two factors: pretreatment restless legs symptoms commencing earlier than 6 PM and administration of a total daily dosage of levodopa of 200 mg or more. Some physicians believe that the risk of daytime augmentation may be decreased by administering levodopa five nights a week and using other agents on the other two nights, but this approach has not been tested scientifi-
Dopamine Agonists.—Pergolide is a potent long-acting dopamine agonist that clinically has proved to be effective for treating RLS. Because of a relatively high frequency of minor side effects, I do not advise it as a first-line agent. It is especially helpful in patients who experience levodopa-induced daytime augmentation of symptoms. Efficacious doses are usually considerably lower than those needed for the treatment of Parkinson’s disease. Treatment should commence with 0.05 mg before sleep, and this dose can be increased by 0.05 mg every two nights until relief is obtained, side effects develop, or a dose of 0.6 to 0.8 mg is attained. The average effective dose is 0.15 to 0.20 mg. Occasionally, an additional dose is needed during the early evening. Side effects include nausea (often controllable with a snack), insomnia (well controlled with the addition of a benzodiazepine such as temazepam), light-headedness, and nasal congestion. Daytime augmentation is considerably milder and less frequent with pergolide than with levodopa therapy, but it may occur in about 25% of patients.

Bromocriptine mesylate has also been shown to be effective in a controlled study. Effective dosages range from 5 to 15 mg daily.

Opioids.—Opioids have been shown to be effective in many patients, but their use is somewhat limited because of side effects and concern about potential addiction. Low-potency agents such as codeine (initial dose, 30 mg) and propoxyphene (initial dose, 65 to 130 mg) may be useful in mild cases with intermittent symptoms. Higher potency agents such as oxycodone hydrochloride (initial dose, 4.5 to 5 mg) or methadone (initial dose, 5 to 10 mg) have a definite role in the treatment of patients with resistant symptoms in whom other therapies have failed.

Benzodiazepines.—Benzodiazepines such as clonazepam (0.5 to 2 mg), temazepam (7.5 to 30 mg), and triazolam (0.125 to 0.25 mg) may be effective in relieving RLS. Most studies have shown that these drugs seem to reduce arousals from PLMS rather than eliminate the movements. Concerns about their use include theoretic potential to exacerbate coexisting obstructive sleep apnea syndrome; daytime sedation, especially with longer acting agents such as clonazepam; and in elderly patients, risks of falls at night. These drugs are often useful in patients with mild or intermittent symptoms and are occasionally beneficial in combination with levodopa or a dopamine agonist in patients with more severe symptoms.

Anticonvulsants.—Carbamazepine was found to be superior to placebo in relieving RLS in a double-blind study, but subsequent clinical experience has not suggested a high degree of efficacy.

In a recently published abstract, investigators suggested that gabapentin (300 to 2,700 mg daily in divided doses) may be effective in some patients. A controlled trial is needed, however, to assess its efficacy more objectively.

Clonidine.—In a recent controlled study, clonidine (mean dose, 0.5 mg) provided some relief from RLS symptoms but did not affect PLMS. Frequent side effects were noted, including dry mouth, decreased cognition, and light-headedness. Treatment should be initiated with 0.1 mg daily.

PRACTICAL APPROACH

Practical management of RLS can be challenging and must be adapted to the individual patient. No single method is correct. The following suggested approach is based on personal experience at the Mayo Sleep Disorders Center. Dosage schedules are those discussed in the preceding sections on the specific medication. Associated disorders should be excluded, as discussed in the preceding section on Diagnosis.

Step One.—For mild RLS (symptoms are intermittent or only mildly disruptive to onset or maintenance of sleep), consider use of either a benzodiazepine, such as temazepam, clonazepam, or triazolam, or a low-potency opioid, such as codeine or propoxyphene. Often, these medications can be taken intermittently, at least initially.

Step Two.—For moderate or severe RLS (symptoms are continuous, moderately to severely disruptive to onset or maintenance of sleep or unresponsive to the medications listed in Step One), carbidopa-levodopa is the drug of choice.

Step Three.—If levodopa is ineffective, use is limited by side effects, or daytime augmentation develops, discontinue use and institute pergolide.

Step Four.—If pergolide is ineffective, use is limited by side effects, or daytime augmentation develops, consider use of higher potency opioids such as oxycodone or methadone, bromocriptine, clonidine, or gabapentin. Some patients respond to combination therapy, such as a benzodiazepine and levodopa. In some patients, levodopa or pergolide can be reintroduced at a later time after a period free of the drug.

REFERENCES

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Questions About Restless Legs Syndrome
(See article, pages 261 to 264)

1. Which one of the following is not a clinical feature of restless legs syndrome?
   a. Lying or sitting exacerbates the symptoms
   b. Walking relieves the symptoms
   c. Symptoms are worse during the afternoon than during the evening
   d. Legs may jerk spontaneously if patient tries to hold them still
   e. Sleep onset and sleep maintenance insomnia may occur

2. Which one of the following is most helpful in the diagnosis of restless legs syndrome?
   a. Clinical history
   b. Physical examination
   c. Electromyography
   d. Polysomnography
   e. Suggested immobilization test

3. Which one of the following pharmacologic agents is most likely to cause daytime augmentation of restless legs?
   a. Clonazepam
   b. Clonidine
   c. Codeine
   d. Levodopa
   e. Pergolide

4. Which one of the following statements is true regarding treatment of restless legs syndrome?
   a. Levodopa should be administered with food
   b. Levodopa should initially be prescribed three times a day
   c. Risk of levodopa-induced dyskinesias is high
   d. Pergolide therapy may cause insomnia and nasal stuffiness
   e. Clonidine therapy is remarkably free of side effects

5. Which one of the following statements is true of periodic limb movements of sleep?
   a. They are commoner in the third than in the seventh decade of life
   b. They are most likely generated by the cerebral cortex
   c. They are usually of little clinical consequence in the absence of restless legs syndrome
   d. They occur at a frequency of approximately one every 1 to 2 minutes
   e. They occur in 20% of patients with restless legs syndrome

Correct answers: 1. c, 2. a, 3. d, 4. d, 5. e