Restless legs syndrome: chasing the diagnosis

Restless legs syndrome (RLS) refers to a symptom complex of spontaneous, continuous lower limb movements that may be associated with paraesthesias. RLS is often under-diagnosed and under-treated, but its impact on a patient's quality of life is significant. **Dr Rayessa Rayessa** and **Tayyab Haider** explore the diagnostic criterion of an oft-missed illness and discuss the management of this extremely distressing but potentially treatable condition.

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Restless legs syndrome (RLS) is often referred to as the 'most common movement disorder you have never heard of'[1]. It has a prevalence in the general population of between 2.5–15 per cent with an estimated nine million affected individuals in the UK[1,2]. There is also an age-related increase in prevalence[3]. The frequency in men is twice that of women[4]. Family history is usually common in young-onset RLS while patients presenting after 50 years of age usually do not have family history but might have other neuropathic symptoms, such as paraesthesias and dysaesthesias[5,6]. An increased awareness and high index of suspicion is needed to alleviate the resultant misery.

Clinical features

The core feature is an uncontrollable urge to move the legs (akathisia)[7,8]. This may be accompanied by deep pain or paraesthesias that are usually perceived as 'crawling', 'throbbing' or 'bubbling'. These sensations may extend to arms and legs and are usually brought on by rest. The intensity of these symptoms increase as the patient becomes physically more comfortable. Although initially symptoms occur at night, in the later stages of the disease, they occur earlier in the day and then intensify during the night.

RLS is accompanied, in almost 75 per cent of patients, by semi-rhythmic limb movements during sleep that are referred to as periodic limb movements of sleep (PLMS) and indeed may have been observed by the patient's partner long before patient recognised the symptoms[9,10]. PLMS can fragment sleep and can often cause excessive daytime sleepiness. Sometimes patients may present with these symptoms in the form of insomnia, fatigue and, in some cases, worsening attention and memory as a result of loss of sleep.

Clinical types

In primary or idiopathic RLS a positive family history is present in almost 40 per cent of patients[11-13]. Studies suggest an autosomal dominant inheritance. Functional brain imaging in patients has also revealed reduced dopamine uptake in the basal ganglia[14,15]. This might be of interest as there is an increased incidence of RLS in Parkinson's disease (PD)[16]. In addition, a small clinical study found increased levels of brain hypocretin levels[17,18]. These are hypothalamic neuropeptides neurotransmitters that participate in the control of the sleep/wake cycle and are thought to be involved in the disruption of sleep.

Secondary RLS is found in iron deficiency anaemia, uraemia (20–60 per cent of patients undergoing dialysis)[19,20], diabetes mellitus, rheumatic disease and venous insufficiency. Twenty per cent of pregnant women also express signs and symptoms of RLS[21,22]. Diagnosing RLS involves

Table 1 Treatment choices for RLS*

Frequency or quality of symptoms	First choice	Second choice	Third choice
Nightly	Dopamine agonists (DAs)	Opiates	Gabapentin, sedative-hypnotic
Frequent	Sedative-hypnotic	Opiates	Levodopa
Occasional	Levodopa, DAs	Sedative-hypnotic	Opiates
Painful	Gabapentin, opiates	DAs	Sedatives
Refractory	Change to gabapentin, change to a different DA, change to high potency opioid or tramadol		

- Symptoms that occur nightly need daily treatment.
- Symptoms that occur three to five times a week are considered frequent and such patients should be treated as often as necessary
- If symptoms occur fewer than thrice a week they are considered occasional
- Painful symptoms are those which occur with neuropathy or arthritis and are more than just uncomfortable.

* Adapted from Restless Legs Syndrome; Earley CK; *NEJM* 2003; **348**: 2103–9

careful history-taking and a comprehensive neurological examination. Using the diagnostic criterion that has been proposed by the US National Institutes of Health (NIH) and International Restless Legs Study Group (IRLSG), diagnosis is made if the following criteria are fulfilled:

> Irresistible urge to move legs which may be accompanied by deep seated paraesthesias (which may be described as 'creepy-crawly', throbbing, tearing, 'ants marching', 'bubbling like soda water in veins')
> Unpleasant sensations usually happen at rest
> Symptoms are relieved on movement and this relief triggers continuous movement
> Symptoms worsen or may occur only at night.

Features that support diagnosis include:

> Response to dopaminergic therapy
> Family history
> Periodic limb movements.

Diagnosis is largely clinical. The only laboratory test that is warranted is serum ferritin and iron status. Polysomnography is only indicated if there is clinical suspicion of sleep apnoea or if sleep is still disrupted after treatment of symptoms[23].

Primary care management

Current diagnosis and management of RLS in primary care is not optimum with low rates of correct diagnosis (46 out of 357 patients in the REST study[24]). Information and reassurance about the condition is of primary importance.

General self-help measures: Activities that might help include walking, stretching, biofeedback, hot and cold baths, massaging affected limbs and removing aggravating factors. For those with low or borderline ferritin levels a trial of iron therapy is recommended before resorting to pharmacological treatment[25].

Complementary therapies: Selected patient groups report benefit from usage of alternative treatments like holistic massage, acupuncture, transcutaneous electrical nerve stimulation (TENS) and nutritional supplements, though there does not seem to be much evidence behind this.

Pharmacological treatment: Pharmacological therapy is only needed in 20–25 per cent of patients who have severe disabling symptoms. For treatment purposes, RLS can be divided into five categories: intermittent, nightly, frequent, painful and refractory.

Dopamine agonists (DAs): They are effective first-line agents for the treatment of RLS symptoms and can provide 90–100 per cent relief of symptoms and can reduce the PLMS by 70–100 per cent. Pramipexole (the licensed dose for pramipexole for RLS is 0.125mg for four to seven days, rising if necessary to 0.25mg for four to seven days, then 0.5mg and 0.75mg.) and ropinirole (0.25mg daily, increased by 0.25mg every two to three days until relief is obtained) have been licensed for use in RLS in UK. The doses used are significantly lower than that needed for PD and hence side-effects are less and usually transient. Patients may experience nausea, light-headedness, fatigue and insomnia. Ergot DAs (eg, cabergoline) can be used; however, their long-term use is limited by the higher incidence of fibrotic complications. Levodopa is no

Key points

- The diagnosis of RLS is largely clinical and a high index of suspicion is needed.
- The core feature is an uncontrollable urge to move legs and can be associated with leg movements that fragment sleep.
- In the older population it is associated with iron-deficient states, diabetes and uraemia.
- Dopamine agonists remain the mainstay of pharmacological treatment.
- Trials of iron are usually beneficial in iron deficient states.
- Referrals for specialist opinion should be sought in all cases of diagnostic uncertainty and treatment failures.

longer the drug of choice due to the common side-effect of augmentation, which takes the form of onset of symptoms earlier in the day and often extension of symptoms to the arms and the face. These symptoms are less common in DAs (20–30 per cent) as compared with levodopa (80 per cent).

Benzodiazepines: These are usually recommended if symptoms are intermittent, especially if sleep is fragmented. Short acting agents may be used for sleep onset insomnia (difficulty going to sleep or fragmented sleep soon after) caused by RLS (eg, zolpidem) whereas intermediate acting agents (eg, temazepam) can be used for RLS that awakens patients later in the night. Though most trials have been done using clonazepam, its long duration of action may result in more adverse effects (eg, unsteadiness, drowsiness and worsening of cognitive impairment).

Gabapentin: This is an alternative choice for people with daily RLS. It is particularly helpful in patients with painful RLS, especially in the setting of neuropathies (eg, diabetic, uremic), chronic pain syndromes or other neurodegenerative disorders (eg, dementia or PD).

Conclusion

Most cases can be managed in primary care. In the following cases specialist help may be sought:

> Diagnostic uncertainty
> Treatment failure
> Severe refractory RLS for admission and treatment with subcutaneous apomorphine.

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