Restless legs syndrome and periodic limb movement disorder

Anil N. Rama, MD, MPH\textsuperscript{a,\,*}
Clete A. Kushida, MD, PhD\textsuperscript{b}

\textsuperscript{a}Department of Neurology, The Permanente Medical Group, 273 Hospital Parkway, Suite 800, San Jose, CA 95119, USA
\textsuperscript{b}Stanford University Center of Excellence for Sleep Disorders, 401 Quarry Road, Suite 3301, Stanford, CA 94305–5730, USA

Restless legs syndrome (RLS) is a common neurologic condition characterized by unpleasant sensations deep inside the legs, occurring at rest, especially at bedtime. The paresthesias are accompanied by an irresistible urge to move the limb, which results in a temporary relief of the symptoms. In virtually all patients with RLS, periodic limb movements of sleep are observed. These are stereotyped, periodic, jerking movements typically consisting of flexion of the ankle, knee, and hip. Periodic limb movements of sleep are sometimes accompanied by an awakening resulting in sleep fragmentation and subsequent excessive daytime sleepiness, although this is controversial. Dopamine agonists are now considered the treatment of choice for RLS and periodic limb movement disorder (PLMD). This article reviews the clinical features, epidemiology, hereditary transmission, pathophysiology, management, and treatment strategies for both disorders.

Clinical features

Restless legs syndrome

The International Restless Legs Syndrome Study Group met in 2002 to formulate the new diagnostic criteria for RLS. The diagnostic criteria for RLS are as follow: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and

\* Corresponding author.

\textit{E-mail address: anil_rama@yahoo.com (A.N. Rama).}
sometimes the arms or other body parts are involved in addition to the legs); (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and (4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present) [1].

Patients with RLS often have difficulty describing their sensory symptoms. The sensory symptoms are usually unpleasant but not painful. Common descriptions of RLS symptoms include creeping, crawling, tingling, cramping, pulling, pain, electric, tension, itching, stinging, nervousness, growing pains, and burning. The symptoms are described as affecting the depth of the extremity as opposed to affecting the superficial skin. Most patients describe these symptoms between the ankle and knees, although the entire leg and arms can be involved [2]. Furthermore, the paresthesias and dysesthesias may be bilateral or unilateral. Volitional movements, such as walking, stretching, or shaking their legs, attenuates the sensory symptoms in most patients.

Restless legs syndrome can occur in either the idiopathic form or the secondary form [3]. The secondary form of RLS is associated with a variety of conditions but is more commonly seen with uremia, iron deficiency, polyneuropathy, pregnancy, fibromyalgia, rheumatoid arthritis, Sjögren’s syndrome, radiculopathy, cobalamin deficiency, folate deficiency, and attention-deficit hyperactivity disorder [4–13].

**Periodic limb movement disorder**

Periodic limb movement disorder is a disorder characterized by limb movements while asleep that may result in a complaint of insomnia and excessive daytime sleepiness. Periodic limb movements affecting the lower extremities can be described as intermittent extensions of the big toe and dorsiflexion of the ankle with occasional flexion of the knee and hip [14]. The movements are often bilateral but may predominate in one leg or alternate between legs [15]. Periodic limb movements may affect the upper extremity and manifest as intermittent flexion at the elbow. Periodic limb movements of sleep are predominant in the first half of the night and show a typical pattern of progressive decline through the course of the night [16].

Although RLS is a clinical diagnosis made by the characteristic symptoms of the disorder, the diagnosis of PLMD is made by polysomnography using electromyography recordings from the tibialis anterior muscles. Movements are counted if they last 0.5 to 5 seconds and occur in a series of four or more at intervals of 5 to 90 seconds. The electromyography amplitude of the nocturnal limb movements must be 25% or more of the baseline electromyography amplitude while awake [17].
The severity of PLMD is determined by the periodic limb movement index, which equals the number of periodic limb movements per hour of sleep. The periodic limb movement arousal index is the number of periodic limb movements associated with electroencephalographic arousals per hour of sleep. Mild PLMD is defined as 5 to 25 periodic limb movements per hour of sleep, moderate as 25 to 50 periodic limb movements per hour of sleep, and severe as greater than 50 periodic limb movements per hour of sleep or greater than 25 periodic limb movements associated with arousals per hour of sleep [18].

When symptoms of insomnia and excessive daytime sleepiness exist, the diagnosis of idiopathic PLMD can be made if no other medical, psychiatric, or sleep disorders can be found to account for these symptoms. PLMD may also occur in association with medications or a variety of other conditions, such as narcolepsy and obstructive sleep apnea [19,20].

Since the designation of PLMD as a distinct sleep disorder, issues have arisen concerning the validity of this nosology. It has been recently suggested that there is no significant association between periodic limb movements and either objective or symptomatic reports of insomnia or daytime sleepiness [21–23]. Furthermore, periodic limb movements are rarely diagnosed in patients under the age of 30 but are found in 44% of subjects aged 65 and older [24]. The common finding of PLMD in the elderly has cast doubt to the validity of PLMD as a true sleep disorder [25].

Differential diagnosis

Anxiety disorders often involve motor activity but evidence of sympathetic activity, such as sweating and palpitations, also are present. Akathisia is an inner sense of restlessness accompanied by a desire to move, but this is usually found in association with neuroleptic usage. "Vesper’s curse" is a transient lumbar stenosis caused by venous plexus engorgement from increased right atrial filling pressure while lying down, resulting in lower-extremity paresthesias and lumbosacral pain that arouses the patient from sleep [26].

Attention-deficit hyperactivity disorder children have high levels of nocturnal activity [27]. Furthermore, the sleep disruption of PLMD and motor activity of RLS while awake could contribute to the inattentiveness and hyperactivity seen in children with attention-deficit hyperactivity disorder [28].

Periodic limb movements of sleep must be distinguished clearly from upper airway resistance syndrome [29,30]. With technologic advancements in polysomnographic and respiratory monitoring, it is now recognized that periodic limb movements of sleep may be triggered by subclinical hypopneas or respiratory effort-related arousals and improve after nasal continuous positive airway pressure is administered.
Nocturnal epilepsy can manifest as localized or generalized tonic-clonic activity. Enuresis and postictal confusion may accompany seizures but not PLMD.

Nocturnal leg cramps are painful spasms of the calf or foot that may occur with increased frequency in pregnancy, women, elderly, after intense exercise, diabetes, fluid and electrolyte imbalances, and musculoskeletal disorders. Nocturnal paroxysmal dystonia is a disorder characterized by stereotypic dystonic movements that can follow sudden awakenings from non-rapid eye movement sleep.

Rapid eye movement sleep behavior disorder occurs when rapid eye movement sleep-related muscle atonia is lost. Body movements ranging from simple motions to highly elaborate enactment of dreams may occur and typically begin 90 minutes following sleep onset.

Rhythmic movement disorder typically affects young children and is characterized by repetitive, stereotypic, rhythmic movements (e.g., head banging, head rolling, body rolling, and body rocking) that precede sleep onset and continue transiently into early light sleep. Sleep starts are brief asymmetric contractions of the extremities at sleep onset that can be accompanied by a feeling of falling.

Epidemiology

Restless legs syndrome is a common neurologic disorder with a prevalence of approximately 1% to 10% in different ethnic populations [31,32]. The prevalence of RLS significantly increases with age [33]. RLS starts at a mean age of 27.2 years and before age 20 years in 38.3% of patients [34]. Approximately 70% to 90% of patients with RLS have periodic limb movements of sleep on polysomnography studies and approximately one third of those with periodic limb movements of sleep have RLS [35].

Hereditary characteristics

Restless legs syndrome can occur with an autosomal-dominant mode of inheritance [36,37]. It has been reported 92% of individuals with the idiopathic form have a family history of RLS, whereas only 13% of individuals with secondary RLS have a family history of RLS. In a study of monozygotic twins, 10 of 12 twin pairs were concordant for RLS symptoms. Despite the high concordance rate, however, the disease severity, age at onset, and symptom descriptions often varied between twins [38].

Pathophysiology

The pathophysiology of RLS and periodic limb movements is unknown. Pharmacologic evidence of RLS being highly responsive to dopaminergic
agents suggests an underlying defect in dopaminergic function. Positron emission tomography and single-photon emission CT evidence suggests that decreased D-2 receptor binding and a mild nigrostriatal presynaptic dopaminergic hypofunction may cause the disorders [39,40]. Furthermore, the symptoms of RLS and periodic limb movements are worse during the night, a time when the circadian levels of dopamine are at their lowest [41,42].

Reduced ferritin and elevated transferrin levels found in the cerebrospinal fluid are indicative of low brain iron in patients with idiopathic RLS [43]. MRI of brain iron found decreased iron concentrations in the substantia nigra and somewhat less significantly in the putamen of RLS patients [44]. Neuropathologic specimens of RLS patients were found to have markedly decreased iron staining and H-ferritin staining in the substantia nigra [45].

Hypocretin-1 levels were increased in evening cerebrospinal fluid samples from RLS patients. This indicates an altered hypocretin mechanism is also involved in this sleep disorder [46].

High-resolution functional MRI indicates that cerebellar and thalamic activation is associated with the sensory leg discomfort of RLS. Additional activation of the red nucleus and brainstem is involved in the generation of periodic limb movements [47].

Management

Investigate and treat secondary causes

Serology for iron, ferritin, folate, cobalamin, urea, and creatinine should be obtained. Patients with a history of iron deficiency should undergo a thorough evaluation for an etiology. Serum transferrin saturation and ferritin levels should be measured before initiation of iron therapy. Furthermore, patients who have histories suggestive of hemochromatosis or iron overload or elevated pretreatment transferrin saturation or serum ferritin levels should under evaluation to determine the cause of these abnormalities before they are treated with iron. In all persons with RLS treated with oral iron, serum iron parameters should be remeasured once or twice yearly during therapy [48].

Additional serology for serum protein electrophoresis, antinuclear antibody, rheumatoid factor, thyroid-stimulating hormone, liver function tests, and hemoglobin A1c should be considered if a peripheral neuropathy is suspected either as an associated condition or as a differential diagnosis. Electrodiagnostic testing with nerve conduction studies and electromyography are useful to detect subtle peripheral neuropathies. A complete connective tissue disorder work-up should be conducted if clinically indicated [49]. A polysomnogram with esophageal pressure monitoring is warranted if other sleep disorders, such as upper airway resistance syndrome, are suspected.
Lifestyle modification

Sleep hygiene

Conservative treatment begins by instituting proper sleep hygiene [50]. Adhering to fixed bedtimes and wake times, obtaining adequate amount of sleep, and establishing proper nutritional intake are important [51].

Avoid exacerbating factors

Alcohol intake may aggravate RLS symptoms and periodic limb movements and should be avoided [52]. Caffeine increases nervous system arousal and heightens the toxic sensory experience of RLS [53]. Antidepressant medications, such as fluoxetine, paroxetine (Paxil), sertraline (Zoloft), mirtazapine (Remeron), and mianserin, have been reported to worsen RLS and PLMD [54–59]. Neuroleptics, such as olanzapine (Zyprexa) and risperidone (Risperdal), can also induce RLS [60,61]. Other medications, such as β-blockers, phenytoin (Dilantin), zonisamide (Zonegran), methosuximide, and lithium, have been reported to worsen RLS symptoms [62–65]. Stress, shift work, and engaging in strenuous physical activity close to bedtime may exacerbate RLS and PLMD [66]. There are conflicting results regarding tobacco smoking in terms of worsening RLS and periodic limb movements of sleep [67,68].

Pharmacologic agents

Iron therapy

Iron deficiency has been associated with the induction or perpetuation of RLS [69]. RLS patients have fewer symptoms if they have ferritin levels greater than 50 μg/L [70].

Nonergotamine dopamine agonists

Pramipexole (Mirapex) has been shown dramatically to reduce the sensory discomfort of RLS and frequency of periodic limb movements of sleep [71]. The optimal dosage may range from 0.25 to 0.75 mg at bedtime. A single dose at bedtime seems to have lasting effects throughout the night and following day. Furthermore, the therapeutic effect was intact 7.8 months after initiation of treatment [72].

Ropinirole (Requip) has been shown to reduce the sensory discomfort of RLS [73,74]. Furthermore, ropinirole given at a dose of 0.5 mg at bedtime dramatically reduced the number of periodic limb movements of sleep and the arousals caused by periodic limb movements [75]. The benefits of ropinirole seem to remain intact 12 months after initial treatment [76].
Ergotamine dopamine agonists

Pergolide (Permax) when given at a mean dosage of 0.51 mg 2 hours before bedtime resulted in a reduction in periodic limb movements and symptoms of RLS and an increase in total sleep time [77]. Pergolide has also been demonstrated to be superior to levodopa with long-term follow-up demonstrating that efficacy persists after an average of 517 days [78,79]. These results suggest that augmentation may not be as a significant problem with pergolide as it is with levodopa [80]. The starting dose of pergolide is 0.05 mg at bedtime.

Bromocryptine (Parlodel), 7.5 mg at bedtime, has been demonstrated to produce a subjective improvement in restlessness and paresthesias and reduce the number of periodic limb movements of sleep and improve sleep efficiency [81]. The usual starting dose is 1.25 mg at bedtime.

Cabergoline at a mean dosage of 2.1 mg and a range from 1 to 4 mg was found to be effective and well tolerated in RLS, especially in patients with severe RLS and those who developed augmentation under levodopa therapy [82].

Levodopa

Levodopa is administered with a peripheral decarboxylase inhibitor usually in the form of carbidopa. One to two tablets of Sinemet 25/100 (carbidopa-levodopa) can be taken 1 to 2 hours before bedtime effectively to reduce symptoms of RLS and periodic limb movements [83]. Once-a-night bedtime treatment with carbidopa-levodopa has been reported, however, to result in morning end-of-dose rebound increases in periodic limb movements in about 25% of patients [84]. A controlled-release formulation termed Sinemet CR 50/200 (carbidopa-levodopa) can be given if this problem develops or if the patient's symptoms occur later in the night. A combination of regular-release levodopa and sustained-release levodopa may be ideal to reduce restless legs symptoms and periodic limb movements and improve sleep quality [85,86].

Levodopa has been demonstrated to be an efficacious treatment for RLS and periodic limb movements of sleep. Chronic treatment with levodopa, however, especially at doses of levodopa greater than 200 mg, usually results in augmentation of restless legs symptoms and periodic limb movements. Augmentation is defined as the symptoms of RLS developing earlier in the day (eg, morning or afternoon versus evening) and being more severe than the symptoms that occurred before treatment with levodopa was started. The temptation to increase the dosage of levodopa to overcome augmentation should be avoided because increasing the dosage only further exacerbates the problem. A medication change is required for 13% to 70% of patients and the best option is to switch to dopamine-agonist therapy [87,88].
Benzodiazepines

Clonazepam (Klonopin, Clonapam, Rivotril) has shown conflicting results in the treatment of RLS and periodic limb movements of sleep. One small clinical trial found clonazepam was ineffective in the treatment of RLS [89]. Another small clinical trial found clonazepam did not significantly reduce the number of periodic limb movements of sleep but did improve the sleep of those individuals with insomnia [90]. Other studies, however, including two small double-blind studies, have demonstrated that clonazepam effectively reduces the sensory discomfort of RLS and number of periodic limb movements of sleep [91–93]. The dosage of clonazepam ranges from 0.5 to 2 mg at bedtime.

Temazepam (Restoril) at a dose of 30 mg at bedtime effectively treated the insomnia associated with periodic limb movements of sleep but did not reduce the number of nocturnal myoclonic events [94]. Triazolam (Halcion) at a dose of 0.25 or 0.50 mg is effective in diminishing daytime sleepiness and in improving sleep continuity and duration in patients with periodic limb movements of sleep. Interestingly, although the frequency of periodic limb movements was unchanged, the frequency of associated arousals decreased after treatment [95]. Alprazolam (Xanax) has also been suggested possibly to control the symptoms of RLS [96].

Adrenergic agonists

Clonidine (Catapres) at a mean dosage of 0.05 mg per day has been shown to reduce the sensory symptoms of RLS but not the number of periodic limb movements of sleep. Clonidine may be an effective treatment for RLS patients who do not have a large number of periodic limb movements [97].

Antiepileptic drugs

Gabapentin (Neurontin) improves the sensory and motor symptoms in RLS and also improves sleep architecture and reduces the number of periodic limb movements of sleep [98,99]. In a head-to-head study of gabapentin versus ropinirole, both drugs were similarly effective in the treatment of RLS and periodic limb movements of sleep [100]. The starting dose of gabapentin was 300 mg at bedtime with a mean dose of 800 mg and range of 300 to 1200 mg.

Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Atrelot, Epitol) has been shown to be effective in treatment of the sensory discomfort of RLS [101,102]. Treatment with carbamazepine, however, does not modify the pattern of nocturnal myoclonus and its relationship to arousal during sleep [103].
Opioids

Oxycodone (Roxicodone, OxyContin, Percolone, OxyIR, OxyFAST, Endocodone, Supeudol) at an average dose of 15.9 mg subjectively reduces leg sensations and motor restlessness and improves daytime alertness. Furthermore, oxycodone significantly reduces the number of periodic limb movements and arousals during sleep [104]. When naloxone is given parentally to patients treated with opioids for RLS and periodic limb movements of sleep, their signs and symptoms of RLS and periodic limb movements reappeared [105]. Long-term effectiveness ranging from 1 to 23 years has been documented in patients taking opioids for the treatment of RLS and periodic limb movements of sleep [106].

N-methyl-D-aspartate antagonists

Amantadine (Symmetrel, Endantadine) started at 100 mg per day and increased to a maximum of 300 mg per day resulted in subjective improvement of RLS in 52% of patients. The mean effective dose was 227 mg per day [107]. Oral ketamine has also been used to treat RLS [108].

Other medications

Buproprion (Wellbutrin) is not associated with antidepressant-induced PLMD. In contrast, treatment with buproprion is associated with a reduction in the objective measures of PLMD [109]. Consequently, buproprion may be appropriate for patients with depression and PLMD.

Folate may ameliorate the symptoms of RLS in patients with acquired folate deficiency and those with familial symptomatology [110].

Tramadol (Ultram) is a central analgesic that has fewer side effects and a lower abuse potential than opioids. Tramadol given at a dose range of 50 to 150 mg per day for 15 to 24 months resulted in clear amelioration of symptoms in 10 of 12 patients. No major tolerance against treatment effect emerged among those who needed only a single evening dose [111].

Selegiline (Eldepryl, Endantadine) has been shown to decrease the number of periodic limb movements of sleep. The alerting effect associated with the medication did not have a significant effect on sleep efficiency or sleep-onset latency [112].

Entacapone (Comptan) is a catechol O-methyltransferase inhibitor that increases the duration of action of carbidopa-levodopa. When given in conjunction with carbidopa-levodopa, it resulted in longer periods of symptomatic relief in a patient with RLS [113].

Special cases

Kidney transplantation in uremic patients has been reported successfully to treat RLS [114]. An intrathecal pump delivering morphine and bupivacaine resulted in resolution of RLS symptoms in two patients [115].
Summary

Restless legs syndrome and PLMD are common neurologic entities that may be associated with insomnia and excessive daytime sleepiness. Considerable research has been directed toward elucidating the basic mechanisms and optimizing the management of RLS and PLMD. The goal of future research should be directed toward the application of the fundamental principles learned in the laboratory to the clinical setting.

References


