Middle East Journal of Family Medicine

Restless Legs Syndrome and Periodic Limb Movements in Sleep: a review for family physicians

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INTRODUCTION

Restless legs syndrome (RLS) is a common condition with prevalence between 1% and 15%, and with complex symptoms principally including discomfort sensations deep inside the legs (or arms) that occur at rest and are worse at bedtime. These paresthesias are accompanied by an irresistible urge to move the limbs, which results in a temporary relief of symptoms. Periodic limb movements of sleep (PLMS) occur in 80% of patients with RLS. PLMS are periodic, repetitive, jerking movements typically consisting of flexion of the big toe, ankle, and less often the knee, hip, or arm. These are sometimes associated with cortical arousals resulting in sleep fragmentation and subsequent excessive daytime sleepiness.

CLINICAL FEATURES OF RLS & PLMS

Common descriptions used by patients with RLS to describe the paresthesia and dysesthesia that affect the depth of the extremity include "creeping, crawling, tingling, cramping, burning, tension, stabbing, growing pains, and itching[1]." The majority of patients describe these symptoms occurring predominantly between the ankle and knee, although the entire leg, as well as the arms[2], can be involved. RLS symptoms are usually bilateral, but can be unilateral. Walking, stretching, or shaking the legs will relieve the sensory symptoms for most patients.

Symptoms characteristically worsen at the end of the day.[3] The circadian temperature cycle has been suggested to play a role in the pathogenesis of RLS as the symptoms worsen with the falling of body temperature early at night, and improve with rising body temperature in the morning.[4] The majority of patients with RLS complain of difficulty with falling asleep and as many as two-thirds report nocturnal awakenings.[5] RLS tends to get worse with age, pregnancy, fatigue, very warm weather, or prolonged cold exposure.[6-7]

RLS can occur in either a primary (idiopathic) or secondary form.[1] 76% of RLS patients suffer from the idiopathic form while 24% of cases are secondary to other disorders.[8] Secondary RLS is associated with a variety of conditions such as uremia, iron deficiency, polyneuropathy, pregnancy, fibromyalgia, rheumatoid arthritis, Sjögren's syndrome, radiculopathy, cobalamin deficiency, folate deficiency, and attention deficit hyperactivity disorder.[9-18] Besides these medical conditions, many drugs may induce or exacerbate RLS or PLMS. These include dopamine D_2 receptor blocking agents,[19] lithium carbonate,[20-21] caffeine,[22] tricyclic antidepressants,[23] and selective serotonin reuptake inhibitors.[24]

PERIODIC LIMB MOVEMENTS OF SLEEP (PLMS)

PLMS are associated features in up to 80% of RLS patients.[5] These are repetitive limb movements that occur every 5 to 90 seconds during NREM sleep, at times causing sleep disruption and a complaint of insomnia or excessive daytime sleepiness. PLMS affecting the lower limbs are described as intermittent extension of the big toe and dorsiflexion of the ankle with occasional flexion of the knee and hip.[25] PLMS predominantly occur early in the night, improving through the rest of the night.[26] Polysomnography using surface electromyography (EMG) recordings from the tibialis anterior muscles is the diagnostic method of choice. The movements are diagnostic if they last 0.5 to 5 seconds, occur in a series of 4 or more within 5 to 90 seconds. The EMG amplitude of the nocturnal limb movements must reach 25% or more above the baseline tonic EMG amplitude of the limbs while awake.[27] Severity is determined by the periodic limb movement of sleep index (PLMI), which is the number of periodic limb movements per hour of sleep or the periodic limb movement arousal index (PLMAI), which is the number of PLMS associated with electroencephalographic arousals per hour of sleep. Mild PLMS is defined as PLMI of 5 to 25 / hour; moderate as PLMI of 25 to 50 / hour; and severe as either a PLMI over 50 / hour or a PLMAI more than 25 / hour.[28] Controversies exist as to whether PLMS in the absence of RLS are a true sleep disorder or simply part of the aging process given that PLMS are rare before the age of 30 but are found in 44% of people aged 65 and older,[29] coupled with the fact that there is a lack of significant association between PLMS and either objective or symptomatic reports of insomnia or daytime sleepiness.[30-32]

EPIDEMIOLOGY

In a Canadian population-based questionnaire survey of 2019 unrelated subjects, Lavigne and Montplaisir estimated the prevalence of RLS to be 10% to 15%. There was no gender predominance and a considerable tendency to underdiagnose RLS was noted.[33] Another study of 2099 US primary care patients found that 24% experienced RLS symptoms and 15.3% noted these symptoms at least weekly. Symptoms of RLS were reported significantly more often by women than men.[34] The prevalence of RLS significantly increases with age.[35,36] The mean age of onset of RLS is 27.2 years, but in 38.3% of patients, the onset is before age 20.[5] Another large study involved 18,980 people chosen via random selection of telephone numbers after geographical stratification with a household member selected by age and sex. The study was conducted in five European countries (United Kingdom, Germany, Italy, Portugal, and Spain) in

the mid-1990s. The survey found 1 person in 25 had PLMS, about 1 in 20 RLS, 1 in 15 had either, and an unlucky 1 in 100 had both. PLMS was constant across ages, but RLS increased with age. .[36]

A positive family history is found in the majority (92%) of those with idiopathic RLS, whereas only 13% of individuals with secondary RLS have a family history of RLS.[1] An autosomal dominant mode of inheritance has been suggested for RLS.[37,38]

PATHOPHYSIOLOGY

The pathophysiologic basis of the sensory symptoms is unknown, but recent studies have started to explore this very complex problem. Nigrostriatal presynaptic dopaminergic hypofunction has been suggested as an underlying cause of the disorder.[39,40] Reduced ferritin and elevated transferrin levels in the cerebrospinal fluid (CSF) and in the substantia nigra have been noted.[41-43] Magnetic resonance imaging (MRI) and electrophysiological studies have not shown any structural abnormalities of the brainstem or cervical spinal cord in those with RLS.[44] Interestingly, functional MRI scanning in patients with RLS demonstrates thalamic and cerebellar activation during the abnormal sensations and additional activation in the brainstem and red nuclei during movement.[45]

DIAGNOSTIC CRITERIA FOR RLS

The International Restless Legs Syndrome Study Group (IRLSSG) have developed Essential diagnostic criteria (Table 1), Supportive features (Table 2), and Associates features (Table 3) for RLS in adults.[46] They have also developed an Essential diagnostic criteria (Table 4), and supportive or suggestive criteria (Table 5) for cognitively impaired elderly given the limited data in this age group.[46]

The IRLSSG has also developed a rating scale to assess severity of RLS symptoms (Table 6).[47] It consists of 10-questions where the patient must rate his or her symptoms on a scale of 0 to 4, with 0 representing "none" and 4 representing "very severe."

Polysomnography is necessary to diagnose and assess the severity of PLMS without RLS. Actigraphy has not been established yet as a reliable tool in assessing PLMS.

MANAGEMENT

Investigation of Secondary Causes

Serum ferritin, red blood cell folate, serum cobalamin (Vit B12), urea, glucose (hemoglobin A1C in established diabetics), and creatinine levels should be obtained. Further work up is indicated if abnormalities are found in these blood tests. Rheumatologic serologies should be done if clinically indicated.[48] Nerve conduction studies and EMG may uncover a subtle underlying peripheral neuropathy. A polysomnogram with or without a "Multiple Sleep Latency Test" (MSLT) is warranted only if either isolated disruptive PLMS or another sleep disorder (such as sleep apnoea or narcolepsy) are suspected.

Nonpharmacologic Treatment

Lifestyle modification is an important aspect of RLS/PLM management. Maintaining sleep hygiene using a scheduled bedtime and wake time, sufficient sleep hours, avoidance of daytime naps, proper nutrition, and avoiding heavy meals prior to bedtime. [49,50,51] Alcohol intake and caffeine may both aggravate RLS and PLMS and should be avoided.[52,53] Various antidepressant medications have been reported to induce or worsen RLS and/or PLMS, such as fluoxetine, paroxetine, sertraline, mirtazapine, and mianserin.[54-59] Neuroleptics such as olanzapine and risperidone can also induce RLS.[60,61] Other medications, such as beta-blockers, phenytoin, zonisamide, methsuximide, and lithium, have also been reported to worsen RLS symptoms.[62-65] Stress, shift work, and strenuous physical activity close to bedtime may also exacerbate RLS and/or PLMS.[36] The effect of tobacco smoking on symptoms of RLS and PLMS is conflicting, but smoking cessation is clearly warranted for overall health.[66,67]

Pharmacologic Treatment

The patient and the treating physician need to understand that medications are for symptom relief not cure. Any secondary cause of RLS/PLMS needs to be treated first. Specific pharmacological treatment of RLS/PLMS must take into account the patient's general condition, age, comorbidities, the severity of RLS/PLMS, and the frequency of symptoms. The goal is to relieve the majority of symptoms with the lowest effective dose of any drug being used. Monotherapy using dopaminergic agents, benzodiazepines, or opiates should be tried first before considering combination therapy. If treatment fails after an initial success, drug holidays (weekends or up to 2 weeks), or a rotating schedule of effective agents may be helpful. There is no published data to support such an approach. Given the potential loss of efficacy with chronic treatment and a risk of recurrence occurring at any time, treating physicians should attempt to reduce drug therapy whenever long lasting remission is achieved. Particular vigilance is required for either an *AUGMENTATION* effect or *REBOUND* effect of medications. Augmentation refers to either an increase in symptom severity, involvement of other limbs, or an advancing progression of symptoms into the day. Rebound refers to the wearing off of drug effect, typically in the early morning hours. The strategies to overcome these problems are quite different (Table 7).

Dopamine Agonists

Dopamine agonists are commonly used with good results in RLS and are presently considered to be the drugs of choice. Doses are slowly titrated up until a desired clinical response to reduce the side effects of nausea, orthostatic hypotension, dizziness, hallucinations, and vivid dreams.

Nonergotamine Dopamine Agonists

Pramipexole (Mirapex, starting dose of 0.125 mg and increasing by an increment of 0.125mg every few days to a maximum dose of 0.75mg), a new dopamine agonist with additional D_3-receptor agonist properties has been shown in randomized-placebo controlled trials (RCTs) to be an effective therapy for symptom relief of RLS/PLMS with a sustained response up to nearly 8 months.[68,69] Ropinirole (Requip, 0.25-4.0mg) has also been demonstrated in many RCTs to significantly reduce the symptoms of RLS as measured by the IRLS scale,[70-76] reducing the number of PLMS with associated arousals,[77,78] and with a sustained benefit up to 12 months.[79] An unusual side effect of both agents are sudden daytime sleep episodes in Parkinson's disease patients that have resulted in motor vehicle accidents.[80]

Ergotamine Dopamine Agonists

Pergolide (Permax, starting dose of 0.05mg and increasing by 0.05mg every few days until 0.25mg is reached, then increasing by an increment of 0.125mg, mean dose of effect 0.51mg), in a randomized controlled trial, resulted in a reduction in PLMS and symptoms of RLS as well as an increase in total sleep time.[81] It was superior to levodopa with less augmentation effect, and sustained efficacy after an average of 17 months.[82-84] Bromocriptine (starting dose of 1.25mg up to 7.5mg),[85] and Cabergoline (1-4mg),[86] were also shown to be effective in relieving symptoms of RLS/PLMS. Cabergoline was also shown to be efficacious in those patients who develop augmentation with levodopa therapy.[86]

Levodopa

One to two tablets of carbidopa/levodopa (Sinemet) 25/100 mg can be taken 1 to 2 hours before bedtime to effectively reduce symptoms of RLS and PLMS.[87] Up to 25% of patients develop morning rebound worsening of periodic limb movements.[88] To overcome this effect either a controlled-release formulation of carbidopa/levodopa 50/200 mg can be given, or a combination of regular-release levodopa and sustained-release levodopa may be ideal to reduce RLS symptoms and PLMS as well as to improve sleep quality.[89,90] Chronic treatment with levodopa, especially at doses above 200 mg, usually results in augmentation of RLS symptoms and periodic limb movements. Increasing the dose of levodopa to overcome augmentation should be avoided because increasing the dosage will further exacerbate the problem. A medication change is required for 13% to 70% of patients and the best option is to switch to other dopamine-agonist therapy.[91,92] Levodopa –induced nausea and orthostatic hypotension may be treated with additional Carbidopa 25 to 75mg prior to each dose of Levodopa, or by adding Domperidone, 10 to 30mg three or four times daily, which is a "peripheral" dopamine receptor blocker that cannot cross the blood brain barrier. Other central nervous system side effects, including drowsiness, fatigue, and hallucinations, may improve on reducing the daily dosage of Levodopa. The sudden withdrawal of dopamine should be avoided as this has been associated with potentially fatal neuroleptic malignant syndrome.

Benzodiazepines

It is generally accepted that benzodiazepines are more likely to improve sleep quality rather than the number of PLMS per night. Downsides include their morning drowsiness, addictive potential and that they may worsen sleep apnea. Of the benzodiazepines, triazolam (Halcion) at a dose of 0.25 to 0.50 mg has been found to be effective in diminishing daytime sleepiness with improved sleep continuity and duration in patients with PLMS. Although the frequency of periodic limb movements was unchanged, the frequency of associated arousals declined after treatment.[93] Other benzodiazepines such as clonazepam, temazepam, and alprazolam have shown variable efficacy.[94-100]

Antiepileptic Drugs

In a study comparing gabapentin vs ropinirole, both drugs were similarly effective in the treatment of RLS and PLMS. The starting dose of gabapentin was 300 mg at bedtime, with a mean dose of 800 mg and range of 300 to 1200 mg.[101] It has been shown that Gabapentin improves both the sensory and motor symptoms of patients with RLS and also improves sleep architecture and reduces the number of PLMS.[102,103] Gabapentin may be useful in PLMS patients who also require adjunctive analgesia for chronic pain. Carbamazepine does not modify the pattern of nocturnal myoclonus (PLMS) and it also had a strong placebo effect.[104] In general antiepileptic drugs are not as potent as dopaminergic drugs or opioids..

Opioids

This class of agents has long been known to reduce symptoms of RLS, but patients are reluctant to take these drugs and physicians are reluctant to prescribe them. Usually, milder narcotics are given first. More potent opioids are reserved for those patients refractory to dopaminergic agents and benzodiazepines.

Several double-blind trials have shown benefit, including a study using oxycodone at an average dose of 15.9mg which showed improvement in sleep efficiency and PLMS with fewer arousals.[105] These drugs may be contraindicated in patients with compromised respiratory function.

Other Medications

Clonidine, at a mean dose of 0.05 mg per day, has been shown to be beneficial in reducing the symptoms of RLS patients who do not have severe PLMS as it did not reduce the number of PLMS in clinical trials.[106]

Patients with RLS have been noted to have fewer symptoms when their ferritin levels are higher than 50 mcg/L,[107] thus oral iron therapy has been suggested as a treatment. Iron indices need to be measured before initiating iron supplements and while on therapy to avoid iron overload. More evidence is needed with regards to such maintenance therapy.

Treatment with bupropion has been found to reduce the objective measures of PLMS,[108] consequently bupropion may be appropriate for patients with depression and PLMS.

Tramadol is a centrally acting analgesic that has fewer side effects and a lower abuse potential than opioids. Tramadol given at a dose ranging from 50 to 150 mg per day for 15 to 24 months resulted in clear amelioration of symptoms in 10 of 12 PLMS patients,[109] with no major tolerance to the treatment effect among those who needed only a single evening dose.

Selegiline, and entacapone (increase the duration of action of carbidopa/levodopa) are also among the drugs that been used in treating RLS/PLMS.[110,111]

Table 1. *International Restless Legs Syndrome Study Group (IRLSSG) Essential Diagnostic Criteria for RLS in adults (all 4 criteria are required).[46]*

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. 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 down 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.
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.

Table 2. *Supportive clinical features of RLS in adults[46]*

Family History

The prevalence of RLS among first-degree relatives of people with RLS is 3 to 5 times greater than in people without RLS.

Response to dopaminergic therapy

Nearly all people with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine-receptor agonist at doses considered to be very low in relation to the traditional doses of these medications used for the treatment of Parkinson disease. This initial response is not, however, universally maintained.

Periodic limb movements (during wakefulness or sleep)

Periodic limb movements in sleep (PLMS) occur in at least 85% of people with RLS; however, PLMS also commonly occur in other disorders and in the elderly. In children, PLMS are much less common than in adults.

Table 3. *Associated features of RLS in adults[46]*

<u>Natural clinical course</u>

The clinical course of the disorder varies considerably, but certain patterns have been identified that may be helpful to the experienced clinician. When the age of onset of RLS symptoms is less than 50 years, the onset is often more insidious; when the age of onset is greater than 50 years, the symptoms often occur more abruptly and more severely. In some patients, RLS can be intermittent and may spontaneously remit for many years.

Sleep disturbance

Disturbed sleep is a common major morbidity for RLS and deserves special consideration in planning treatment. This morbidity is often the primary reason the patient seeks medical attention.

Medical evaluation/physical examination

The physical examination is generally normal and does not contribute to the diagnosis except for those conditions that may be comorbid or secondary causes of RLS. Iron status, in particular, should be evaluated because decreased iron stores are a significant potential risk factor that can be treated. The presence of peripheral neuropathy and radiculopathy should also be determined because these conditions have a possible, although uncertain, association and may require different treatment.

Table 4. *Essential criteria for the diagnosis of probable RLS in the cognitively impaired elderly (all five are necessary for diagnosis).[46]*

1. Signs of leg discomfort such as rubbing or kneading the legs and groaning while holding the lower extremities are present

2. Excessive motor activity in the lower extremities such as pacing, fidgeting, repetitive kicking, tossing and turning in bed, slapping the legs on the mattress, cycling movements of the lower limbs, repetitive foot tapping, rubbing the feet together, and the inability to remain seated are present

3. Signs of leg discomfort are exclusively present or worsen during periods of rest or inactivity

4. Signs of leg discomfort are diminished with activity

Table 5. *Supportive or suggestive criteria for the diagnosis of probable RLS in the cognitively impaired elderly.[46]*

(a) Dopaminergic responsiveness
(b) Patient's past history - as reported by a family member, caregiver, or friend – is suggestive of RLS
(c) A first-degree, biologic relative (sibling, child, or parent) has RLS
(d) Observed periodic limb movements while awake or during sleep
(e) Periodic limb movements of sleep recorded by polysomnography or actigraphy
(f) Significant sleep-onset problems
(g) Better quality sleep in the day than at night
(h) The use of restraints at night (for institutionalized patients)
(i) Low serum ferritin level
(j) End-stage renal disease
(k) Diabetes
(l) Clinical, electromyographic, or nerve-conduction evidence of peripheral neuropathy or radiculopathy

Table 6. *International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale.[47]*

1. Overall, how would you rate the RLS discomfort in your legs or arms?
2. Overall, how would you rate the need to move around because of your RLS symptoms?
3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?

4. Overall, how severe is your sleep disturbance from your RLS symptoms?

5. How severe is your tiredness or sleepiness from your RLS symptoms?

6. Overall, how severe is your RLS as a whole?

7. How often (days/week) do you get RLS symptoms?

8. When you have RLS symptoms how severe (number of hours) are they on an average day?

9. Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs?

10. How severe is your mood disturbance from your RLS symptoms?

Table 7. *Characteristics and Treatment Strategies for Augmentation and Rebound*

	Characteristics	*Treatment*
Rebound	-Wearing off of drug effect, typically in the morning.	-Adding a middle-of-the-night dose. –Switching to a dopamine agonist with a longer half-life or controlled-release levodopa. –Using a combination of regular-release and controlled-release levodopa.
Augmentation	-Increase in symptom severity and involvement of other limbs. -Symptoms undergo time shift from bedtime to early evening to daytime.	-Reducing the dose of the provocative medication. –Switching to an alternate dopaminergic medication with a longer half-life or to a different class of medication (opioid or anticonvulsant). –Using a drug combination with a lower dopaminergic dose.

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