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REVIEW

Restless legs syndrome

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Sujith Ovallath
P Deepa

James Parkinson's Movement Disorder Research Centre, Kannur Medical College, Kerala, India

Background: Restless legs syndrome (RLS) is a common sleep-related disorder characterized by abnormal sensation and an urge to move the lower limbs. Symptoms occur at rest in the evening or at night, and they are alleviated by moving the affected extremity or by walking. Although the exact etiopathogenesis of RLS remains elusive, the rapid improvement of symptoms with dopaminergic agents suggests that dopaminergic system dysfunction may be a basic mechanism. Dopaminergic agents are the best-studied agents, and are considered first-line treatment of RLS.

Objective: To review the diagnostic criteria, clinical features, etiopathogenesis, and the treatment options of RLS.

Methods: The suggestions are based on evidence from studies published in peer-reviewed journals, or upon a comprehensive review of the medical literature.

Results/conclusion: Extensive data are available for proving the link between the dopaminergic system and RLS. A possible genetic link also has been studied extensively. Dopamine agonists, especially pramipexole and ropinirole, are particularly useful in the treatment of RLS. Pharmacological treatment should however be limited to those patients who suffer from clinically relevant RLS with impaired sleep quality or quality of life.

Keywords: dopamine, levodopa, pramipexole

Introduction

Restless legs syndrome (RLS) is a common neurologic and sleep-related disorder that probably has multiple causes. It is characterized by uncomfortable sensations deep inside the limbs during periods of rest or inactivity, encompassing an irresistible urge to move them, occurring especially during evening hours. The symptoms are typically relieved by movements.[1–3] The American Sleep Disorder Association has listed RLS among the causes of intrinsic insomnia.[4] Moreover, the majority of RLS patients suffer from periodic leg movements in sleep (PLMS).[5–9]

History

The English physician and anatomist Sir Thomas Willis probably made the first descriptions regarding RLS in the seventeenth century.[10,11] Symptoms comparable to RLS were described by Boissier de Sauvages in 1763, Magnus Huss in 1849, and Gilles de la Tourette in 1898.[12,13] In 1945, the Swedish neurologist Karl Axel Ekbom coined the expression "restless legs syndrome" and conducted the first clinical and epidemiological studies on the topic.[14,15] In 1995, the International Restless Legs

Correspondence: Sujith Ovallath
Department of Neurology, James Parkinson's Movement Disorders Research Centre, Kannur Medical College, Anjarakandy, Kannur, Kerala, India
Tel +91 497 285 6410
Fax +91 497 285 2500
Email sujithok@gmail.com

Syndrome Study Group developed standardized diagnostic criteria for the disease, which was updated in 2003.[3]

Epidemiology

The prevalence of RLS among Caucasians ranges from 5% to 15%.[2,16–18] The prevalence tends to escalate with age, with a higher occurrence among women. The disease manifests itself usually in the fourth and fifth decades.[2,19–21]

Epidemiological studies are available mostly in Caucasians. Reports from Asian countries document a lower prevalence.[22,23] The discrepancy could be explained by the interplay of genetic and environmental factors and cultural differences.

Possible etiological factors

RLS is a disease with multisystem correlates, and so its exact etiology has not been delineated Table 1. It has been documented that dopamine antagonists that cross the blood–brain barrier (like metoclopramide) aggravate features of RLS. However, the peripheral antidopaminergic domperidone, which does not cross the blood–brain barrier, does not result in RLS either.[24,25] On high-resolution functional magnetic resonance imaging, increased activity was uncovered in the cerebellum, thalamus, red nucleus, and inferior olive. No cortical activation was noted, and no structural abnormality was discovered.[26–28] Bara-Jimenez and colleagues described an abnormally increased spinal flexor reflex excitability during sleep in RLS patients,[29] hinting at the probability of a reversal of circadian-associated spinal cord inhibition.[30] Therefore, the accessible evidence suggests that RLS is a disorder of the central nervous system, more or less subcortical in nature. This also suggests the hypothesis of a neuronal network connecting the aforementioned areas, resulting in the sensorimotor symptoms of RLS.[30,31]

An abrupt, universal, and almost overall response to RLS symptoms follows the administration of dopaminergic medications. Double-blinded and placebo-controlled studies have validated the advantages of levodopa[32–34] and dopamine agonists like pergolide,[35,36] pramipexole,[37] and ropinirole[38] over other medications. Additionally, they are beneficial at substantially lower doses when compared to their respective doses for Parkinson's disease. All other medications used to treat RLS need high doses for symptomatic relief.[39,40] The opioid antagonist naloxone does not increase RLS symptoms, whereas dopaminergic antagonists like pimozide and metoclopramide have been well documented to exacerbate it.[41]

Even though evaluation during a symptomatic period has not been attempted,[42] brain-imaging studies using positron emission tomography and single-photon emission computed tomography have disclosed that presynaptic D_2 receptor binding was remarkably reduced, whereas postsynaptic binding was more or less normal. A possibility of decrease in either the number of D_2 receptors or their affinity towards dopamine was suggested. The rate of dopamine production seems to be normal or slightly decreased.[43–46]

Research by Garcia-Borreguero and colleagues revealed that levodopa-induced inhibition of prolactin secretion links significantly with polysomnographic findings in RLS/PLMS.[47] Dopaminergic pathology was thus proposed. Dysfunction in a number of pathways is suggested, the most appropriate candidate being the A11 or dorsoposterior hypothalamus system. However, the contributions of nigrostriatal (A9) and tuberoinfundibular systems cannot be excluded.[31,48]

The recognized secondary causes of RLS, including end-stage renal disease,[49–51] pregnancy,[52,53] iron-deficiency anemia,[54] gastric surgery,[55,56] and frequent blood donations,[57] are all linked with a decrement in body iron stores. Remission has been reported with iron therapy.[58,59] Earley and colleagues demonstrated that cerebrospinal fluid (CSF) concentrations of ferritin were significantly lower in RLS patients while maintaining a more or less normal serum ferritin level.[60] A reduced central nervous system iron status was proposed, even with a high normal serum ferritin level, the slope of their relationship being abnormally low in RLS.[61] Studies using magnetic resonance imaging have revealed diminished iron content in substantia nigra.[62] Autopsy reports suggest reduced H-ferritin and iron content, and abnormal distribution of L-ferritin in the nigral cells.[63]

Iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. Hence iron deficiency may result in dopaminergic dysfunction. Studies show that rats fed an iron-deficient diet had reduced D_1 and D_2 receptors in caudate putamen, with decreased dopamine transporter function.[64] Reports regarding brain iron content and dopaminergic dysfunction often converge at identical points. Moreover, the circadian patterns of serum iron and dopamine levels coincide smoothly with those of RLS symptoms. A possible, yet to be explored, interplay of iron and dopamine pathophysiology is thus hinted at.[30]

Genetics of RLS

Roughly 65% of RLS patients, especially those with an early onset of symptoms, have at least one first-degree relative with the disease.[7,65–67] The concordance rate between monozygotic twins also has been reported to be high.[68] Most pedigrees suggest an autosomal dominant inheritance, even though

Table 1

Etiological classification
Primary/idiopathic RLS
Secondary RLS
• Iron deficiency
• End-stage renal disease
• Pregnancy
• Frequent blood donations
• Rheumatic disease
• Drugs
– Antihistamines
– Dopamine antagonists
– Mirtazapine
– Tricyclic antidepressants
– Selective serotonin reuptake inhibitors

recessive models have been proposed as well. Differences in penetrance and anticipation may explain the heterogeneity in expression.[66,69] Several chromosomal loci have been reported (on 12q, 14q, 9p, 2q, 20p, and 16p). Sequence variants have also been proposed, in or around genes on 6p, 2p, or 15q.[70–77] The most significant gene identified to this point would be *MEIS1*,[78] others being *NOS1*[74] and *BTBD9*.[79]

Cardinal features

Uncomfortable and unpleasant sensations in the limbs

RLS is characterized by uncomfortable or distressing sensations deep inside the limbs, commonly between the ankle and knee. Arms are involved now and then, and so are thighs and feet. The sensory experience may be described as "creepy-crawly," burning, tingling, aching, or cramping. The perception is generally bilateral and symmetrical, but unilateral presentations are not infrequent. Predominant symptoms in the upper limbs without involving legs and extension to other body parts are unusual and atypical of RLS.[1,2]

An urge to move

The sensations are accompanied by an irresistible urge to move the affected limb. This is different from the generalized inner restlessness or fidgetiness of neuroleptic-induced akathisia[1,2] and may persist for hours on end until a movement is initiated.

Association with rest and circadian rhythm

The symptoms appear classically when the patient puts his limbs at rest or during evening hours. He may feel them during a train or air journey, at the theater, or during a conference; alternatively, he suffers on getting to bed. Many patients experience a worsening of symptoms during the night, regardless of them resting. Thus, the diurnal variation seems independent from inactivity.[1,2,80]

Relief on movement

Dramatic and immediate symptomatic relief, either complete or partial, is gained by movement of the affected limb. It prevails as long as the activity is continued. Activities like walking, stretching, or massaging may be helpful. The patient may wake up from sleep and be forced to walk around for relief, the behavior being termed 'night-walker syndrome.'[1,2,9]

Periodic limb movements

RLS is commonly accompanied by involuntary, rhythmic muscular jerks in lower limbs, called periodic limb movements. The classic picture is a regular extension or fanning of toes and dorsiflexion of the ankle, with infrequent flexion at knee and hip. When occurring during sleep, it is termed PLMS. This may occur every 20–40 seconds, occurring throughout the sleep span. Each movement results in a brief microarousal (of which the patient may not be aware), resulting in sleep fragmentation. Thus most of the time, the only complaint regarding PLMS is insomnia or excessive daytime sleepiness. History noted from a bed partner is often valuable. Diagnosis is essentially by an overnight polysomnogram. In fact, more than 80% of RLS patients suffer from PLMS. PLM occurring during a wakeful period is called PLMW, usually provoked by a suggested immobilization test.[5,81–84]

Disease course

RLS can present at any age.[30,85–87] Generally regarded as a chronic disease with progressive intensification of symptoms over years, two major phenotypes have been described. There are people in whom symptoms manifest before 45 years of age. The probability of them having a positive family history is high, and the disease assumes rather a slow course in them (early onset phenotypes). In the other group, in which the disease appears late (the late-onset group), the symptoms are rapidly progressive. The disparities in clinical course suggest a marked difference in pathology between the two.[2,23,30,88,89] The early onset group comprises mainly those with the familial form of the disease, whereas the late-onset cluster consists more of sporadic RLS. The latter has been more often associated with secondary causes of RLS.[87]

Diagnosis

The diagnosis of RLS is essentially based on history. In 1995, the International Restless Legs Syndrome Study Group developed standardized diagnostic criteria for the disease, which were updated in 2003.[2,3,90] See Table 2.

Diagnosis of PLM

PLMS is diagnosed based on an overnight polysomnogram. To diagnose PLMS, a PLM index (number of periodic limb movements per hour of sleep) ≥5 is required.[83] PLMS itself is not diagnostic of RLS, since it may occur as a result of sleep-disordered breathing or adverse drug effects. Nonetheless, a high PLMS index offers a sensitive and specific diagnostic norm.[4,7,8] Montplaisir and colleagues suggested that the incidence of PLMW in RLS strongly supports the diagnosis.[8] It even seems to be more specific than PLMS, but adequate evidence is lacking.[91,92]

Studies affirm that 1.9% of school-going children and 2% of adolescents suffer from RLS/PLMS.[93] Identification of symptoms and an effective communication regarding the same can be quite challenging for a child. Up to the age of 12 years, a definite diagnosis of RLS is made only if the child describes in his or her own words a set of sensations coherent with leg discomfort, besides fulfilling the four essential criteria. The adult criteria are considered appropriate for an adolescent (>12 years old).[94]

Differential diagnosis

Many diseases mimic RLS but do not fulfill the essential diagnostic criteria. A few examples are given below.

Table 2 Diagnostic criteria for restless legs syndrome (RLS)

Essential criteria

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in 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.
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.

Supportive clinical features

1. Positive family history.
2. Positive response to dopaminergic therapy.
3. Presence of periodic limb movements (during wakefulness or sleep).

Associated features of RLS

1. Variable clinical course, but typically chronic and often progressive.
2. Physical examination normal in idiopathic/familial forms.
3. Sleep disturbance is a common complaint in more affected patients.

Notes: All four essential criteria have to be fulfilled for a definite diagnosis of RLS. The supportive criteria are helpful but not necessary. Needed investigations include serum ferritin and other investigations to rule out secondary causes.

- Akathisia: a generalized motor restlessness with movement stereotypy, usually neuroleptic-induced
- Nocturnal leg cramps
- Positional discomfort: relieved by changing the limb position
- Painful legs and moving toes: involuntary, spontaneous flexion and extension of toes, secondary to cord or root lesions
- Peripheral neuropathy
- Lumbosacral radiculopathy
- Attention deficit/hyperactivity disorder (ADHD)

Consequences of RLS/PLMS

Increased daytime sleepiness results in an overall decline in the quality of life in these patients. Depression is found frequently, possibly due to underlying brain pathology, insomnia, or psychological stress due to the chronic illness.[95,96] Treatment should be cautious, since antidepressants can aggravate the symptoms. Social and occupational disruption,[18,19] headaches,[18,19] sleep-disordered breathing,[100] difficulty in concentration, and short-term-memory defects have been reported.[97] RLS and PLMS are associated with increased risk of hypertension,[98,99] cardiovascular disease,[100] and stroke.[101] Sympathetic overactivity,[102,103] increment in atherosclerotic plaque formation[104] and rupture, and sleep disturbances are the proposed causal factors. ADHD has been reported in children with RLS.[97]

Treatment

Primary RLS

Primary RLS can be treated by nonpharmacological and pharmacological measures.

Nonpharmacological treatment

Improvement of sleep hygiene has been found effective in combating sleep fragmentation.[105] A regular sleep pattern; avoidance of alcohol, coffee, and tobacco; moderate exercises; thermal baths; and massages may help in assuring a sound sleep.[106] Hornyak and colleagues studied the impact of cognitive behavioral therapy in RLS and reported symptomatic improvement.[107]

Pharmacological treatment

Levodopa

The response to levodopa is immediate and occurs at low doses relative to that used in Parkinson's disease.[32–34] In spite of this, the therapeutic benefit is limited by afternoon augmentation and morning-rebound phenomena. Augmentation

is characterized by an earlier onset of RLS symptoms (in the afternoon or early evening), with greater intensity or with involvement of other body parts. Curiously, intense dopaminergic therapy as well as iron deficiency and sleep deprivation result in augmentation.[108–111] The reappearance of symptoms can occur in the morning hours, possibly owing to the short plasma half-life of levodopa, and is termed morning rebound.[106]

Dopaminergic agonists

Presently, dopaminergic agonists are considered the first-line pharmacological therapy for RLS/PLMS. A longer half-life and fewer incidences of side effects like augmentation[123] are the major reasons for their current status, backed by double-blind placebo-controlled trials. The non–ergot derived drugs pramipexole and ropinirole are both effective,[112–117] and can be used long-term.[118,119] Between these, pramipexole seems to be the better choice in view of earlier efficacy, superior response, and fewer adverse effects.[120,121] Trenkwalder et al demonstrated the benefits of transdermal rotigotine in RLS. Interestingly, the transdermal preparation did not accommodate signs of augmentation during the study.[122] Concerns with regard to pulmonary fibrosis and cardiac dysfunction have made treatment with pergolide obsolete.[124–127]

Antiepileptics

Gabapentin is the favored treatment for a patient who cannot tolerate dopaminergics. It is as effective as ropinirole in relieving RLS/PLMS.[128,129] The mechanism of action is unclear. The only known side effect is minimal daytime sleepiness. The other evaluated anticonvulsants, like carbamazepine and valproate, are better avoided because of worse side effects and drug interactions.[130]

Opioids

Short-term as well as long-term therapeutic benefits have been described in RLS when opioids were administered, as per clinical trials.[123] They could be considered as second-line therapy in refractory RLS.[131,132] The drugs proved beneficial were oxycodone,[133] methadone,[134] and tramadol.[135] Side effects like nausea, vomiting, urinary retention, constipation, and dizziness are common. Apprehension regarding abuse potential and respiratory depression is also a factor. Vetrugno et al reported augmentation on long-term tramadol therapy.[136]

Benzodiazepines

Benzodiazepines work mainly on the quality of sleep, and not on the pathology of RLS, clonazepam being the most recognized one.[137] In the current scenario, they are not regarded as an ideal therapy for RLS. Psychological dependence and physiological tolerance are major concerns about their prescription. However, they may be useful in RLS-associated insomnia refractory to treatment.[138]

Secondary RLS

The management of secondary RLS is converged at identifying and treating the specific causes. Provocative medications like dopaminergic antagonists, antipsychotics, and antidepressants should be discontinued, tapered, or administered early during daytime. In the depressed, bupropion may be used, considering its beneficial effect on PLM.[4]

Therapeutic benefits have been observed in studies concerning parenteral iron treatment (intravenous iron dextran) in idiopathic as well as secondary RLS.[58,59] Since higher serum levels of ferritin are sometimes associated with low normal CSF ferritin, it is advisable to consider parenteral iron therapy if first-line pharmaceuticals fail to bring about a response. This could be done irrespective of serum ferritin levels. If serum ferritin drops beneath 50 μg/mL, oral iron may be started in the form of 325 mg iron sulfate three times a day, along with vitamin C. Gastrointestinal irritation is a limiting factor for oral therapy; allergic reactions often restrict intravenous iron treatment.[4]

RLS associated with ESRD is often refractory and does not improve with hemodialysis.[139,140] A fruitful renal transplantation may result in significant symptomatic improvement.[141,142]

Pregnancy-related RLS has been reported to resolve completely after delivery.[143] Vitamin B_{12} and folic acid deficiency may lead to RLS, and so do neuropathies. The primary condition should be treated then.[146,154,156,157] Papers based on clinical trials suggest that gabapentin[131] and pregabalin[147] are especially useful in neuropathy-associated RLS.[97]

Treatment in children and during pregnancy

There is no single FDA-approved medication for pediatric RLS. Studies have stated the efficacy of levodopa and dopaminergic agonists in childhood RLS and associated ADHD.[148–150] However, clonazepam may be avoided in children with ADHD since it may aggravate hyperactivity.[151] Iron therapy may be beneficial when serum ferritin levels are low.[152,153] Drugs are generally not recommended in pregnancy-related RLS in view of inconsistent reports on their safety and the benign nature of the condition.[4]

RLS studies from the Indian subcontinent

There are a few reports of prevalence of RLS from India. The first Indian population study on RLS revealed prevalence of the disorder in South India at 2.1%.[159] Another trial reported that RLS had a predominance of females, and that they were younger than the male counterparts.[160] A Hindi-language version of the RLS scale has been developed for easy administration of the questionnaire in the local language.[161]

Conclusion

RLS is a very common sleep-related movement disorder, but it is mild in the majority of cases. The etiology of RLS is only partly understood. Some medical conditions, including renal failure, iron deficiency, and pregnancy, are associated with high rates of RLS. Most patients with idiopathic RLS respond well to dopaminergic agents. Second-line treatment options include gabapentin or similar antiepileptic drugs and opioids. Pharmacological treatment should be limited to those patients who suffer from clinically relevant symptoms.

Disclosure

The authors report no conflicts of interest in this work.

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