A Clinical Primer on Restless Legs Syndrome: What We Know, and What We Don't Know

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Abstract

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common sensorimotor disorder that may be idiopathic (primary) or secondary to a diverse group of conditions. The pathophysiology of primary RLS is only partly understood, but a strong association with brain iron deficiency possibly resulting in impaired dopaminergic function has been recognized. Genomic studies have established a genetic basis for primary RLS as well, and at least 42% of people with primary RLS possess a first-degree relative with the disorder. Secondary RLS is often associated with renal insufficiency, pregnancy, iron deficiency anemia, diabetic neuropathy, and Parkinson's disease. Approximately one-fourth of pregnant women experience RLS, with more intense symptoms experienced during the third trimester, and resolution of symptoms typically occurring within a few months after delivery, though RLS may resolve as early as 2 weeks after delivery. Restless legs syndrome is associated with increased prevalence of mood disturbances, sleep disturbances, and an impaired quality of life. The diagnosis of RLS involves 4 essential criteria related to a compelling urge to move the legs with an accompanying unpleasant sensation in the legs that is worse in the evening and at rest and improved by movement. Treatment of RLS incorporates both pharmacologic and nonpharmacologic approaches. Dopamine agonists are the mainstay of RLS treatment, but other therapies, including gabapentin, benzodiazepines, and low-potency opioids, are also commonly employed.

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Characteristics and Epidemiology of RLS

Restless legs syndrome (RLS) is a sensorimotor disorder notable for its characteristic symptoms, including strong feelings of restlessness and distressing paresthesia-like sensations in the lower legs.[1] RLS typically manifests when the patient is at rest, and a state of relaxation or comfort is associated with a greater likelihood of symptom occurrence. Conversely, symptoms usually resolve when the patient initiates movement, and as symptoms arise, patients will experience an intense urge to begin moving in order to relieve the discomfort.[1] In addition, the symptoms have a circadian pattern and are worse in the evening. However, it must be emphasized that daytime symptoms that may require intervention may occur in up to 50% of patients.[2]

RLS is a common disorder; in the RLS Epidemiology, Symptoms, and Treatment (REST) study, 7.2% of US and European adults reported having experienced symptoms of RLS at some point during a 1-year period, and 5% reported experiencing symptoms on a weekly basis.[3] Overall, RLS symptoms occur nearly twice as often in women compared with men: data from the REST study found that 9.0% of women and 5.4% of men had experienced RLS symptoms within the previous year. The gender difference increases when comparing the rates of symptoms experienced at least once per week. These more frequent symptoms were seen among 2.8% of men in the REST study versus 6.2% of women.[3] Among the subgroup of persons with RLS who experienced symptoms at least twice a week (3.7% of women and 1.7% of men), 81% had sought treatment from a primary care physician at some time, and 61.3% had consulted a physician in the previous year.[3]

The prevalence of RLS in the pediatric population is somewhat lower, with approximately 2% of children between the ages of 8 and 17 years experiencing symptoms at least once a month, and 1.2% experiencing symptoms at least twice per week. Among pediatric patients, RLS is slightly more common in males than females overall (53.9% vs 46.1%), but the male preponderance is more striking when moderate-to-severe RLS (occurring at least twice a week) is measured (59.8% vs 40.2%).[4]

Etiology and Pathophysiology

RLS is delineated into primary and secondary forms. Primary RLS is, by definition, idiopathic, lacking comorbidities or physiologic context that can explain a patient's symptoms.[5] Patients

with secondary RLS possess comorbidities or other recognizable causes—such as iron deficiency, medications, chronic renal failure, and iron deficiency anemia.[6,7] The pathophysiology of RLS is not fully understood. Dopaminergic dysfunction and brain iron deficiency have long been regarded as the key culprits in the pathophysiology of RLS.

Dopaminergic Dysfunction. The most persuasive argument in favor of dopaminergic dysfunction is the striking improvement in symptoms with dopaminergic drugs.[8] However, the mechanism of this improvement has never been fully elucidated. Imaging of the nigrostriatal system has yielded conflicting results and the substantia nigra does not demonstrate cell loss at autopsy.[2,9] Most studies utilizing single-photon emission computed tomography (SPECT) scan to assess dopamine transporter density have shown normal results, but a recent positron emission tomography (PET) study showed a decreased number of dopamine transporters (DAT).[10] The authors hypothesized that this was reflective of a decreased amount of membrane-bound DAT.[10] However, this could also be a reflection of increased extracellular dopamine.

The number of D2/D3 receptors may be decreased in the mesolimbic areas as shown by raclopride binding.[11] Also, lesioning of the A11 area that gives rise to a dopaminergic pathway projecting to the spinal cord results in overactivity in mice.[12] However, an autopsy study did not show a dramatic cell loss in the A11 hypothalamic region of patients with RLS.[13]

Physiological studies have shown altered spinal excitability with decreased inhibition.[14]

Iron Deficiency. Iron deficiency has also been repeatedly shown to be associated with RLS. Several secondary causes of RLS (end-stage renal disease, iron deficiency, and pregnancy) are associated with problems maintaining adequate iron.[15] In idiopathic RLS it is central nervous system (CNS) iron storage that may be impaired, while the systemic iron may be normal. The discordance between systemic and CNS iron is demonstrated by the observation that patients with hemochromatosis (iron overload disease) may develop RLS.[16] Brain magnetic resonance imaging (MRI) studies of patients with RLS have demonstrated decreased iron in the midbrain, and a correlation between decreased brain iron and RLS severity has been demonstrated.[17] An autopsy study found that H-ferritin was markedly reduced while L-ferritin was present but had a different morphology.[9] In addition, another autopsy study found that iron regulatory protein (IRP) 1 levels were decreased in the brains of patients with RLS while IRP2 was upregulated.[18]

The mechanism by which iron deficiency leads to dopaminergic dysfunction is unclear. Iron has a complex effect on dopaminergic function. It is a cofactor for tyrosine hydroxylase and is integral to D2 receptor function.[9,15] However, iron deficiency does not lead to reduced dopamine levels. A study of rats deficient in iron showed an increase in extracellular dopamine.[19]

One of the challenges of evaluating the role of iron deficiency in RLS arises from the fact that serum iron levels are highly variable and can be impacted by a variety of confounding factors such as circadian rhythms, sleep disturbance (itself an RLS symptom), diet, and other lifestyle factors. It has, therefore, been hypothesized that serum ferritin (a protein that stores iron in tissue) might be a more clinically appropriate means of measuring and understanding the role of iron in RLS.[20] Mizuno et al conducted a study comparing sleep patterns, including periodic leg movement (PLM) index, in 10 subjects with diagnosed RLS and 10 matched subjects with psychophysiological insomnia but no RLS symptoms.[20] The 2 groups were compared for sleep patterns as well as disposition of iron, ferritin, and transferrin (a protein responsible for binding and transportation of iron) in both serum and cerebrospinal fluid (CSF). With regard to serum levels of iron, ferritin, and transferrin, no significant differences were observed between the groups. However, CSF iron and ferritin were both significantly lower in the RLS group, while transferrin was significantly higher. The higher transferrin levels indicate greater requirements for iron in the brain.[20] Subjects with RLS also experienced significantly longer sleep latency, less sleep efficiency, and a higher PLM index (all $P < .01$).[20]

RLS in Pregnancy. Approximately one-fourth of pregnant women experience symptoms of RLS, with the most severe symptoms occurring in the third trimester. In most cases, women who experience RLS symptoms in pregnancy have not had symptoms of RLS previously.[21] Typically, RLS symptoms resolve in most women within a few weeks to a few months after delivery.[21] The transient restless legs syndrome during pregnancy is a significant risk factor for the development of a future chronic idiopathic restless legs syndrome.[22] A variety of hypotheses have been offered to explain RLS in pregnancy. Several hormonal theories have been suggested, including the possibility that an increase in prolactin, which is associated with a lessening of dopamine activity, is responsible for RLS symptoms.[21] The effects of pregnancy on increasing stress levels and promoting poor sleep have also been suggested as factors contributing to worsening of RLS symptoms.[21] A metabolic hypothesis points to reductions in folate, iron, and ferritin, particularly in the later stages of pregnancy, which may increase RLS risk during pregnancy.[21]

Other Potential Associations. A wide spectrum of different diseases and pathologies has been associated with RLS, although the extent to which they have a causative relationship with the condition is poorly understood. End-stage renal disease is one of the most common comorbidities associated with RLS, and kidney transplants have been observed, in many cases, to resolve RLS symptoms.[7] Other conditions linked with RLS include Parkinson's disease, congestive heart failure, neuropathy, depression, and sleep apnea.[1] Certain lifestyle behaviors appear to be associated with increased risk for RLS, such as alcohol, tobacco, and caffeine consumption, although compelling data on these factors are lacking.[7] Increased age, up until the age of approximately 79 years, has also been shown to be a risk factor for RLS.[3] Several types of medications and medication classes known to aggravate RLS are shown in the **Table**.[6,7]

Table. Medications Associated With Exacerbating Restless Legs Syndrome[6,7]

SSRIs
Tricyclic antidepressants
Dopamine antagonists (eg, antipsychotics and antiemetics)
Antihistamines
Lithium
Caffeine

SSRI indicates selective serotonin reuptake inhibitor.

Genetics of RLS. It is clear that, at least in some cases, RLS is inherited. However, the extent of the hereditary link remains difficult to precisely quantify. A hereditary link study by Winkelmann et al involved 300 RLS patients: 232 with idiopathic RLS and 68 patients with RLS secondary to uremia. The authors observed a definite family history of RLS, defined as at least 1 first-degree relative with verified RLS, in 42% of idiopathic RLS patients and 12% of patients with RLS secondary to uremia. An additional 13% of subjects with idiopathic RLS and 6% of those with secondary RLS were designated as having "possible positive" RLS inheritance; in these cases, examination of the first-degree relative was not possible.[23]

Subjects with and without evidence of inherited RLS were similar in most respects, with the notable exception that those with a family history had a significantly earlier age of onset compared with those without a genetic connection (35 vs 47 years; $P < .05$). Subjects without a family history of RLS were significantly more likely to describe their symptoms as painful (85% versus 61%; $P < .05$), while those with a family history reported a greater influence of alcohol consumption on their symptoms. Finally, female subjects in the study with a family history of RLS had notably more frequent worsening of symptoms during pregnancy.[23]

A study of 12 monozygotic twins, where at least 1 of the twins had an RLS diagnosis, found concordance in 10 of the twins (83.3%). Interestingly, all 10 pairs in which concordance was observed, in addition to 1 of the other 2 twin pairs, possessed a relative with an RLS diagnosis. In 4 cases, the relative was the twins' mother, in 4 cases it was their father, and in 3 cases, the relative was unknown to the study authors. These data point to a highly penetrant autosomal dominant heredity in RLS. However, particular manifestations of RLS—including age at onset and severity of symptoms—varied in a high proportion of cases. In 1 twin pair, the age of onset differed between twins by 43 years, while a difference of 38 years was observed in age of onset with another twin pair. The gender of the parent with RLS was not associated with either severity of symptoms or age of onset.[24]

A number of genomic studies in RLS have been undertaken, including a genomewide association study by Winkelmann et al, an expanded update of which was published in 2011, which included 922 RLS patients and 1526 controls.[25] Out of 301,406 single nucleotide polymorphisms (SNPs) tested for, the study authors successfully identified 6 significant loci associated with RLS risk.[25]

Genetic risk variants for RLS have been identified in 2 genes, 1 of them the homeobox gene MEIS1, known to be involved in embryonic development, and variants in a second locus containing the genes encoding mitogen-activated protein kinase MAP2K5, and the transcription factor LBXCOR1. A third one, the BTBD9 gene with unknown function, encodes a BTB(POZ) domain.[26]

Stefansson et al identified a genetic variation on chromosome 6 that is associated with periodic limb movements during sleep, a symptom commonly but not exclusively experienced by patients with RLS.[27]

Diagnosis and Clinical Features of RLS

The International Restless Legs Syndrome Study Group (IRLSSG) has produced diagnostic criteria that are generally considered the standard for RLS diagnosis. These criteria comprise 4 essential diagnostic criteria in addition to supportive clinical and associated features of RLS.

The first of the 4 essential RLS criteria describes an urge to move the legs, typically accompanied by uncomfortable paresthesia-like sensations in the legs. Some degree of variability, however, exists within this criterion: subjects may not experience unpleasant sensations in the legs or may not be able to distinguish those feelings from the urge to move. Feelings may also not be confined to the legs, in some cases, but may include the arms as well as other parts of the body. It

appears to be the case, though, that patients who seek medical interventions are more likely to experience both the urge to move and unpleasant sensations as well.[28]

The second essential criterion for RLS is that both the urge to move and the sensations described in the first criterion begin, or become exacerbated, while the patient is inactive or resting, typically while he/she is in a sitting or lying down position. The state of restfulness is not confined only to physical rest but also refers to diminished CNS activity and a consequent decrease in alertness. It may be the case that a state of alertness while physically resting—accomplished, perhaps, by engaging in a mental activity—may lessen the likelihood of the urge to move and the onset of unpleasant sensations during the resting state. It should be noted that pain or discomfort engendered by being in a resting position should not be misdiagnosed as RLS.[28]

The third criterion posits that the movement urge and accompanying sensations are relieved when the subject engages in movement, in terms of both mobility and walking, as well as stretching. This relief from symptoms will normally occur immediately or nearly immediately after movement is initiated and will endure so long as movement continues. In many cases, however, symptom relief due to movement may not be total and/or may be accompanied by a sense that the symptoms will return after the cessation of movement.[28]

The final essential criterion for RLS states that the urge to move and unpleasant accompanying symptoms are at their most intense at night or in the evening. This difference may diminish, or even become unnoticeable, among patients experiencing very severe symptoms.[2,28]

The IRLSSG has developed a symptom severity rating scale—a questionnaire filled out by patients—that may help clarify a patient's status, although it is primarily used to determine treatment efficacy. The IRLSSG scale includes 10 items evaluating both the frequency and severity of symptoms over the previous week. A 4-point score is employed where 0 denotes no symptoms and 4 denotes very severe symptoms.[6]

Supportive Clinical Features. Supportive clinical features need not be present for a diagnosis of RLS, but may help confirm diagnosis in patients where the presence of RLS is uncertain. A family history of RLS is one example of a supportive feature, as is response to treatment for RLS. Periodic limb movements in sleep (PLMS) and periodic limb movement disorder (PLMD) are also described as supportive features in the IRLSSG diagnostic criteria.[28] However, sleep studies are not required to make a clinical diagnosis of RLS.

PLMS and PLMD are potentially confounding features in RLS diagnosis. PLMS describes periodic movements that occur during sleep; these movements can be highly disruptive to sleep. PLMS typically involve flexion of the knee, large toe, hip, and ankle; have a duration of between one-half of a second and 5 seconds; and recur approximately every 20 to 40 seconds. Although the timing patterns of PLMS are reasonably predictable, their motor patterns can be highly variable.[5,28] The designation PLMD describes a sleep disturbance that is both significant and characterized by PLMS and which may not be ascribed to another sleep disorder, although PLMS is a feature of other sleep disturbances.[5] Indeed, the overwhelming majority of people with RLS experience PLMS; so much so, in fact, that PLMS and PLMD are frequently mistaken for RLS. However, only a minority of patients that have PLMS have RLS symptoms.

Patients who have RLS symptoms should undergo a neurological examination looking for evidence of neuropathy. A complete blood count, metabolic profile, and serum ferritin should be tested to look for secondary causes of RLS.[1,23]

Disease Burden

The symptoms of RLS can make it difficult to fall asleep and stay asleep; the resulting sleep disruption impacts quality of life (QoL). In the REST study, 60.6% of respondents with RLS reported disturbed or interrupted sleep as a result of their RLS.[3] The impact of RLS on QoL is very substantial, as evidenced by numerous studies on the subject. Abetz et al employed the Medical Outcomes Study 36-Item Short Form health survey (SF-36) to compare 85 RLS patients with published norms for the general population (n = 2474). Highly significant differences were observed across all SF-36 domains, showing RLS patients to have poorer physical functioning and greater bodily pain, as well as worse general and mental health (all P <.001).[29] Kushida et al also used the SF-36 in a nationwide survey that included 158 people with RLS. They also observed significantly lower scores among RLS patients compared with a general population control group. Although mental health scores were substantially lower among RLS patients, the greatest differences were observed in the areas of bodily pain, physical functioning, and general health.[30]

Other studies that have focused on the psychological burden of RLS include a German observational study published in 2011 by Scholz et al which employed 3 separate instruments—the Symptom Checklist 90-R (SCL-90-R) questionnaire, the Beck Depression Inventory-II (BDI-II), and the International RLS Severity Scale (IRLS)—to evaluate mental health effects of RLS on a patient population that included 69 untreated RLS patients and 62 treated RLS patients who were dissatisfied with their treatment.[31] Compared with a sample of the German general population, untreated patients' scores were significantly

worse (although within normative ranges) in the somatization, compulsivity, depression, and anxiety subscales of the SCL-90-R. Compared with the untreated group, RLS patients dissatisfied with their treatment had significantly higher levels of psychological distress, compulsivity, depression, anxiety, and phobic anxiety. An overall correlation was observed between psychological impairment and RLS severity.[31]

A US survey by Allen et al of 250 people with RLS sought to determine the burden, costs, and effects on productivity of RLS. Burden, described in terms of severity of symptoms, broke down as follows: mild 11.7%, moderate 41.5%, severe 38.5%, and very severe 8.3%. Results from application of the EuroQol 5-Dimension (EQ-5D) scale showed very highly significantly lower health utility scores among people with RLS compared with healthy controls (P <.0001).[32] Regarding productivity, half of the RLS subjects in the study were employed, working an average of 30.4 hours per week, and 15% performed volunteer work. The weekly absenteeism rate among employed subjects was 1.1%, or 0.3 hours, while among employees who went to work, on-job effectiveness was diminished by 13.5%. A strong correlation between lost productivity and severity of symptoms was observed (r = 0.54; P <.0001).[32]

Management of RLS

Numerous approaches to the treatment of RLS are regularly employed, including both pharmacologic and nonpharmacologic therapies. Silber et al offer suggestions for therapy in 3 RLS patient categories: intermittent RLS (requiring periodic but not daily treatment), daily RLS (requiring daily therapy), and refractory RLS (ie, daily RLS in which dopamine agonist therapy has been inadequate and/or produced intolerable adverse effects and/or produced augmentation against which the addition of early doses has not proved effective).[33]

Dopamine agonists have, for some time, represented the mainstay of RLS therapy and are employed in all categories of RLS.[33] Non-ergot dopamine agonists—pramipexole, ropinirole, and rotigotine—have generally been preferred to ergot agonists such as pergolide due to a lower risk of side effects.[33] The non-ergot agonist rotigotine, delivered via a transdermal patch, has shown efficacy in the treatment of moderate-to-severe RLS.[34-36] Long-acting dopamine agonists including rotigotine are particularly suited for a significant number of patients with RLS that experience daytime symptoms.[2] Pramipexole, ropinirole, and rotigotine have received approval from the US Food and Drug Administration for the treatment of moderate-to-severe RLS.[37-39]

Levodopa/carbidopa has a rapid onset, but relatively short duration, of action, even in its controlled-release formulation, making it most appropriate only for intermittent symptoms. Although it is certainly an effective treatment, levodopa is associated with high risk for augmentation if used daily.[7,33,40,41] Augmentation is characterized by worsening of symptoms, symptoms that start earlier in the day, or symptoms affecting new areas (eg, the arms).[15] Levodopa preparations should not be prescribed for daily RLS.

A possible adverse effect related to the use of dopaminergic agents for RLS is the development of an impulse control disorder, for example, compulsive shopping, compulsive eating, pathologic gambling, or hypersexuality.[42]

Gabapentin is an alternative treatment for daily RLS, particularly in patients with neuropathic pain, and as an add-on to dopamine agonist therapy in refractory RLS.[7,33,43] Gabapentin enacarbil, a prodrug of gabapentin, has been studied in RLS as an alternative to gabapentin, with preferable pharmacokinetic characteristics (ie, predictable and sustained drug exposure). A 2011 double-blind, placebo-controlled trial found gabapentin enacarbil to be effective and well tolerated in patients with RLS.[44] Among other pharmacologic options, clonazepam and zolpidem may be appropriate for use in intermittent RLS, particularly where insomnia is recurrent, and may also be used in combination with a dopamine agonist in refractory RLS.[7,33,45] Low-potency opioids may be used in intermittent and daily RLS, particularly when pain is present, although clinical trial data supporting their use is not robust, and the risk of abuse must also be taken into consideration.[7,33]

With regard to nonpharmacologic therapies, which are appropriate for both intermittent and daily RLS, Silber et al recommend avoidance of caffeine, nicotine, and alcohol, as well as avoidance of medication that may aggravate RLS (Table). Iron replacement therapy may also be effective, while engaging in activities that increase CNS alertness, as previously discussed, may reduce the occurrence of RLS symptoms.[33] A study by Aukerman et al published in 2006 also points to the potential of exercise to reduce RLS symptoms.[46]

Summary

While the etiology and pathophysiology of RLS remain only partly understood, a growing body of study data have served to establish the central role of dopaminergic dysfunction and the relationship to it of iron deficiency. Heredity and genome studies have also helped to uncover a strong genetic involvement in the risk of developing RLS. The importance of accurate diagnosis and effective treatment for RLS is underscored by the toll that RLS takes upon the lives of affected individuals, in terms of both physical limitations and psychological distress. RLS may manifest in diverse and heterogeneous ways; effective treatment for RLS is available and should be tailored to the specific needs of patients.

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