Optimizing Restless Legs Syndrome Care: Integrating Rehabilitation into Multimodal Management

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Abstract

Restless leg syndrome (RLS) is a common yet frequently under-diagnosed condition. The exact pathophysiology is unknown, however multiple factors including genetic factors, brain iron deficiency and dysfunction of dopaminergic system are associated with RLS. It is a clinical diagnosis confirmed by International Restless Legs Syndrome Study Group (IRLSSG) consensus diagnostic criteria (2012). Several pharmacological and non - pharmacological management options are available for treatment of RLS. Non-pharmacological management options include lifestyle modifications, therapeutic exercises (aerobic training, resistance training and flexibility exercises), physical modalities (pneumatic compression, vibration therapy, and near-infrared light) and mind body approaches (yoga, cognitive behavioural therapy, acupuncture, massage, and mindfulness). Pharmacological management of RLS include drugs from various classes including gabapentinoids, dopamine agonists, opioids and iron therapy. Novel treatment options like peroneal nerve stimulation, botulinum toxin injection, transcranial magnetic stimulation, vagus nerve stimulation, spinal cord stimulation and deep brain stimulation are still in experimental phase.

Keywords: Deep Brain Stimulation; Vagus Nerve Stimulation; Gabapentin; Anemia, Iron-Deficiency; Acupuncture

DOI: https://doi.org/10.47391/JPMA.25-97

Introduction

Restless Legs Syndrome (RLS), also known as Willis–Ekbom Disease (WED), is a chronic neurological sensorimotor disorder characterized by an uncontrollable urge to move the legs. It typically worsen with rest and improves with movement.[1] Clinical presentation varies from mild to severe symptoms, leading to sleep disruption, impaired quality of life (QOL), and increased risk of mental health problems.[1] It is classified into primary (idiopathic) or secondary due to iron deficiency, end stage renal disease (ESRD), pregnancy, cirrhosis, peripheral neuropathy, hypothyroidism, Parkinson's disease and multiple sclerosis.[2]

The estimated global prevalence of RLS in 2019 among adults was 7.12%.[3] Data regarding prevalence of RLS in Pakistan is limited. In a cross sectional study conducted in Punjab, 23.7% of the 400 participants reported symptoms of RLS. RLS is associated with increasing age, smoking, depression, and diabetes.[3]

Despite being prevalent, the diagnosis of RLS is delayed due to patients' difficulty in describing the symptoms and lack of awareness among physicians.[2] Rehabilitation medicine physicians with a multidisciplinary team (including physical therapist, psychologist) can integrate pharmacologic treatment with individualized rehabilitation interventions. This short-review aims to describe the latest evidence regarding pathophysiology, diagnostic criteria and treatment options including rehabilitation interventions for management of RLS in adults.

Pathophysiology

The exact pathophysiology of RLS is not yet fully understood. Multiple factors play a role in the development of RLS including:-

1. Genetic Factors

Genome-wide association studies identified several loci (MEIS1, BTBD9, MAP2K5/SKOR1, PTPRD, and TOX3/ BC034767) strongly associated with RLS.[4,5] MEIS1 is regarded as the strongest risk factor for RLS.[4,5]

2. Brain Iron Deficiency (BID)

Conditions associated with iron deficiency anaemia (like ESRD, pregnancy) increase the risk of RLS by 9 times compared to general population.[5] Majority of the patients with RLS have regional BID (manifested as decreased CSF ferritin) with normal peripheral iron stores due to impaired iron transport across the blood-brain barrier.[4,5] The substantia nigra, putamen, and caudate are commonly affected.[5]

3. Dopaminergic System Dysfunction

Symptomatic relief with dopaminergic drugs suggests

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dopamine deficiency as a possible cause of RLS.[4,5] However, the latest evidence on RLS suggests an increased dopamine production in brain with a resultant compensatory post synaptic down regulation of dopamine receptors (like D2) and cellular functions.[4,5] Dopamine levels naturally follow circadian rhythm - higher in the morning and lower in the evening or at night.[5] While the brain adapts to daytime dopamine spikes by post synaptic down regulation, this adjustment backfires at night when dopamine drops, creating a temporary deficit (thus circadian flare up of symptoms in evening).[5] The paradoxical improvement with dopamine agonists may reflect correction of this relative circadian deficit of dopamine.[5]

4. Abnormalities in Neural Circuits

a. Dysfunction of the A11 dopaminergic pathway may reduce inhibitory control over spinal sensory input, contributing to symptom generation.[5]

b. Trans-cranial Magnetic Stimulation and MRI findings suggests increased excitability, reduced inhibition and abnormal sensorimotor integration across cortical, subcortical, and spinal levels.[6]

c. Hypoadenosinergic and hyperglutamatergic states (reflecting the complex interplay of neurotransmitters in RLS).[5]

d. Research has shown decreased β-endorphin and increased β-Melanocyte Stimulating Hormone in cerebrospinal fluid of patients with painful RLS.[7]

Diagnostic Criteria

RLS remains purely clinical diagnosis as there are no definitive biomarkers or confirmatory laboratory tests.[1] International Restless Legs Syndrome Study Group (IRLSSG) consensus diagnostic criteria (2012) is used to confirm diagnosis.[1] (Table-1) All of the 5 essential diagnostic features must be met.[1,8] Paediatric and adult diagnostic criteria have been integrated in the current 2012 IRLSSG revision.[1] To enhance the characterization of RLS/WED, specifiers related to clinical course and clinical significance have been added (Table-1).[1]

Features such as periodic limb movements, initial response to dopaminergic therapy, a positive family history, and absence of marked daytime sleepiness are commonly associated with RLS and may support clinical assessment.[1,8]

RLS variants refer to atypical presentations where body regions, other than legs, may also be involved. This includes related symptoms in arms (21–57% of cases), abdomen, hips, trunk, genitalia, head or face.[8]

Table-1: International RLS Study Group (IRLSSG) Diagnostic Criteria (2012).[1]

Five Essential diagnostic criteria (all must be met)

1. 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.
2. 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.
3. 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 as long as the activity continues.
4. 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.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

RLS Specifiers

1. **Clinical Course:**
   - ***a.*** *Chronic-persistent RLS: symptoms when not treated would occur on average at least twice weekly for the past year);*
   - ***b.*** *Intermittent RLS: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events*.
2. **Clinical Significance:**
   Symptoms of RLS cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

Assessment Scales

Several assessment scales for RLS have been described in literature, but no single screening tool is currently validated as the standard. Severity is typically evaluated using validated instruments such as the International RLS Study Group Severity Scale (IRLS, most commonly used), Johns Hopkins Restless Legs Severity Scale and RLS-6 Scale.[10] Each scale offers valuable but partial insights into RLS severity, underscoring the need for a more comprehensive assessment tool to better guide clinical management.[8]

Management

Non-Pharmacological and pharmacological management options for treatment of RLS are described below:

A. Non-pharmacological Management:

These are effective in mild RLS and help lower medication requirements in more severe cases.[8] A 2021 systematic review outlined several non-pharmacological strategies for managing RLS, including:

(1) Lifestyle modifications like optimizing sleep hygiene, reducing caffeine and alcohol intake, smoking cessation and discontinuing symptom-exacerbating medications (e.g., selective serotonin and norepinephrine reuptake inhibitors, proton pump inhibitors, antihistamines, dopamine antagonists).[8]

(2) Exercise-based interventions like aerobic training, resistance exercises, and stretching.

(3) Physiotherapeutic modalities such as pneumatic compression, acupuncture, vibration therapy, and near-infrared light.

(4) Mind-body approaches including yoga, cognitive behavioural therapy, massage, and mindfulness.

The combination of these strategies results in enhanced symptom control.[10]

B. Pharmacological management

Pharmacological management of RLS include drugs from various classes including gabapentinoids, iron therapy, opioids and dopamine agonists.[9] Before initiating pharmacotherapy, it is essential to correct iron deficiency and optimize non-pharmacological interventions.[7] Oral iron is recommended when serum ferritin is <75 µg/L or transferrin saturation is <20%. IV iron is an effective alternative in cases of oral intolerance or if ferritin is <300 µg/L or transferrin saturation is <45%.[7] Monotherapy at the lowest effective dose is suggested, typically administered in the evening, either as a single dose or divided (e.g., before dinner and again at night) to maintain sleep quality.[7] Alpha-2 delta ligands (gabapentin enacarbil, gabapentin, pregabalin) are the first line of drugs for management of RLS. Caution should be practiced while prescribing dopaminergic agents due to their high risk of paradoxical worsening of symptoms over time.[1,9] Opioids may be considered only in severe, treatment-refractory cases or in patients exhibiting augmentation on other therapies.[9]

C. Novel Strategies:

1. Bilateral Peroneal Nerve Stimulation

High-frequency Peroneal Nerve Stimulation (HPNS) and Tonic Motor Activation (TOMAC) utilizes electrical stimulation to activate peroneal muscles.[9,11] A meta-analysis reported a clinically meaningful reduction in IRLS score i-e, -3.4 (-5.0 to -1.8) with bilateral HPNS. In a trial, TOMAC reduced opioid requirement in refractory RLS, with 70% of participants maintaining a ≥20% reduction in opioid dosage over 20 days.[8,11]

2. Botulinum Toxin (BTX)

BTX reduces involuntary muscle contractions in RLS by inhibiting acetylcholine release at the neuromuscular junction.[12] A meta-analysis found that BTX injections significantly reduced IRLS scores (SMD, −0.819, 95% CI, −1.377 to −0.262) compared to placebo at four weeks. However, the small sample sizes, protocol variability, and increased risk of bias limit the strength of these conclusions.[12]

3. Transauricular Vagus Nerve Stimulation (tVNS):

Given the efficacy of antiepileptic agents in RLS management and the anticonvulsant properties of VNS, its potential role in treating RLS has gained interest.[13] A 2023, non-randomized pilot study (n=15) showed 66% patients with severe, pharmaco-resistant RLS responded to tVNS with significant reduction in IRLS (from 31.9±2.9 to 24.6±5.9; *p*-value=0.0003).[13]

4. Repetitive Transcranial Magnetic Stimulation (rTMS)

Recent evidence suggests that RLS is associated with motor cortex disinhibition and dysfunction in spinal inhibitory systems.[14] Based on this, a pilot study (2024) used high frequency rTMS targetting the leg motor cortex (n=18). Following treatment, mean RLS severity scores significantly decreased (from 23.9±5.9 to 11.2±7.2; $p<0.0001$) and remained low at two months.[14]

5. Spinal Cord Stimulation (SCS):

SCS is proposed to alleviate symptoms by modulating central hyperexcitability across spinal, subcortical, and cortical sensorimotor pathways.[15] In a literature review, Gabriel L. et al. described symptom improvement in all 16 patients given SCS. However, current evidence is insufficient to support routine use of SCS in RLS.[15]

6. Electrical stimulation (ES)

Proposed mechanism of ES includes massage-like effects which enhance muscle relaxation and blood perfusion through nitric oxide-mediated vasodilation triggered by endothelial shear stress.[16] In a pilot study, 77.3% patients showed significant reduction in severity of RLS symptoms with a handheld device (tapping mode, 3Hz).[16]

7. Deep Brain Stimulation (DBS)

Makharia A. et al., suggested that subthalamic DBS and thalamic DBS decreased RLS symptoms in patients with Parkinson's disease and essential tremors, respectively.[8] The mechanism likely involves the modulation of sensory pathways by subthalamic nuclei on the thalamic nuclei.[8]

Conclusion

RLS is an underdiagnosed and sub-optimally treated condition, particularly in lower middle income countries like Pakistan. Non-pharmacological interventions including life-style modifications, exercise and physiotherapy enhance symptom control and reduce reliance on medication. While pharmacological management (gabapentinoids, iron therapy, opioids and dopamine agonists) is the mainstay of treatment, emerging therapies such as tVNS , rTMS, SCS and DBS show promise. Large-scale studies are needed to validate these interventions and guide their integration into routine clinical care, particularly in rehabilitation settings.

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