

Restless legs syndrome

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ABSTRACT

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), is a common movement disorder characterised by an uncontrollable urge to move because of uncomfortable, sometimes painful sensations in the legs with a diurnal variation and a release with movement. The pathophysiology is only partially known and a genetic component together with dopaminergic and brain iron dysregulation plays an important role. Secondary causes for RLS need to be excluded. Treatment depends on the severity and frequency of RLS symptoms, comprises non-pharmacological (eg lifestyle changes) and pharmacological interventions (eg dopaminergic medication, alpha-2-delta calcium channel ligands, opioids) and relieves symptoms only. Augmentation is the main complication of long-term dopaminergic treatment of RLS. This article will provide a clinically useful overview of RLS with provision of diagnostic criteria, differential diagnoses, possible investigations and different treatment strategies with their associated complications.

Definition and diagnostic criteria

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), is a common neurological movement disorder characterised by an uncontrollable urge to move (mainly the legs).¹ Diagnosis of RLS is based primarily on the patient's history and on a neurological examination to exclude differential diagnoses. The diagnosis can be made if all of the following five criteria are met (International RLS Study Group (IRLSSG) diagnostic criteria):²

- 1 A need to move the legs usually accompanied or caused by uncomfortable, unpleasant sensations in the legs.
- 2 Symptoms are exclusively present or worsen during times of inactivity/rest.
- 3 Partial or total relief of symptoms by movement, such as walking or stretching, at least as long as the activity continues.
- 4 Symptoms are generally worse or exclusively occur in the evening or during the night.

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- 5 The occurrence of the first four essential criteria must not be solely accounted for as symptoms primary to another medical or a behavioural condition.

A single standard question for rapid screening of RLS has been validated by the IRLSSG,³ which is: 'when you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?' This question can be used to effectively screen large patient groups as it has 100% sensitivity and 96.8% specificity for the diagnosis of RLS. However, the final diagnosis should always be confirmed by matching the patient's history and symptoms with the IRLSSG diagnostic criteria, accompanied by an exclusion of secondary conditions.

Aetiology and differential diagnoses

The aetiology of RLS can be categorised as primary (idiopathic) or secondary. The majority of cases are primary

Key points

Restless legs syndrome (RLS) is a common neurological movement disorder, characterised by an uncontrollable urge to move the legs combined with an uncomfortable sensation in the legs.

Diagnosis of RLS is mainly based on history and physical examination, but laboratory tests are essential to rule out secondary RLS and differential diagnosis as demanded in the fifth criterion of the International RLS Study Group diagnostic criteria.

Treatment depends on the severity and frequency of RLS symptoms, comprises non-pharmacological and pharmacological interventions to relieve symptoms only and needs to be tailored to the patient, taking into account age, comorbidities and co-medication.

Dopaminergic medication, alpha-2-delta calcium channel ligands and opioids are commonly used for treatment.

Augmentation is the main complication of long-term dopaminergic treatment of RLS.

KEYWORDS: Restless legs syndrome, RLS, Willis-Ekbom disease, WED, treatment, side effects ■

with unknown origin, affecting middle-aged individuals in a progressive clinical manner. The pathophysiology is partially known and includes a genetic component; six different genes (*BTBD9*, *MEIS1*, *PTPRD*, *MAP2K5*, *SKOR1*, *TOX3*) play an important role, along with dopaminergic and brain iron dysregulation.^{4,5} There are several reports of RLS occurring in families, which suggest an autosomal dominant mode of inheritance with variable expression and possible anticipation as there was evidence for an earlier age at onset in later generations.^{6–8}

Secondary RLS occurs as a result of certain conditions and the three major reversible causes are iron deficiency anaemia, pregnancy and end-stage renal disease.^{9,10} Other secondary causes include vitamin B12/folate deficiency, peripheral neuropathy (associated with diabetes mellitus), rheumatoid arthritis, spinal disorders such as spinal nerve root irritation, Parkinson's disease, fibromyalgia, spinocerebellar ataxia (particularly SCA 3) and Charcot-Marie-Tooth disease (type 2). For differential diagnoses, the following symptoms or diseases should be considered: nocturnal leg cramps, volitional movements such as positional discomfort or habitual foot tapping, painful legs/moving toes syndrome, akathisia, myalgia, vascular disease (eg varicose veins, venous stasis, leg oedema or deep vein thrombosis), intermittent claudication (vascular/neurogenic), arthritis and drug-induced RLS.

Investigations

Diagnosis of RLS is based primarily on the patient's history and neurological examination, which should be normal, and it is important to exclude peripheral nervous system and vascular causes. If peripheral neuropathy is suspected, an electrophysiological examination should be considered – electromyography and nerve conduction studies are normal in RLS patients. Recommended blood tests are summarised in Box 1.¹¹ Levodopa in a test dose can be used as a clinical 'challenge test' for RLS diagnosis.¹² Patients with severe RLS and insomnia may require sleep studies such as polysomnography or immobilisation tests in specialised centres.

Treatment

Treatment depends on the severity and frequency of RLS symptoms, which can be assessed with the help of the RLS severity scale; this scores disease burden from mild to very severe.¹³ Mild RLS may be managed with reassurance

and lifestyle changes, whereas severe RLS may require drug therapy.

First of all, secondary causes and exacerbating factors should be identified and corrected, for example:

- > iron supplementation for anaemia (low serum ferritin levels (<50 µg/L); ferritin needs to be rechecked after iron supplementation)
- > concomitant medications that can induce RLS symptoms or worsen (antidepressants, neuroleptics, beta-blockers, dopamine antagonists, anti-nausea drugs, antihistamines, anticonvulsants, L-thyroxine, lithium).¹⁴

Non-pharmacological interventions involve lifestyle changes (eg avoid high intake of caffeine or alcohol before bedtime) and sleep hygiene (eg sleep in a quiet, comfortable, cool environment, and keep regular bed and wake hours). Furthermore, advice for behavioural strategies during an attack may enable a patient to cope with the RLS symptoms, eg walking and stretching, massaging the affected limbs, bathing in hot or cold water, relaxation exercises (biofeedback or yoga) and distracting the mind.

Pharmacological treatment should be used in a step-by-step approach considering patient age and concomitant diseases. It is only required when the symptoms are clinically significant with impairment of night-time sleep, daytime alertness and quality of life, which occurs in about 10–15% of RLS patients.^{15,16} As the pharmacological treatment only targets symptoms and is not preventive and as RLS is a chronic disorder, it is likely that once the patient starts, the treatment will be lifelong. Table 1 summarises the recommended pharmacological treatment options.^{11,17–22} In general, the dosage should be kept as low as possible and should be administered as a single evening dose. If the patient shows intolerance to one dopamine agonist then another dopamine agonist should be tried first before levodopa or a second-line treatment.

Treatment-related adverse effects

The most common treatment-related adverse effect is augmentation. This is characterised by an overall increase in the severity of RLS symptoms like a paradoxical response to treatment: symptoms get worse with increasing dose of the medication and improve following decrease in medication. The Max Planck Institute (MPI) has defined diagnostic criteria for augmentation.²³ It is the worst long-term problem of dopaminergic treatment of RLS and occurs with the use all dopaminergic agents. Augmentation is highest with levodopa and among the dopamine agonists, it is lowest with rotigotine.²⁴ A few cases have been reported with the use of tramadol.^{14,24} In general, augmentation rates are lower using drugs with a longer half-life and the lowest effective dose. Low plasma ferritin levels, previous episodes of augmentation and longer treatment duration could be identified as predictors of augmentation.^{24,25}

Early morning rebound means a reappearance of RLS symptoms in the morning as medication effects are wearing off. It occurs more frequently with short half-life medication, such as levodopa.²⁶ To manage this complication, the dose of the currently prescribed medication can be increased, the medication intake can be delayed or a dopaminergic medication with a longer half-life can be tried.

Box 1. Recommended blood tests to rule out secondary RLS¹¹

- > iron studies (specifically serum ferritin level)
- > full blood count (to exclude anaemia)
- > serum vitamin B12 and folic acid
- > serum glucose and HbA1C
- > urea and electrolytes
- > serum creatinine
- > thyroid function tests

Table 1. Pharmacological treatment of restless legs syndrome (RLS) with recommended dose, time to full therapeutic effect, half-life and possible adverse effects.^{11,17–22}

Medication		Minimum starting dose – maximum recommended dose	Time to full effect of the therapeutic dose	Half-life	Adverse effects
First-line treatment: dopaminergic agents					
Non-ergot dopamine agonists	Ropinirole	0.25–4.0 mg	4–10 days	6 hours	Augmentation, impulse control disorder, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients
	Pramipexole	0.125–0.75 mg	at first dose	8–12 hours	Augmentation, impulse control disorder, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients
	Rotigotine (transdermal patch)	1–3 mg/24 hours	1 week	5–7 hours	Skin irritation, low risk of augmentation, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients
Levodopa formulation*	Levodopa / carbidopa or levodopa / benserazid	50/12.5 mg –200/50 mg	At first dose	1.5–2 hours	High rates of augmentation and loss of efficacy with rebound phenomena
Second-line treatment for refractory cases					
Alpha-2-delta calcium channel ligands	Pregabalin	2–300 mg	3–6 days	10 hours	Sleepiness, dizziness, headache, fluid retention
	Gabapentin	300–2400 mg	3–6 days	5–7 hours	Sleepiness, dizziness, fluid retention
Hypnotics	Clonazepam	0.5–2.0 mg	First dose: effect mainly on sleep	30–40 hours	High risk of sleepiness, dizziness, morning drug hangover
Opioids	Prolonged-release oxycodone-naloxone	5.0/2.5 mg –40/20 mg twice daily	7 days	1 hour	Constipation, nausea, dizziness, addiction and tolerance, increased sleep apnea, fatigue, somnolence, pruritus, dry mouth
	Tramadol	50–100 mg	At first dose	6.3±1.4 hours	Constipation, nausea, dizziness, addiction and tolerance, increased sleep apnea, fatigue, somnolence, pruritus, dry mouth, augmentation
	Methadone	5–40 mg	At first dose	15–60 hours	Constipation, fatigue, sedation, flush, depression and anxiety

*If patients are intolerant to dopamine agonists or if symptoms are not completely controlled under dopamine agonists, levodopa has shown good short-term effects and is useful for intermittent RLS (symptoms less than three times a week) and as rescue medication.

Impulse control disorders (ICD) as an adverse effect of dopaminergic agents are well known in patients with Parkinson's disease. Despite the lower doses of dopaminergic medication used, the incidence of ICDs during RLS treatment is estimated to be between 3% and 17% and include obsessive-compulsive behaviour, hypersexuality, binge eating, pathologic gambling, punding and compulsive shopping.^{27,28} If ICDs appear, the dopaminergic medication needs to be reduced (or even completely stopped) until the adverse effect resolves. A non-dopaminergic treatment should be tried instead.

Conclusions

RLS is a common neurological movement disorder that can have a great impact on quality of life, mainly as a result of disturbed night-time sleep and daytime somnolence. Secondary causes need to be excluded so treatment can be tailored specifically, eg by iron supplementation. Symptomatic treatment depends on the severity and frequency of RLS symptoms and depends on age, concomitant diseases and medication. In mild RLS, reassurance and lifestyle changes

might be sufficient, whereas in moderate to severe cases, pharmacological treatment is required. ■

Conflicts of interest

The authors declare no conflicts of interest.

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