REVIEW

Update on the management of restless legs syndrome: existing and emerging treatment options

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Abstract: Restless legs syndrome (RLS) is a sensorimotor disorder, characterized by a circadian variation of symptoms involving an urge to move the limbs (usually the legs) as well as paresthesias. There is a primary (familial) and a secondary (acquired) form, which affects a wide variety of individuals, such as pregnant women, patients with end-stage renal disease, iron deficiency, rheumatic disease, and persons taking medications. The symptoms reflect a circadian fluctuation of dopamine in the substantia nigra. RLS patients have lower dopamine and iron levels in the substantia nigra and respond to both dopaminergic therapy and iron administration. Iron, as a cofactor of dopamine production and a regulator of the expression of dopamine type 2-receptor, has an important role in the RLS etiology. In the management of the disease, the first step is to investigate possible secondary causes and their treatment. Dopaminergic agents are considered as the first-line therapy for moderate to severe RLS. If dopaminergic drugs are contraindicated or not efficacious, or if symptoms are resistant and unremitting, gabapentin or other antiepileptic agents, benzodiazepines, or opioids can be used for RLS therapy. Undiagnosed, wrongly diagnosed, and untreated RLS is associated with a significant impairment of the quality of life.

Keywords: pathophysiology, quality of life

Overview of the pathology of restless legs syndrome

Diagnostic criteria

Restless legs syndrome (RLS) is a common neurological sensorimotor disorder characterized by a circadian variation of symptoms. It is counted either as a neurological movement disorder or as a "nonapnea" sleep disorder. The diagnosis is based on 4 essential clinical consensus criteria: (1) a compelling urge to move the legs (sometimes also the arms are involved), usually accompanied or caused by uncomfortable and unpleasant sensations deep in the legs (sometimes the urge to move is present without the unpleasant sensations); (2) the symptoms begin or worsen during periods of rest or inactivity; (3) they are partially or totally relieved by movement; and (4) symptoms are worse in the evening or at night 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).[1] In addition to the 4 essential criteria, there are 3 criteria that can support the diagnosis: family history, response to dopaminergic treatment, and presence of periodic leg movements in sleep (PLMS; Table 1). RLS might also be present in a pediatric environment: in addition to the 4 essential adult criteria, children should be able to describe in their own words sensations that would be consistent with leg

Table I Essential clinical consensus criteria for the diagnosis of RLS and supportive criteria[1]

Essential diagnostic criteria	
1. Uncomfortable sensations, urge to move	Urge to move the limbs (usually legs), associated to or caused by uncomfortable sensations
2. Rest brings on the symptoms	Onset of urge to move or uncomfortable sensations during periods of rest or inactivity – independent of the body position
3. Movement relieves the symptoms	Urge to move or uncomfortable sensations are partially or totally relieved by movement, such as stretching or walking
4. Evenings and night time are worse	Urge to move or uncomfortable sensations are worse in the evening or night or occur only in the evening or night (for severe RLS, the worsening at night time might not be noticeable, but must have been present previously)
Supportive criteria	
5. Family history	
6. Response to dopaminergic treatment	
7. Periodic leg movements in sleep (PLMS)	

Abbreviations: PLMS, periodic leg movements in sleep; RLS, restless legs syndrome.

discomfort.[2] Other supportive evidence for the diagnosis in children include the presence of sleep disturbance specific for age, a family history of RLS, and the presence of PLMS, after excluding other potential causes of discomfort, such as breathing disorders, medication-related side effects, neuropathies, arthritis, and certain types of dermatitis.[2,3] RLS is one of the few disorders for which no laboratory or clinical test is available to confirm the diagnosis; the physical examination is generally unremarkable and neurological signs, apart from PLMS, are lacking.

Historical perspective

RLS symptoms were described for the first time by Willis[4] in 1672 as "leapings and contractions of the tendons, and so great a restlessness and tossings of their members ensue that diseased are no more able to sleep than if they were in place of greatest torture".[4] The first description of RLS as a hereditary disorder dates back to the "Textbook of Nervous Diseases" published by Oppenheim[5] in 1923 and it was first clinically described by Ekbom[6] in 1945.

Prevalence of RLS

Most of the studies performed in Europe and North America report a prevalence between 4% and 12% in the general population.[7–11] Several studies have shown a predominance in women who are affected approximately twice as often as men,[9,12,13] and in the elderly with a prevalence of 10%–24%.[14,15] A large-scale survey revealed that RLS is also common in children and adolescents with an estimated prevalence of 1.9% in school-aged children and 2% in adolescents, with no significant gender differences.[2] Two studies show unexpectedly low prevalence in Asian populations: the prevalence in a Turkish population was 3.2% and in 2 samples of Singapore, a prevalence of 0.6% and 0.1%, respectively, was determined.[16,17]

Primary vs secondary RLS

RLS is classified as either primary (idiopathic, familial) or secondary (acquired, symptomatic) RLS. Primary RLS has a clear genetic component: and it is estimated that approximately 50% of first-degree relatives of RLS patients will eventually develop RLS. This frequency is 3–5 times higher when compared with first-degree relatives of individuals without RLS.[1] RLS-pedigrees point in most cases to an autosomal dominant transmission pattern. Also the age at onset seems to play an important role in primary RLS: patients with an age at onset before 45 years were shown to have a significantly higher number of affected relatives compared with patients with an onset after 45 years.[18] Thus, RLS with an early age at onset and a positive family history points to underlying genetic factors as being responsible for the pathology.

Secondary RLS is due to other underlying clinical conditions, such as pregnancy, end-stage renal disease, iron deficiency, rheumatic disease, and drug intake. Many of these circumstances involve altered iron homeostasis. Symptomatic RLS remits with correction of the underlying condition.

Rating of symptom severity

To evaluate the severity of symptoms, 2 rating scales were developed and validated. The Johns Hopkins restless legs severity scale provides a reliable, valid, and easily used clinical assessment for RLS severity.[19] It judges severity by the time of symptom onset on a 4-point scale with 0 for no symptoms, 1 for symptoms at bedtime only, 2 for evening and bedtime symptoms, and 3 for day and night symptoms. The International Restless Legs Syndrome (IRLS) Study Group has developed a 10-item scale with questions related to the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence and impact of RLS on activities of daily living and mood.[20] The responses are graded from 0 to 4 (i,e. 0 for absence of symptoms and 4 for very severe symptoms). A correlation between IRLS and objective parameters of

motor dysfunction such as PLMS was demonstrated.[21] The IRLS is used especially in evaluating treatment efficacy.

Periodic leg movements in sleep

In about 80% of RLS patients, PLMS are associated with the syndrome.[22,23] PLMS are recorded by leg actigraphy using an accelerometer,[24] or by electromyography (EMG) during polysomnography, and they are defined as repetitive movements of the lower limbs (at least 4 in a series) with a duration of 0.5–10 seconds at intervals of 5–90 seconds. In addition, quantitative requirements, such as increase of the EMG amplitude to ≥ 8 μV above the resting level, have been defined.[25] Results from the Suggested Immobilization Test have also shown that RLS patients frequently have PLM while awake (PLMW), whereas in control subjects the frequency of these movements is very low.[26] PLMS are not limited to RLS alone, but occur in several other medical conditions[27,28] and sleep disorders involving a dopaminergic impairment.[29] PLMS lead to multiple awakenings at night and severe sleep disruption and may, at least in part, be responsible for the sleep impairment in RLS. In a polysomnographic study of 26 RLS patients, sleep efficiency was decreased by 50% and 30% of patients obtained less than 3.5 full hours of sleep per night.[30]

Genetic aspects

Ekbom[31] described RLS families with an autosomal dominant inheritance pattern and estimated the frequency of hereditary RLS to be one-third compared with sporadic RLS. Several studies have confirmed these early observations, and familial aggregation of RLS symptoms has been well documented. Between 40% and 90% of patients report having at least one affected first-degree relative with RLS.[32,33] However, the different phenotypic expression of RLS, the presence of sometimes mild and intermittent forms, and the absence of a biological marker for the diagnosis make genetic studies demanding. The presence of PLMS can support the diagnosis; however, it often occurs also in unaffected family members as an asymptomatic condition in individuals who later may develop RLS, and therefore caution needs to be taken.

Linkage studies have identified several genomic loci to be associated with RLS (*RLS1 – RLS5* on chromosomes 12q, 14q, 9p, 2q, and 20p, respectively) in single families, but no gene mutation has yet been identified.[34–38] Further evidence of a locus on chromosome 9p, which is probably distinct from *RLS3,*[39] and of a locus on chromosome 16p[40] was detected by linkage, and suggestive evidence exists for linkage to chromosome 19p.[41] Given the subjective nature of the RLS phenotype, until specific variants are identified within the

loci described above, care should be taken in interpreting their significance. The locus on chromosome 12q (*RLS1*) was further investigated and an association between variants in the *NOS1* gene and RLS was detected, which suggests the involvement of the nitric oxide/arginine pathway in the pathogenesis of RLS.[42]

Genome-wide association studies with high density single nucleotide polymorphism (SNP) data have identified regions with a major contribution to RLS on chromosomes 6p (*BTBD9*), 2p (*MEIS1*), and 15q (*LBXCOR1/MAP2K5*).[43,44] In Icelandic and American RLS patients, a common intronic variant in the *BTBD9* gene was associated with RLS with PLMS.[43] Interestingly, the highest odds ratio was observed in subjects with PLMS without RLS and the association disappeared completely in subjects with RLS without PLMS. A second important aspect of the Icelandic study is the association of the variant in *BTBD9* with reduced serum ferritin levels (decrease of 13% per copy of the risk allele). This is the first time a clear association of a major genetic risk factor for RLS and PLMS with reduced iron in serum is described.

A second study also detected an association between RLS and an intronic variant in *BTBD9*, as well as 2 additional intronic SNPs in *MEIS1* and a region containing the genes *MAP2K5* and *LBXCOR1* on chromosome 15q.[44] The results were replicated in 2 further case-control samples from Germany and a French-Canadian population. Since the authors of this study did not report on PLMS, it is unclear how much of the association is due to RLS, PLMS, or the combined phenotype. An RLS-associated risk haplotype consisting of 2 SNPs in the *MEIS1* gene was shown to be correlated with a decreased *MEIS1* mRNA and protein expression in lymphoblastoid cell lines and brains of RLS patients compared with carriers of the nonrisk haplotype, suggesting that reduced expression of *MEIS1* predisposes to RLS.[45] Vilarino-Guell et al[46] identified an arg272-to-his substitution (R272H) in *MEIS1* in 4 RLS patients of 1 family, but also in 1 unaffected family member. The R272H variant was not found among 378 additional RLS cases or 528 controls from North America, but it was found in 1 of 325 European controls. This is an interesting finding, but warrants replication.

The risk variants in the 3 genomic regions have been calculated to carry a combined population attributable risk (PAR) of approximately 68.6% in the German population and 74.2% in the Canadian population.[44] The PAR for the variation in the *BTBD9* gene was calculated to be 50% in the combined Icelandic and American populations.[43]

In addition to these 3 regions, the *PTPRD* gene was identified as the fourth genome-wide significant locus for RLS.[47] Despite

the risk captured by variants at these loci, additional major susceptibility loci for the disease might still exist.

Association of RLS and other movement disorders

Several studies have assessed the association between Parkinson disease (PD) and RLS.[48] Overall, these studies indicate that RLS is more frequent in PD patient cohorts compared with controls. However, the consensus criteria for RLS diagnosis have not been validated in PD patients,[49] and symptoms of restlessness could be partially explained by the presence of parkinsonism and associated sensory complaints. On the other hand, RLS as well as PD responds to dopaminergic agents and a positive response to levodopa supports the diagnosis of both conditions. In addition, a co-occurrence of RLS and *Parkin* mutations (that are associated with familial parkinsonism) has been described[50] and the authors were able to show that the presence of a heterozygous *Parkin* mutation in RLS patients linked to *RLS4* can lower the age at onset of RLS.[51] Taken together, these data suggest a possible connection between both diseases, although more accurate assessments are necessary.

A high frequency (33%) of RLS in patients with essential tremor has been described and these RLS patients had a high rate of familial history. In fact, in several families, essential tremor cosegregated with RLS, suggesting that these 2 conditions share some common genetic determinants.[52]

A higher frequency of RLS is also reported for spinocerebellar ataxia patients, compared with controls, but the probability of developing RLS did not increase with CAG repeat length[53] and there was no reduction of the dopamine type 2-receptor (D2) availability in the striatum of ataxia patients with RLS.[54]

Pathophysiology

The excellent response to treatment with dopamine agonists (DA) and levodopa, and the exacerbation of RLS symptoms with the use of dopamine antagonists[55,56] provided the basis for the hypothesis that dopaminergic pathways are involved in RLS. The circadian nature of RLS symptoms with the worsening during the night, when dopamine levels decrease, further supports the correlation between RLS and altered dopaminergic metabolism or signaling.[57] Iron has been implicated in the pathophysiology of RLS, given that several secondary causes of RLS (iron deficiency, pregnancy, and end-stage renal disease) share a common factor (i,e. iron insufficiency), and in a small nonrandomized study, intravenous iron supplementation improved symptoms of both primary and secondary RLS.[58]

This suggests that abnormal use and/or storage of iron is related to the development of RLS symptoms.

Positron emission tomography (PET) studies have shown mild, but significant decrease in D2-receptor binding in both the putamen and the caudate, and a decreased uptake of ^{18}F-dopa in the striatum in patients with RLS.[59,60] ^{18}F-dopa uptake was reduced by approximately 10%–12% in RLS patients compared with controls. This relatively small reduction might reflect the fact that imaging was not performed at night when RLS symptoms are most pronounced. A similar finding was reported in a study using [123I] beta-CIT and [123I] IBZM single photon emission computed tomography (SPECT).[61] A study on autopsy samples from patients with very severe RLS showed a 30% decrease in D2-receptor compared with controls.[62] These results are consistent with prior animal studies, where iron deficiency strongly correlates with a decrease in D2-receptor binding in the rat striatum.[63] In addition, the RLS tissue showed a significant increase in tyrosine hydroxylase (TH) and phosphorylated (active) TH in the substantia nigra.[62] These data are surprising, but consistent with a recent cerebrospinal fluid (CSF) study reporting greater 3-ortho-methyldopa (3-O-MD), a product of levodopa metabolism, in patients with severe RLS indicating possible increased dopamine production.[64]

To assess the iron status in RLS patients, magnetic resonance imaging (MRI) measures of regional brain iron and measurements of ferritin and transferrin levels in CSF have been performed. MRI studies have consistently shown decreased iron stores in the substantia nigra,[65] and these data were confirmed also by different techniques, such as transcranial ultrasound.[66] In a neuropathologic examination of 7 RLS brains, no histopathologic abnormalities were detected, but staining for iron and H-ferritin was reduced in the substantia nigra and transferrin receptor staining was reduced in neuromelanin-containing cells, suggesting that the iron acquisition by the neuromelanin cells may be impaired in RLS.[67] Earley et al[68] found significantly reduced ferritin and increased transferrin in the CSF of 16 RLS patients compared with age-matched controls. This finding, observed in the presence of normal serum iron values, is consistent with deficiencies in central nervous system (CNS) iron levels and is confirmed in a second study of Mizuno et al.[69] CSF analyses also provide evidence for a dysregulation in the dopaminergic system in RLS. Both 3-O-MD and tetrahydrobiopterin, a cofactor for TH, were increased in CSF samples of RLS patients compared with controls.[64] These data from CSF analyses from RLS patients support the concept of low brain iron and impaired dopaminergic function in RLS patients.

Recently, higher mitochondrial ferritin (FtMt) levels and higher numbers of mitochondria were detected in the substantia nigra of 8 RLS patients compared with 8 controls.[70] Neuromelanin-containing neurons in the substantia nigra were the predominant cell type expressing FtMt. An induction of mitochondriogenesis seems to take place in RLS; this may be the result of cellular attempts to correct metabolic insufficiency and leads to cytosolic iron deficiency. This would be consistent with the previous reports of lower brain iron levels in RLS.

Rationale of treatment options

With RLS being both a sensory and motor disorder (with the presence of PLMS), it is hard to precisely localize the anatomic areas involved in this clinical condition. Nevertheless, the responses to medication that cross the blood-brain barrier suggest the involvement of the CNS. This hypothesis is supported by 2 types of evidence the administration of metoclopramide, an antiemetic dopamine antagonist that crosses the blood-brain barrier, worsens the symptoms of RLS, while domperidone, another dopamine antagonist that does not cross the blood-brain barrier, is well tolerated and does not exacerbate any RLS symptom.[71] Second, although it is still not well known whether PLMS and RLS share the same pathogenetic pathway, despite the frequent association of the 2 symptoms, it is interesting to note that dopaminergic receptors are also distributed throughout the spinal cord, both in the ventral and dorsal horns, as well as in the white matter.[72] The involvement of the ventral horn might underlie some of the motor symptoms, such as PLMS, whereas the dorsal horn could address the paresthesias and pain perceptions.[73,74]

Several authors have shown an increased spinal flexor reflex excitability in RLS individuals during waking and sleep, and the fact that sensory and motor symptoms are usually bilateral and segmentally localized in the legs strengthens the hypothesis of spinal cord involvement. In addition, several case-reports describe the onset of RLS shortly after spinal pathologies, such as lumbosacral radiculopathy, traumatic lesions, transverse myelitis, vascular injury of the spinal cord, multiple sclerosis, and syringomyelia.[75] Finally, studies that aimed to evaluate the cortical activity before the appearance of involuntary PLMW or PLMS showed that these movements are not preceded by a Bereitschafts-potential, thus making a cortical origin of the movements unlikely.[76] However, some desynchronization in the beta activity at a cortical level is present before both voluntary and involuntary leg movements in RLS.[77]

As already described, an association between RLS and systemic iron deficiency has been long recognized. A possible etiologic role of iron deficiency was suggested more than 50 years ago, after the successful treatment of RLS with intravenous iron.[78] Low iron storage and disturbances in iron transport or metabolism may lead to RLS,[30] and abnormalities in brain iron storage are strongly associated with RLS severity. The exact mechanisms contributing to RLS development are still unknown. It has been hypothesized that although iron stores and metabolism may be sufficient for assuring normal erythrocyte production, they may be insufficient for maintaining normal brain iron stores.[65,68,79] The distribution of iron in the brain is heterogeneous, but it is prevalent in dopaminergic regions, such as the substantia nigra and the striatum. There are several interactions between iron and dopamine: first, iron is a cofactor for TH, which is the rate-limiting step in the production of dopamine.[80] Second, iron modulates the expression of D2-receptors in animal brains.[81] Iron deprivation in rats results in a 40%–60% reduction in postsynaptic striatal D2-receptors, but not in D1-receptors.[63] In addition, in patients with RLS, ferritin concentration in the CSF was shown to be reduced, whereas transferrin concentration was increased.[18] These studies support the hypothesis that local, rather than general changes in iron status may account for clinical manifestations of RLS. Ferritin provides a measure of whole body (including brain) iron storage, whereas transferrin reflects tissue requirement for iron. Since serum iron values are directly affected by diet, stress, sleep behavior, and circadian patterns, low serum ferritin levels are a better indicator of iron depletion. Transferrin helps identifying excessive iron, but does not accurately identify reduced iron stores.

The involvement of the dopaminergic system in RLS is supported by numerous lines of evidence, including lower concentrations of dopamine metabolites and homovanillic acid levels in nocturnal urinary excretion from subjects with PLMS,[82] significant differences in CSF dopamine metabolite concentrations between morning and evening from RLS patients compared with healthy controls,[83] and the dramatic improvement of RLS symptoms with dopaminergic agents.

In addition to a dopaminergic system involvement, an involvement of the pain system in RLS was first highlighted in 1945 when Ekbom[84] described 2 forms of RLS: one classically characterized by paresthesias and the other characterized by the presence of pain, more difficult to diagnose and to treat. Pain discrimination seems to be impaired in RLS individuals, both in idiopathic and in secondary RLS.[84,85] In addition, in a sample from a psychiatric practice the occurrence of RLS was related to the intake of nonopioid pain killers, speculating therefore that central sensitization by nonopioid overuse could play a role in RLS.[86] Nevertheless, as for dopaminergic

drugs, the most convincing evidence supporting the involvement of the opiate system is the effectiveness of the opioid therapy in RLS patients, and most precisely those agents that specifically target opioid μ-receptors.[87] In addition, there is strong evidence that endogenous opioids modulate dopamine systems in the brain and endogenous as well as exogenous opioids appear to increase extracellular dopamine levels.[88]

Management issues: efficacy and tolerability/safety in the treatment of RLS
Nonpharmacological treatment

Figure 1 summarizes an algorithm for RLS management.[89] The treatment for RLS is mainly pharmacological.

Nevertheless, nonpharmacological treatment should be first tried in the management of this condition. Sleep hygiene (regular hour to go to bed at night, use of the bed only for sleep and sexual activity – not, for example, for reading or watching TV) and avoidance of stimulating substances, such as caffeine, nicotine, and alcohol, or medications such as antidepressants, antipsychotic and antihistaminic agents have been suggested to be efficacious, especially in younger patients with mild or intermittent symptoms.[89,90] However, in clinical practice, nonpharmacological strategies have shown little efficacy, even if controlled studies are still lacking. Physical activity in the evening hours, although not strenuous exercise, may delay the need for pharmacologic intervention into a time later in the evening. During times of forced immobilization, such as airplane flights, patients may
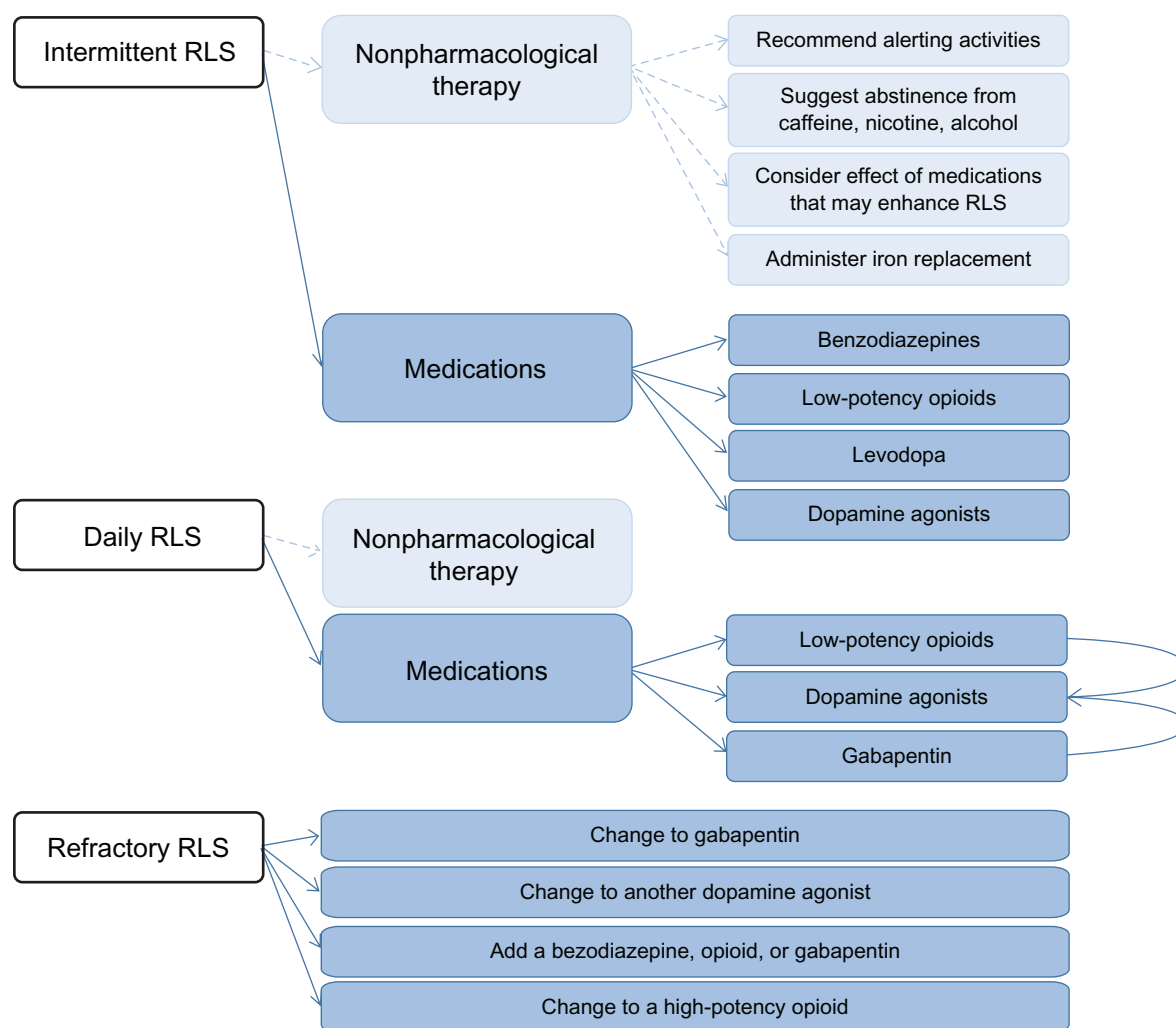
Figure 1 Algorithm for the management of RLS.
Source: Adapted from Silber et al.[89]
Notes: Dopamine agonists are the treatment choice in most patients. Low-potency opioids and gabapentin are valuable alternatives for the treatment of daily RLS, but dopamine agonists should be used if they are unsuccessful.
Abbreviation: RLS, restless legs syndrome.

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find that mentally stimulating or alerting activities such as playing computer games, performing intricate needlework, or reading an engaging novel may lessen their symptoms of RLS.

Recognizing a secondary cause of RLS and targeting its specific treatment is instead of much greater importance. For example, polyneuropathies (including diabetic, alcoholic, amyloid, etc) or radiculopathies inducing dysesthesias or severe pain may worsen RLS symptoms, elevate complaints above the perception threshold in RLS individuals, or even completely mimic RLS. The exclusion of such conditions, or their treatment, is therefore essential for the correct management of RLS patients.

Uremia secondary to kidney failure is highly associated with RLS, although the mechanism by which uremia causes RLS is not known. Dialysis does not improve RLS, but it seems that RLS symptoms correlate with greater dialysis frequency. Contrarily, kidney transplantation seems to drastically improve RLS symptoms within days or weeks.[91,92] Pharmacologic treatment of uremic RLS is similar to idiopathic RLS, but might require higher dosages (especially of dopaminergic agents) and these patients are more prone to be refractory. A recent study shows an association between RLS and chronic renal failure (CRF) in nondialyzed patients. Interestingly, CRF patients with RLS showed the presence of an iron deficiency compared with the CRF patients without RLS.[93]

Iron therapy

Iron deficiency is by far the most common cause of secondary RLS, and can account also for RLS during pregnancy, where hemoglobin levels have been found to be lower than normal.[94] In order to establish whether there is an iron deficiency, serum ferritin more accurately captures whole body iron storage, as serum iron does not allow the estimation of the brain iron storage. Oral iron supplementation may improve RLS symptoms,[95,96] but its usage has always been hindered by either a low efficacy[97] or the poor absorption and tolerability at required doses. The absorption of oral iron supplementation is indeed inversely related to the concentration of serum ferritin, dropping to 1%–2% when ferritin levels are normal.[98] Iron delivered intravenously does not have this limitation. Intravenous iron sucrose is a well-tolerated iron supplementation which has demonstrated evidence to reduce RLS symptoms in the acute phase (7 weeks) in RLS patients with variable degrees of iron deficiency.[99] Still, its efficacy has been argued for the long-term follow up.[100] Iron dextran has been shown to increase brain iron content and

to improve refractory RLS,[98] but results are inconsistent and not free of possible side effects, such as anaphylactic reactions. In addition, it has been shown that ferritin levels progressively decline in patients after high intravenous iron supplementations, maybe explaining why high iron doses do not have sustained benefits.[58] Yet, iron dextran may be superior to other intravenous iron preparations for the treatment of RLS[101] and supplemental iron treatments can sustain previously achieved improvements with a single intravenous iron treatment.[58] Nevertheless intravenous iron supplementation has been considered likely efficacious only for the treatment of RLS secondary to end-stage renal disease and remains investigational for RLS patients with normal renal function.[102]

Pharmacological treatment

Pharmacological therapy is considered the most efficient form of treatment for RLS patients. As for many neurological conditions, the aim of the therapy is to provide symptomatic relief. Because RLS is a chronic condition, therapy must usually be continued indefinitely.

Dopaminergic agents

For a vast majority of individuals, moderate to severe forms of RLS can be treated with dopaminergic therapy.[103–106] Both levodopa and DA are normally used and are well tolerated,[106–108] as the dosage used for treatment of RLS is significantly lower than the one used for treatment of PD.[73] DA should be considered as first-line therapy for moderate to severe RLS patients.[109,110] Usually, the administration of the drug is limited to 2–4 hours prior to bedtime.[111] However, particularly if daytime symptoms are present, DA can be given in divided dosages[112] or using prolonged-release formulations,[113–115] favoring the concept of low and continuous dopaminergic stimulation and increasing the benefit of therapy by reducing the risk of augmentation.

Augmentation

Augmentation is the most commonly encountered complication of long-term therapy of RLS with levodopa[116,117] and probably, to a lesser extent, with DA.[102,118–120] It is more likely to occur in patients with low serum ferritin levels.[121,122] Augmentation is defined as an anticipation of RLS symptoms (at least 2 hours before they normally would occur prior to the initiation of drug therapy), intensification and spread to previously noninvolved parts of the body (particularly the arms). In addition, PLMW either occur for the first time or are worse than with initial therapeutic response or before

treatment was started and the time from onset of quiescence to onset of symptoms is typically shortened.[1] The treatment of augmentation may involve adjusting the timing or the dose of the medication or switching to another agent.

If dopaminergic drugs are contraindicated or not efficacious, benzodiazepines, gabapentin and other antiepileptic agents, or low-potency opioids, can be also proposed as therapy for RLS.[89,122]

Benzodiazepines

Benzodiazepines cause CNS depression by directly binding to the receptor for the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and by increasing the affinity for its natural ligand. By improving sleep, benzodiazepine therapy may reduce arousals due to PLMS,[123] but it could be less effective in eliminating movement and sensory abnormalities associated with RLS.[89,124–126] Overall, benzodiazepines seem to have a low risk of adverse effects (mainly somnolence, decreased libido, risk of falls during the night, particularly in elderly patients, and exacerbation of comorbid obstructive sleep apnea) and to remain effective in the long term. Depending upon dosage levels, therapy with benzodiazepines may result in tolerance and dependency; in addition, if therapy is discontinued abruptly rather than through gradually tapered dosages, there may be precipitation of withdrawal. Patients with mild or intermittent symptoms of RLS, particularly young individuals, may receive the most benefit from such therapy. If combined with carbidopa/levodopa or DA, benzodiazepines may assist in the management of severe RLS symptoms and are usually administered orally shortly before or at bedtime.

Antiepileptic drugs

Gabapentin is considered efficacious for the treatment of RLS and therefore, is the most used second-line drug among the anticonvulsant medications. Although its mechanism of action is not clear, it is believed that RLS benefits from gabapentin via a combination of sedative and sensory modulating action.[102,127,128] Carbamazepine, lamotrigine, valproate, levetiracetem, and pregabalin have been also used in the treatment of RLS, although their efficacy has not been confirmed, as the studies showing their efficacy included only few subjects or were open label.[129–137]

Opiates

Opiates seem to be the best of the second choice therapies for patients with resistant or unremitting symptoms,[138] as they are supposed to decrease the release of neurotransmitters producing analgesic effects in the CNS. Some studies have shown that the use of opioids, also those with a lower potency, was able to alleviate paresthesias or dysesthesias, motor restlessness, and sleep disturbances associated with RLS.[89,139–144] Opioid therapy seems to produce minimal side effects (such as nausea and constipation, but also sleep apnea via respiratory depression); however, there is always a risk of opioid addiction among RLS patients and augmentation is also reported.[143,145] Nevertheless, tramadol, a weak μ-receptor agonist, may be considered as an alternative treatment of RLS,[146] whereas oxycodone and methadone (the latter a very potent opioid) can be considered only for the treatment of daily and refractory RLS, respectively.[102,147,148]

Treatment of RLS in children

Untreated RLS in children could potentially lead to severe consequences such as cognitive deficits, attention-deficit hyperactivity disorder (ADHD), sleepwalking, nightmares, and parasomnias.[149,150] Similar to the management of RLS in adults, secondary RLS should be excluded in children. When neuropathies are suspected, thyroid function, fasting blood sugar and insulin, as well as serum levels of vitamins B6, B9, and B12 should be investigated.[151] Sleep hygiene and avoidance of possible triggers (such as serotoninergic drugs, diphenhydramine, metoclopramide, nicotine, caffeine, and alcohol) are essential.[151] Children with low iron stores (defined by low serum ferritin) might benefit from oral iron supplementation. To date, DA agents are not approved in pediatrics and there is very little experience regarding the use of dopaminergic medications in children. Nevertheless, published case-reports show the long-term effectiveness of levodopa and other dopaminergic agents on both RLS and PLMS, as well as ADHD symptoms.[152]

Patient considerations, quality of life (QoL), satisfaction/preference

RLS patients present with a wide range of sensory and motor symptoms, which occur in quiet wakefulness or in sleep, and are often disabling, interfering with sleep and social functions and therefore impairing the QoL.[153] The sensorimotor disorder can cause insomnia and lead to daytime sleepiness. In addition, several other symptoms may occur, such as depression, fatigue, poor concentration, fidgetiness, lower limb pain, and burning feet. The onset of symptoms can be at any age; however, prevalence increases with age.[14] The clinical course is usually chronic progressive with periodic exacerbations. However, in some individuals, symptoms occur in paroxysms or cluster. The sensory symptoms may vary so greatly, that several

misdiagnoses have been posed in the course of the time. There-fore, the diagnosis is now based on the 4 essential consensus criteria.[1] Most frequent sensory symptoms of RLS are general discomfort, cramps, and even pain.[56,154] Lower limb involvement is the commonest presentation, but hand involvement has also been described. There is often bilateral involvement of the limbs, but the symptoms can be asymmetrical.

Motor restlessness is another specific feature of RLS.[8] Patients develop an urge to move the limbs, which partially or completely resolves the unpleasant sensations.[154] The most important differential diagnosis is with akathisia, a condition of constant motor restlessness secondary to neuroleptic use.[154] Pain is an important aspect of symptom expression and can cause difficulties for a correct RLS diagnosis. Upper limb, chin and, posterior neck pain mimicking radicular pain have been described.[155]

Quality of life

The QoL of patients with RLS is primarily impaired by sleep loss, extreme discomfort, reduction of job performance and job tenure, and disruption of normal activities[156] mainly caused by the inability to tolerate sedentary activities. In addition, medications used to treat RLS, including dopaminergic drugs and opiates, are associated with side effects[157] possibly affecting patient's QoL. Furthermore, RLS therapy carries some limitations, for example, levodopa might lead to augmentation, especially with higher dosages.

In order to assess QoL, specific questionnaires have been developed. Both the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI)[158] and the Restless Legs Syndrome Quality of Life (RLSQoL)[157] are specific for RLS. The latter, is an easy-to-administrate, 18-item questionnaire that only takes 10 minutes to administer, and therefore is a valuable tool for clinicians. In a specific study on QoL in RLS individuals, 85% of patients complain that RLS symptoms impair specific aspects of daytime functioning.[8] The most commonly reported problems were negative influence on mood (50.5%), lack of energy (47.6%), and disturbance of normal daily activities (40.1%).[8] The authors concluded that the reduced QoL in patients with RLS was comparable to that experienced by patients who had other serious medical conditions, such as diabetes and clinical depression.[8]

In another study, 36.3% of participants reported that RLS symptoms had a highly negative impact on their lives. Symptoms appeared to have the greatest impact on sleep: 88.4% of participants had sleep-related symptoms (eg, inability to fall asleep, inability to stay asleep, or disturbed sleep) and 43.4% rated sleep disturbance as their most troublesome symptom.[56] Typically, patients with RLS do not report excessive daytime sleepiness, but they do feel tired and not fully alert.[19]

In addition to sleep disturbances, depression seems to be significantly more common among individuals with RLS compared with normal individuals.[14,159–161] The impact that sensorimotor manifestations of RLS have on sleep disturbance (proportion of time kept awake, awakened from sleep, and prevented from falling back to sleep) seem to play the major role on emotion and alertness. Although sleep loss is a major problem for patients with RLS, these individuals tend not to complain of sleepiness but do experience cognitive impairment, in particular in exercises focused on prefrontal cortex activity that are sensitive to sleep deprivation.[162] It is possible that the deficits might be a result of sleep deprivation rather than a direct effect of RLS pathology.

Future research directions

Further studies using consistent diagnostic criteria and large-scale prospective studies are needed to assess the prevalence and incidence of RLS across different populations. A substantial research effort is needed to develop validated diagnostic and severity measures of RLS in children. In addition, there is a strong need for further research about RLS risk factors, including socio-demographic factors, lifestyle, medical conditions, and the use of medications, as well as factors that modify the disease (eg, age at onset and family history). Large epidemiologic and laboratory studies in humans are needed to extend the understanding about the known associations between RLS/PLMS and hypertension, heart disease, and stroke. Although the candidate genes identified so far have provided some more insight into the pathophysiology of RLS, it is important to perform further functional studies and to identify additional genetic factors that modify the expression of the common variants in these genes. In addition, it might be interesting to test these genes also in relation to conditions associated to RLS, such as cardiovascular disease. Genotype–phenotype correlations may be the basis for pharmacogenomic studies to identify more specific medication strategies. In addition, the definition of major genes for RLS is extremely important to gain more insight into the pathogenesis of the disease and therefore to facilitate the development of new therapeutic agents. Genetic data can also contribute to a better understanding of the possible interaction with other movement disorders, like PD, essential tremor, and ataxia. A decisive step in understanding the RLS pathogenesis would be also the development of an RLS animal model. For this attempt, reliable and objectively measurable diagnostic criteria to diagnose RLS in animals should be

developed. Iron pathology is central in the disease process, and iron availability to the brain does at least contribute to the RLS symptoms. Data showing an increased mitochondriogenesis in the substantia nigra in RLS open up an interesting avenue to explain the mechanism of low brain iron levels. The role of iron supplementation, especially for patients who do not have serum iron deficiency, is another important area for future research. Clinical studies addressing iron treatment and focussing on different iron formulations will need to be conducted.

Conclusion

RLS is a sensorimotor disorder, classified either as a movement or a sleep disorder. A significant number of individuals are affected by this disorder that is associated with a substantial impairment of the QoL. It is a major cause of insomnia and has in consequence a negative impact on daytime functioning, job performance, and tenure. Therefore, and because it is still frequently undiagnosed, RLS needs more awareness among health care providers.

There is a strong genetic component, and several genetic linkages and associations that are reflected by the heterogeneity of the phenotypic expression have been identified. The current understanding of the pathophysiology is a local dopaminergic dysfunction in the brain as well as insufficient levels of brain iron. Recent research has provided additional data to support the hypothesis that a primary iron deficiency leads to a dopaminergic abnormality. These data reinforce the empirical results of benefit with dopamine or DA treatment as well as iron injections in RLS. Despite these advances in our knowledge, there remain unanswered questions about the genetics, risk factors, and the pathogenesis, and further research is warranted to better dissect the complex architecture of this disorder, a prerequisite necessary for the development of new treatment strategies.

Disclosure

The authors report no conflicts of interest in this work.

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