



A Review of the Identification and Treatment of Restless Leg Syndrome

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Abstract

Restless Leg Syndrome (RLS) is a sensorimotor neurologic and sleep-wake disorder that is commonly associated with involuntary, jerking movements of the legs during sleep which causes to significant sleep disturbances. The accurate diagnosis and treatment of RLS would lead to restful sleep restoration and subsequently result in improved quality of life of patients suffering from this disabling condition. This article will review the diagnosis and differential diagnosis of RLS and summarize its various available treatment interventions.

Keywords: Restless Leg Syndrome; Sleep-Wake Disorder; Review; Diagnosis; Treatment

Introduction

Restless legs syndrome (RLS) is a disorder that is associated with an overwhelming urge to move the legs, due to unpleasant sensations. that feel like pins and needles. Other uncomfortable sensations include crawling, tingling, burning, or itching. The urge to move the legs is typically worse at rest and especially in the evening or at night than during the day and usually relieved by movement. RLS is commonly associated with sleep -wake disturbances and with involuntary, jerking movements of the legs during sleep, known as periodic leg movements in sleep (PLMS). When significant sleep disturbances or impaired daytime functioning coexist with PLMS in the absence of RLS or other associated disorders, the term periodic limb movement disorder (PLMD) is then used [1]. RLS need to be accurately diagnosed prior to treatment initiation, since other medical and psychiatric disorders could mimic its

clinical presentation. The characteristics of PLMD are illustrated in table 1.

- The condition is characterized by behavior ranging from shallow, continual movement of the ankle or toes, to wild and strenuous kicking and flailing of the legs and arms.
- Furthermore, abdominal, oral, and nasal movement sometimes accompanies PLMD.
- Movement of the legs is more typical than movement of the arms in cases of PLMD.
- Movements typically occur for 0.5 to 10 seconds, in intervals separated by five to 90 seconds.
- A formal diagnosis of nocturnal myoclonus requires three periods during the night, lasting from a few minutes to an hour or more, each containing at least 30 movements followed by partial arousal or awakening. (ASDC 1979)
- These limb movements usually occur in deep stage two sleep, but often cause arousal.

Table 1: Periodic Limb Movement Disorder Characteristics (PLMD).

Historical background

Historically RLS was known as Willis-Ekbom disease and was initially described by Sir Thomas Willis in 1685 [2]. It was later brilliantly elucidated by Karl-Axel Ekbom in 1945 [3]. Ekbom himself estimated a prevalence of 5% to 10% of the Scandinavian population. However, subsequent authors have suggested that as many as 29% of the population may have RLS [4].

Diagnosing RLS

The diagnosis of RLS is primarily clinical and should be focused on obtaining a detailed history and a thorough physical examination. The history would identify the severity of symptoms; prior treatments for RLS; current medications; family history of RLS; and the use of substances including caffeine, alcohol, tobacco, illicit or recreational drugs. Although laboratory analysis is not necessary for the diagnosis, it can help in excluding other causes of RLS. Initial laboratory tests include a basic metabolic panel and checking Iron, ferritin levels and transferrin saturation, to measure the body's iron stores, since iron stores could be low in some individuals with RLS. Additional testing may be required including a sleep study to explore other medical or neurological conditions that could contribute to the worsening of the sleep difficulties that are associated with RLS.

The accurate diagnosis of RLS is based on the criteria that are proposed by the International Restless Legs Syndrome Study Group (IRLSSG) [5], which include:

- An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
- The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
- The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least if the activity continues.
- The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
- The occurrence of the above features is not solely accounted for as symptoms primarily due to another medical or behavioral condition.

According to Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM -5) [6], RLS is categorized as a sleep-wake disorder, involving an uncomfortable sensation of tingling, or burning, and a continuous urge to move the legs. It is described as a sensation that starts at the soles of the feet, and creeps up the calves, often starting around bedtime. Individuals affected by RLS usually stomp their feet, shake their legs, stand up, and rub their calves, which provide a temporary relief. The uncomfortable sensation as caricatured in figure 1. These sensations immediately reemerge during resting, which then further disrupt ongoing efforts to resume sleep. In RLS the uncomfortable and irritating sensations are not related to anxiety, or a medical problem, and lead to a delayed onset of sleep, resulting in poorly maintained and non-restorative sleep, with residual daytime fatigue and tiredness affecting daily functioning and productivity.



Figure 1: Caricatured Depiction of RLS.

Patients suffering from RLS have described the disabling effects of their conditions in various terms [7] such as Pain, Burning, Tearing, Throbbing, Creepy-crawly, Ant's crawling, Jittery, The gotta moves, Pulling, Soda bubbling in the veins, Heebie jeebies, Grabbing sensation, Jimmy legs, Elvis legs, Worms moving, Itching bones, Tight feeling, Electric current, Shock-like feelings, Crazy legs and Fidgets. Despite its widespread disabling effects, RLS remains underdiagnosed and undertreated, resulting in substantial impact on the quality of life of patients.

Demographic characteristics

The typical age of onset of RLS is during the 20’s and 30’s, with symptoms worsening with age. Although RLS may occur in children, it is not readily recognized due to difficulty in accurate self-reporting of symptoms by children [6]. It is estimated that RLS could occur in approximately 2% of children [8]. The prevalence of RLS is 2% - 7%, and women are about 1.5 to two times more likely to have RLS than men [6]. It is also estimated that RLS could be roughly affecting 35 million Americans [4]. The risk factors for RLS include the female gender, especially during pregnancy, older age, and family history of RLS. Dysregulation of dopaminergic neurotransmission, specifically in the nigrostriatal and mesolimbic pathways in addition to the serotonergic and glutaminergic systems have been implicated in RLS [9]. Disturbances in iron metabolism have also been identified in some patients with RLS [6].

Impact on functioning

The sleep-wake disturbances that are caused by RLS have adverse consequences such as daytime fatigue, with impaired occupational and educational performance, and in about 50% of patients, anergia and depressed mood occur [6], thus resulting in a marked reduction in quality of life [8]. In addition, RLS could have a negative impact on family and sleep partners by disturbing their sleep as well, leading to increased stress and adverse effects on relationships.

Co-occurring disorders

It is important to assess depression, anxiety disorders, and attention deficit hyperactivity disorder ADHD which are common in patients with RLS [6]. Migraine headache also appears to be present in many patients with RLS and particularly in those with severe migraine [10]. There seem also to be a correlation between RLS and bruxism which is manifested by nocturnal jaw grinding and teeth clenching [11]. In addition to the association between RLS and iron deficiency [6], renal failure, hemodialysis, neuropathy, pregnancy, multiple sclerosis, Parkinson’s disease, and other psychiatric conditions, have also been reported in patients with RLS [12-16]. RLS can be a side effect of medications, especially antipsychotics, antihistaminic, antidepressants, and metoclopramide [17].

Differential diagnosis

Several conditions could mimic RLS and need to be assessed and excluded to reach an accurate diagnosis. These conditions

may include arthritis, peripheral neuropathy, and lower extremity edema, restlessness due to anxiety, leg cramps, positional ischemia with paresthesia and numbness, in addition to awkward positioning of the legs while in bed or sitting [6]. The differential diagnosis of RLS is summarized in table 2 [18].

Conditions	Descriptive Characteristics
Akathisia	This movement disorder is characterized by a subjective feeling of inner restlessness accompanied by mental distress and an inability to sit still. It most prominently affects the legs. The individuals may fidget, rock back and forth, or pace, while some may experience an uneasy feeling within their whole body. In severe cases akathisia may lead to aggression, violence, or suicide. It can be an adverse effect of antipsychotic medication, particularly the typical or first-generation antipsychotics. Other causes may include selective serotonin reuptake inhibitors, metoclopramide, reserpine, Parkinson’s disease, and in some patients with untreated schizophrenia. Akathisia may also occur upon the discontinuation of antipsychotics. It differs from RLS since its symptoms are not worse at night.
Nocturnal leg cramps	Also referred to as “charley horses” are painful and incapacitating muscle cramps, usually lasting an average of nine minutes per episode. The acute episode may be followed by hours of recurrent episodes and residual pain. The posterior calf muscles usually are involved, but cramps of the foot and thigh also are common. Leg cramps may be described as a spasm, tightening, twinge, strain, tetany, swelling, or muscle seizure. Cramps may be isometric or may cause limb movement, such as extreme plantar flexion of the foot.
Peripheral neuropathies	These neurological disorders affect the peripheral nerves throughout the body and could weaken muscles or limit sensation in the arms, hands, legs, or feet. In their most severe manifestations, they could affect walking, breathing, swallowing, and talking. They may be due to trauma, nerve compression, diabetes, nutritional disorders, infections, or other medical conditions. They differ from RLS in the context of causing sensory disturbances; and not typically being relieved by activity and not necessarily occurring during sleep.

Peripheral vascular diseases	<p>Peripheral arterial diseases are the consequences of atherosclerosis in any blood vessel but are more common in the legs or lower extremities than in the arms. Usually manifested by; cramping-type pains that are exacerbated by activity and improve with rest. They differ from RLS regarding their symptoms severity which do not worsen at night.</p>
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Table 2: Differential Diagnosis of Restless Legs Syndrome.

Treatment of RLS

Treatment of associated medical conditions

When the diagnostic work-up reveals RLS to be related to underlying medical conditions, treatment of the condition may improve or resolve the symptoms of RLS. Individuals with iron deficiency even in the absence of anemia who also have RLS may experience a symptomatic relief by iron supplementation if the ferritin level is less than 50 ng per mL (50 mcg per L). Iron is not beneficial in individuals with ferritin above this level. Because RLS is common during pregnancy, particularly during the third trimester, no recommended treatment is advised since it will likely resolve with delivery. Individuals with RLS due to chronic kidney disease who undergo kidney transplant may also experience remission of their symptoms [18].

Prevention of precipitating agents

Medications that could exacerbate RLS include antipsychotics, the antiemetic metoclopramide, the antihistamine diphenhydramine, the selective serotonin reuptake inhibitors and tricyclic antidepressants, and lithium [17-19]. These medications may need to be gradually discontinued and substituted with alternative medications that do not worsen RLS.

Lifestyle modification

Limiting caffeine, tobacco, and alcohol use may improve RLS symptoms [18]. Being physically active, eating healthy diet and preventing weight gain could also provide a relief of RLS symptoms [18,20].

Pursuing mental stimulation activities such as reading and engaging in hobbies during non-RLS times of the day such as the morning, and scheduling housework during RLS-prone times such as the afternoon or evening in addition to delaying sleep times and

rise times so that sleep no longer coincides with RLS-prone periods of the night could also benefits some patients [21].

Non-pharmacological interventions

- Lower body resistance and aerobic exercise could decrease RLS severity [22].
- A vibratory counter stimulation device that is approved by the FDA could decrease symptoms intensity in 50% of patients [23].
- Implementing sleep hygiene principles, massage, acupuncture, hot or cold baths have also been shown to decrease RLS symptoms intensity [24].

Pharmacological treatment

The persistence and severity of RLS may require pharmacological treatment to provide symptomatic relief and to ease its associated sleep-wake disturbances.

Approved medications

The dopamine agonists and $\alpha 2\delta$ calcium channel ligands are generally considered first-line treatments. The USA Food and Drug Administration (FDA) has approved four medications for treating RLS and these include the non -ergotamine dopamine agonists: Ropinirole (Requip®), Pramipexole (Mirapex®), Rotigotine (Neupro®) and the $\alpha 2\delta$ calcium channel ligand Gabapentin enacarbil (Horizant®) [18,25-28]. Doses of dopamine agonists used for RLS treatment are much lower than the typical doses that are used for the treatment of patients with Parkinson disease [18,29]. Augmentation is a side effect that is characterized by a worsening of RLS symptoms, progression of symptoms to an earlier time during the day, and a more rapid onset of symptoms while at rest [30]. Augmentation occurs less frequently with to the non-ergotamine dopaminergic agents, than with other dopaminergic agents such as carbidopa/levodopa [18]. It is clinically relevant to recognize that some patients with RLS may have an episodic course of illness and may even undergo long-term periods of remission, so medications reduction are usually recommended during RLS periods of symptoms remission.

Other medications

Patients who do not respond well to the FDA approved medications, could be prescribed other off label medications that have been approved for the treatment of other medical conditions [18].

The various medications that have been used for the treatment of RLS are summarized in table 3 [18]. Although the benzodiazepines, such as diazepam and clonazepam, and the hypnotic zolpidem may be widely prescribed, their therapeutic effects on relieving RLS symptoms have not been confirmed [31]. The risk of dependence on the latter two classes of medications must be weighed against

the benefits of relieving RLS, they are contraindicated in individuals with a history of substance use disorders [8] and should not be routinely used due to their potential for the development of addiction and increased risk of accidental or intentional lethal overdose especially when combined with other sedative hypnotics, opioids or alcohol [32].

Medications	Daily dosing	Adverse effects	Special considerations
Ropinirole (Requip®)	0.25 mg	Nausea, orthostasis, daytime somnolence; augmentation occurs, but less so than with carbidopa/levodopa	increase to 0.5 mg on day three and to 1.0 mg on day eight; increase by 0.5 mg every week if needed to. Maximum of 4 mg per day, increased by 0.25 mg after 4-7 days, up to 0.5 mg per day 0.5, 1, 2, 3 and 4 mg/24 h. A dose-response relationship is usually observed between the dosages of 0.5 and 3 mg/24 h
Pramipexole (Mirapex®)	0.125 mg		
Rotigotine (Neupro®)	0.5 -2 mg		
Gabapentin enacarbil (Horizant®)	600 mg	Driving impairment, somnolence/sedation and dizziness. Careful monitoring in patients with renal functions impairment	Should not be increased above the maximum dose of 1200mg/day
Carbidopa/levodopa (Sinemet®)	25/100 mg	Gastrointestinal upset and headache; augmentation common with daily dosing	Rapid onset of action, usually with first dose; beneficial for individuals requiring medications for intermittent symptoms
Cabergoline (Dostinex®)	0.5mg	Nausea, orthostasis, and daytime somnolence. No appearance of augmentation side effect.	0.5, 1.0, or 2.0 mg three hours before bedtime; strongest effects noticed with 2.0 mg
Opioids	Nightly dose varies by choice of opioid. Mostly prescribed is Methadone (Dolophine®) 10 mg	Nausea, constipation; potential for abuse and addiction. Increased risk of accidental or intentional lethal overdose especially when combined with other sedative hypnotics or alcohol.	Methadone range 2.5 - 20 mg. Limited studies of effectiveness, but a reasonable choice in individuals with RLS associated with pain; may be used with dopaminergic agonist in patients with refractory RLS

Table 3: Medications for the Treatment of Restless Leg Syndrome.

Conclusion

RLS is a sensorimotor neurologic and sleep-wake disorder characterized by an irresistible urge to move the legs, accompanied by uncomfortable and unpleasant sensations that decrease with motor activity and worsen at rest. The symptoms of this syn-

drome worsen in the evening and at night, leading to difficulty in sleeping. The USA Food and Drug Administration (FDA) approved four medications for treating RLS and these include the non-ergotamine dopamine agonists; Ropinirole (Requip®), Pramipexole (Mirapex®), Rotigotine (Neupro®) and the α2δ calcium channel

ligand Gabapentin enacarbil (Horizant®) which should be considered in patients with persistent and severe RLS. It is important to accurately identify and diagnose RLS and to differentiate it from other medical or psychiatric conditions that could contribute to the worsening of its symptoms and its associated sleep disturbances. Treatment of RLS includes the appropriate management of its co-occurring medical and psychiatric conditions and the implementation of non-pharmacological as well pharmacological interventions to relieve its symptoms and reverse its disabling effects on the quality of life. This review described the steps that are necessary to accurately diagnose and treat RLS, in order to reverse its severe and devastating effects on the livelihood of patients who are suffering due to their affliction with this sensorimotor neurologic and sleep-wake disorder.

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Disclaimer

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