Restless legs syndrome: symptoms, management and new developments

Restless legs syndrome is a common but misdiagnosed disorder. Symptoms include an intense desire to move the legs when a patient is sitting or lying which is relieved by leg movement or walking. The condition is associated with abnormalities of the dopaminergic system. Drug treatment can be effective but should be confined to more severe cases.

Karl-Axel Ekbom, the Swedish neurologist, published a monograph in 1945 introducing the term 'restless legs' to describe a relatively common but infrequently diagnosed disorder (Ekbom, 1945); his careful, analytic description of the clinical symptoms has not been improved. Ekbom was uncertain as to the aetiology of the condition, suggesting a possible vascular basis, but it is now thought to be caused by a central dopaminergic disturbance. A new approach to treatment using dopamine agonists has produced encouraging results.

Overview of restless legs syndrome

Restless legs syndrome is characterized by an uncontrollable urge to move the legs at rest, with associated unpleasant sensations deep within the legs. The symptoms are relieved by moving the legs, particularly by walking.

Symptoms

The cardinal feature of restless legs syndrome is an irresistible desire to move the legs while sitting or lying down. Dysaesthesia may also be present, variously described by patients as a feeling of crawling, creeping or intense, non-specific discomfort. The patient may describe tingling, twitching or actual pain. The symptoms are localized to the lower limbs, generally the thighs and calves rather than the feet. The complaint is usually symmetrical but can be confined to one leg. Similar symptoms can be experienced in the arms.

The symptoms are improved by stretching or moving the legs and are often resolved by walking rather than simply standing. The symptoms are worse in the evenings and during the night. Many patients describe having to repeatedly get out of bed and walk around the house in an attempt to ease the symptoms. Between 50–80% of patients have involuntary lower limb movements while sitting or attempting to sleep (Coleman, 1982). It is unusual for patients to be troubled by symptoms in the mornings, except in severe cases or with augmentation as a side effect of drug therapy.

The onset is occasionally acute but more commonly patients describe the problem as having been present for 'years', with varied severity. Symptoms generally increase with age. Daytime tiredness is common as a result of a disrupted night-time sleep pattern.

Restless legs syndrome is frequently misdiagnosed. In a population study of over 16 000 adults, the most common alternative diagnoses included 'poor circulation', arthritis, 'back problems', varicose veins, anxiety and 'trapped nerves' (Allen et al, 2005).

Epidemiology

The exact prevalence of restless legs syndrome is unknown, but it is thought that it occurs in about 5–10% of the Western population (Allen et al, 2005); it is less common in Asian population studies (Tan et al, 2001). It is a significant symptomatic problem in about 2% of the population who seek medical advice (Allen et al, 2005). Restless legs syndrome can occur from childhood onwards and prevalence increases with age. Spontaneous remission is unusual unless the condition has been provoked, for example by pregnancy or iron-deficiency anaemia. Females are affected twice as often as males (Allen et al, 2005).

Primary *vs* secondary restless legs syndrome

Primary (idiopathic) restless legs syndrome accounts for most cases, with an age of onset under 30 years. There is familial aggregation in over 60% of cases, and inheritance is thought to be autosomal dominant in over one-third of cases, with some families showing anticipation (Trenkwalder et al, 1996). One study has shown evidence of linkage to a locus on chromosome 14q in a 30-member, three-generation Italian family (Bonati et al, 2003).

Secondary restless legs syndrome is associated with pregnancy, iron-deficiency anaemia and uraemia. It is described in 20% of pregnancies, improving in the last month before birth and resolving post-partum. In a study of pregnant women with the disorder there was no evident association with iron-deficiency anaemia (Goodman et al, 1988). Restless legs syndrome is described in uraemic patients in up to 50% of patients on renal dialysis (Winkelman et al, 1996). Some patients with small-fibre axonal peripheral neuropathy have lower limb symptoms of restless legs syndrome separately from their leg sensory symptoms (Polydefkis et al, 2000).

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There is a possible association between restless legs syndrome and Parkinson's disease (Ondo et al, 2002), hypothyroidism and rheumatoid arthritis.

Pathogenesis

Although the pathophysiology of restless legs syndrome is poorly understood it is considered to be a condition of the central rather than peripheral nervous system, associated with abnormalities of the dopaminergic system. The circadian pattern of restless legs syndrome (symptoms worse in the evening and at night) is associated with decreased levels of central dopamine activity (Chokroverty and Jankovic, 1999). Levodopa and dopamine agonists have been shown to help symptoms. Additionally, functional brain imaging studies suggest decreases in dopamine uptake in the corpus striatum (Turjanski et al, 1999).

Further studies have indicated that low central iron stores can contribute to the alteration in dopamine activity. Brain iron in magnetic resonance imaging studies has been found to be reduced in the substantia nigra and putamen in patients with restless legs syndrome; this reduction was in proportion to the severity of the symptoms (Allen et al, 2001). Low brain iron in patients with primary restless legs syndrome is also suggested by a reduction in ferritin levels in the CSF and high CSF transferrin levels (Earley et al, 2000). The lowered iron stores may influence the synthesis of tyrosine hydroxylase, which in turn is required to convert tyrosine to dopa and then to dopamine; tyrosine hydroxylase requires iron as a cofactor. The hypothesis is that low iron can result in reduced levels of dopamine.

A further study (Wang et al, 2004) demonstrates a reduction in Thy 1 in restless legs syndrome sufferers. It is speculated that this is a possible mechanism to explain why iron deficiency can affect dopaminergic transmission in restless legs syndrome cases.

Historically, opiates have been used to treat restless legs syndrome and there is continued debate about whether the syndrome is linked to opiate neurotransmission (Walters, 2002).

Quality of life

The REST (RLS Epidemiology, Symptoms and Treatment) general population study (Allen et al, 2005) assessed quality of life on a Medical Outcomes Study 36-Item Short Form Health Survey (SF-36 questionnaire), with deficit suggesting a physical rather than mental health or emotional basis. Importantly, the scores were comparable with scores from patients with diabetes, chronic obstructive pulmonary disease and depression, emphasizing that patients with more severe cases of restless legs syndrome are significantly disabled by their symptoms.

The basic complaint of intolerable discomfort in the legs while sitting can affect a patient's ability to perform sedentary work. Leisure time activities such as going to the cinema or the concert are similarly affected. Patients commonly complain of a difficulty sitting in the evenings while attempting to watch television. Travelling by any method of public transport can be uncomfortable.

Impact on sleep

Sleep is disturbed as a result of three mechanisms:

1. Resting while awake in bed provokes the leg symptoms, thus preventing sleep (increased sleep latency)
2. Patients awaken frequently from sleep, probably because of the limb discomfort. The patient rises from bed and walks for a number of minutes and then has difficulty getting back to sleep again
3. There is a strong association between restless legs syndrome and periodic leg movements in sleep. These consist of involuntary flexions or jumping of the legs, especially the feet (Walters, 1995). The movements last several seconds, recurring every 30 seconds or so during non-rapid eye movement sleep. Periodic leg movements in sleep occur in isolation but are described in 80% of people with restless legs syndrome (Allen et al, 2003). The movements can disrupt the patient's sleep, although more commonly the sleep of the patient's partner is disrupted.

It is estimated that patients with moderate to severe restless legs syndrome sleep less than 5 hours a night, compared with 7.5–8 hours for controls (Chokroverty, 2000).

Examination

Neurological examination should be entirely normal in idiopathic restless legs syndrome. The syndrome is not associated with alteration in power, tendon jerks or sensation. Similarly, peripheral pulses are normal.

Diagnosis

The diagnosis should initially be made at a primary care level (Chaudhuri et al, 2004). The National Institute of Health in collaboration with the International RLS Study Group (Allen et al, 2003) proposed the set of criteria required for the diagnosis of restless legs syndrome (*Table 1*).

Differential diagnosis

The differential diagnosis includes peripheral neuropathy (sensory symptoms and signs are distal, involving the feet with reduced or absent tendon jerks), peripheral arterial disease (discomfort or pain in the calves is induced by walking in direct distinction to restless legs syndrome, nocturnal night cramps and sleep-onset myoclonus (these may be mistaken for periodic leg movements in sleep) and akathisia. This is a form of continuous motor restlessness not consistently relieved by activity. The urge to move is associated with an 'inner' restlessness rather than with symptoms specifically in the legs. Most cases are induced by neuroleptic drugs, but the condition has been well described in both treated and untreated Parkinson's disease.

Investigations

In a typical clinical presentation with normal examination, investigations are normally limited to excluding iron-deficiency anaemia and uraemia. A full blood count, serum ferritin level and urea analysis would be adequate. Additional investigations would be required depending upon the clinical situation.

Management

Patients can be distressed by their symptoms and need reassurance that there is no sinister underlying disorder, particularly no circulatory disease. In mild cases there is anecdotal evidence that symptoms can be reduced by avoiding caffeine, reducing alcohol and smoking, and by hot or cool baths just before sleep. In about 80% of cases the symptoms are mild or infrequent and drug treatment is not indicated (Hening et al, 1999).

Care should be taken to avoid drugs that can aggravate restless legs syndrome if possible. Anecdotally these agents include tricyclic antidepressants, selective-serotonin reuptake inhibitors, monoamine oxidase inhibitors, lithium, antihistamines, beta blockers, dopa-antagonists, diuretics, calcium antagonists and phenytoin (Hening et al, 1999).

Drug treatment

Drug treatment should be confined to the more severe cases, that is those patients with symptoms occurring at least once or twice weekly, causing sleep disruption or any impairment of daily living. A rating scale for more accurate assessment of symptom severity can be used (Walters, 2003).

- Clonazepam has been used for over 20 years with reported benefit, particularly for restless legs syndrome-associated insomnia. However, clonazepam has the disadvantages of the class effect of benzodiazepines, such as tolerance, dependence and early morning sedation. Two double-blind, placebo-controlled trials included only six patients each, and the trial results were conflicting (Hening et al, 1999).
- Levodopa was first described as a treatment for restless legs syndrome over 20 years ago (Akpinar, 1982); it can be helpful and is economic. However, its usefulness has been limited by reports of both augmentation and rebound. Augmentation describes the restless legs syndrome symptoms occurring earlier in the day, requiring the drug to be taken at increasingly earlier times. Rebound indicates that patients initially benefit from levodopa, but symptoms recur 2–6 hours later requiring additional dosage through the night (Comella, 2002).
- Oral iron supplements in the absence of iron-deficiency anaemia are ineffective. Intravenous iron replacement may be effective but is not a feasible option in daily clinical practice.
- Gabapentin has been reported to help symptoms, including pain scores, but the study was of short duration (Garcia-Borreguero et al, 2002).
- Opiates can be effective in severe cases of restless legs syndrome refractory to dopamine agonists. Sleep apnoea is a rare complication of such therapy (Ondo, 2005).

Dopamine agonists

Although the precise pathophysiology of restless legs syndrome remains unknown, anecdotal observations that the condition is aggravated by dopamine antagonists and conversely improved with dopamine agonists resulted in trials of agonists in restless legs syndrome. The advantage of these drugs over levodopa is their longer duration of action with reduced risk of both augmentation and rebound.

Pergolide and cabergoline have both been shown to be helpful, and cabergoline has the added advantage of a half life of >60 hours (Stiasny-Kolster et al, 2000). The main disadvantage of both drugs is that they are ergot derivatives, and consequently there is concern of long-term fibrotic complications, including cardiac valvular fibrosis (Horvath et al, 2004). Pergolide has been discontinued in the United States and cabergoline, if prescribed, must be used with caution including 6-monthly echocardiograms.

Pramipexole in a dosage range of 0.125–0.75 mg daily (salt preparation) significantly reduced restless legs syndrome and periodic leg movements in sleep symptoms (Montplaisir et al, 1999), with continued efficacy at 8-month follow up (Montplaisir et al, 2000). Efficacy was also noted in a longer follow-up trial of over 2 years in which mild augmentation occurred in a third of patients requiring modest dosage increase (Silber et al, 2003).

Ropinirole improved symptoms in a double-blind, randomized, 12-week trial (Walters et al, 2004). Ropinirole was also tested in a European, multi-centre trial of 284 patients over 12 weeks with a subsequent 12-month, open-label extension. Restless legs syndrome scores were significantly improved, including quality-of-life measures (Trenkwalder et al, 2004).

Table 1. International Restless Legs Syndrome Study Group diagnostic criteria

Essential criteria	An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
	The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting
	The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
	The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night
Supportive features	Include positive family history of restless legs syndrome, periodic leg movements in sleep, response to dopamine agonist
Associated clinical features	Include symptoms worsen over time, sleep disturbance, normal findings on neurological examination

From Allen et al (2003)

Both pramipexole and ropinirole have the advantage of being non-ergot drugs, and although there has been no direct comparison between the two agents it is likely that they are equally effective. Both drugs are licensed in the UK for treatment of restless legs syndrome. The dosage schedule for pramipexole (salt preparation) is 0.125 mg to be taken in the evening, increasing (if required) at weekly intervals to 0.25 mg, 0.5 mg and finally 0.75 mg daily. The schedule for ropinirole starts at 0.25 mg, increasing at weekly intervals, if required, to 0.5 mg, 1.0 mg, 1.5 mg and finally 2.0 mg daily.

Oral dopamine agonists should now be considered first-line treatment in most patients requiring drug therapy.

Rotigitine is a further non-ergot dopamine agonist available as a cutaneous patch and has been shown to be effective for restless legs syndrome symptoms (Stiasny-Kolster et al, 2004). Apomorphine has also been shown to be effective but its indication should be reserved for exceptionally refractory cases (Tribl et al, 2005).

Conclusions

Restless legs syndrome is a neurological movement disorder that has in the past been neglected in terms of diagnosis despite being relatively common. It is not a difficult diagnosis to make, few investigations are required and a new approach to treatment has produced encouraging results. **BJHM**

Conflict of interest: none.

Akpinar S (1982) Treatment of restless legs syndrome with levodopa plus benserazide. *Arch Neurol* **39:** 739

Allen RP, Barker PB, Wehrl F et al (2001) MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* **56:** 263–5

Allen RP, Picchietti D, Hening WA et al; International Restless Leg Syndrome Study Group (2003) Restless legs syndrome: diagnostic criteria, special considerations and epidemiology. A report from the Restless Legs Syndrome Diagnosis and Epidemiology Workshop at the National Institute of Health. *Sleep Med* **4:** 101–19

Allen RP, Walters AS, Montplaisir J et al (2005) Restless legs syndrome: prevalence and impact. *Arch Intern Med* **165:** 1286–92

Bonati MT, Ferini-Strambi L, Aridon P et al (2003) Autosomal dominant restless legs syndrome maps on chromosome 14q. *Brain* **126:** 1485–92

Chaudhuri KR, Forbes A, Grosset D et al (2004) Diagnosing restless legs syndrome (RLS) in primary care. *Curr Med Res Opin* **20:** 1785–95

Chokroverty S, Jankovic J (1999) Restless legs syndrome: a disease in search of identity. *Neurology* **52:** 907–10

Chokroverty S (2000) Disorders of sleep. *Sci Am Med* **11:** 1–8

Coleman RM (1982) Periodic limb movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C, ed. *Sleeping and waking disorders: indications and techniques.* Addison-Wesley, Menlo Park: 1–2

Comella CL (2002) Restless legs syndrome. Treatment with dopaminergic agents. *Neurology* **58**(Suppl 1): S87–S92

Earley CJ, Connor JR, Beard EA et al (2000) Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology* **54:** 1698–700

Ekbom K-A (1945) Restless legs. *Acta Med Scand* **158**(Suppl): 1–123

Garcia-Borreguero D, Larroja D, DeLaLave Y et al (2002) Treatment of restless legs syndrome with gabapentin; a double blind, cross-over study. *Neurology* **59:** 1573–9

Goodman JDS, Brodie C, Ayida GA (1988) Restless legs syndrome in pregnancy. *BMJ* **297:** 1101–2

Hening W, Allen R, Earley C et al (1999) The treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* **22:** 970–99

Horvath J, Foss RD, Kleiner-Fishman G et al (2004) Severe multivalvular heart disease. A new complication of the ergot-derived dopamine agonists. *Mov Disord* **19:** 656–62

Montplaisir J, Nicolas A, Denesle R et al (1999) Restless legs syndrome improved by pramipexole; a double-blind, randomised trial. *Neurology* **52:** 938–43

Montplaisir J, Denesle R, Petit D (2000) Pramipexole in the treatment of restless legs syndrome: a follow-up study. *Eur J Neurol* **7:** 27–31

Ondo WG (2005) Methadone for refractory restless legs syndrome. *Mov Disord* **20:** 345–8

Ondo WG, Vuong KD, Jankovic J (2002) Exploring the relationship between Parkinson's disease and restless legs syndrome. *Arch Neurol* **59:** 421–4

Polydefkis M, Allen RP, Hauer P et al (2000) Subclinical sensory neuropathy in late-onset restless legs syndrome. *Neurology* **55:** 1115–21

Silber MH, Girish M Izurieta R (2003) Pramipexole in the management of restless legs syndrome: an extended study. *Sleep* **26**: 819–21

Stiasny-Kolster K, Robbecke J, Shuler P et al (2000) Treatment of idiopathic restless legs syndrome (RLS) with D_2-agonist cabergoline: an open clinical trial. *Sleep* **23:** 349–54

Stiasny-Kolster K, Kohnen R, Schollmayer E et al; The rotigotine Sp 666 Study Group (2004) Patch application of the dopamine-agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. *Mov Disord* **19:** 1432–8

Tan EK, Seah A, See GJ et al (2001) Restless legs syndrome in an Asian population: a study in Singapore. *Mov Disord* **16:** 577–8

Trenkwalder C, Seidel VC, Gasser T et al (1996) Clinical symptoms and possible anticipation in a large kindred of familial restless legs syndrome. *Mov Disord* **11:** 389–94

Trenkwalder C, Garcia-Borreguero D, Montagna P et al (2004) Ropinirole in the treatment of restless legs syndrome: results from the TREAT 1 RLS study. *J Neurol Neurosurg Psychiat* **75:** 92–7

Tribl GG, Sycha T, Kotzailias N et al (2005) Apomorphine in idiopathic restless legs syndrome: an exploratory study. *J Neurol Neurosurg Psychiat* **76:** 181–5

Turjanski N, Lees AJ, Brooks DJ (1999) Striatal dopaminergic function in restless legs syndrome. *Neurology* **52:** 932–7

Wang X, Wiesinger J, Beard J et al (2004) Thy1 expression in the brain is affected by iron and is decreased in restless legs syndrome. *J Neurol Sci* **220**: 59–66

Walters A (1995) Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord* **10:** 634–42

Walters A (2002) Review of receptor agonist and antagonist studies relevant to opiate system in restless legs syndrome. *Sleep Med* **3:** 301–4

Walters A (2003) Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. The International Restless Legs Syndrome Study Group. *Sleep Med* **4**: 121–32

Walters A, Ondo W, Dreykluft T et al (2004) Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2. *Mov Disord* **19:** 1414–23

Winkelman JW, Chertow GM, Lazarus JM (1996) Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis* **28:** 372–8

KEY POINTS

- Restless legs syndrome is a common but underdiagnosed neurological disorder.
- Restless legs syndrome is characterized by an intense desire to move the legs when the patient is sitting or lying and is relieved by leg movement.
- Restless legs syndrome is associated with sleep disturbance and is consequently a cause of daytime drowsiness.
- Restless legs syndrome is a movement disorder with associated underlying dopaminergic dysfunction.
- Diagnosis is straightforward and physical examination normal.
- Drug treatment should be reserved for the more severe cases and dopamine agonists are now first-line treatment.