Restless legs syndrome

Dominic Thyagarajan, Associate Professor and Head of Neurology, Flinders Medical Centre, Adelaide

Summary

Restless legs syndrome is common. While many patients are simply inconvenienced, others suffer greatly from wakefulness and disturbed sleep. The condition is readily recognised by history and examination and perhaps simple investigations. Secondary causes should be excluded. Mild symptoms can be managed without drugs, but severe symptoms may require a dopamine agonist. Treatment is usually effective but may present some practical difficulties.

Key words: dopamine agonists, opioids, pramipexole, ropinirole.

(Aust Prescr 2008;31:90–3)

Introduction

About 5–15% of the population are affected by restless legs syndrome.[1] Probably the earliest description was written in 1683 in 'Two discourses concerning the soul of brutes':

> ... whilst they would indulge in sleep, in their beds, immediately follow leapings up of the tendons in their arms and legs, with cramps, and such unquietness and flying about of their members, that the sick can no more sleep, than those on the rack.[2]

This captures the elements of restless legs syndrome: sensory discomfort ('cramps'), motor restlessness ('unquietness'), the associated involuntary movements during sleep and wakefulness ('flying about of their members'), aggravation by night and rest ('in their beds'), sleep disruption, and the tortured condition of the worst affected ('on the rack').

Restless legs syndrome can begin at any age. Earlier, slower onset suggests hereditary restless legs syndrome and later, abrupt onset, secondary restless legs syndrome. At first exacerbations and remissions occur, but then the tendency is for a static or chronic progressive course. Although some people have severe symptoms, most people do not require drug treatment.

Diagnosis and classification

The clinical evaluation of restless legs syndrome, particularly the patient's history, is very important. The diagnosis is based on criteria proposed at a consensus conference held at the National Institutes of Health in the USA (see box).[1] The condition is classified as 'idiopathic' or secondary to several other conditions (Table 1).

Essential diagnostic criteria

Typically, patients complain of limb (usually leg) discomfort at rest, an urge to move the affected part, and unpleasant sensory symptoms. They often find it hard to describe the sensations, or say 'creeping, crawling, itching, burning, searing, tugging, pulling, drawing, aching, hot and cold, electric current-like, restless or painful'. These sensations are felt deep in muscle or bone, seldom in a joint. The whole limb or part of it may be involved, even unilaterally. In about half the cases, arms and legs are affected, but sole involvement of the arms is uncommon. Occasionally, the sensory symptoms are absent.

Usually, the symptoms begin after the patient has been lying or sitting quietly. Symptoms only on sitting are very uncommon. The more mentally rested and physically quiet the patient is, the more intense the symptoms. They can last for a few minutes or an hour.

Voluntary movement, not necessarily of the affected parts, promptly but only temporarily relieves the symptoms. A characteristic history is that the patient moves about in their chair or bed, gets up and paces about, stretches the limbs or rubs the legs to get relief. Placing the limbs on a cold or hot surface sometimes helps.

The worst times are from the evening to the early hours of the morning, whether or not the patient is asleep. This circadian

Diagnostic criteria for restless legs syndrome [1]

Essential criteria

1. An urge to move the legs (and occasionally the arms or other body parts) usually, but not always, accompanied by uncomfortable or unpleasant sensations
2. The symptoms begin or worsen during periods of rest or inactivity such as lying or sitting
3. Movement such as walking or stretching partially or totally relieves the symptoms at least as long as the activity continues
4. A circadian pattern: the symptoms are worse or only present in the evening or at night and this diurnal variation must have once been present if the symptoms are now so severe as to make diurnal variation unnoticeable

Supportive of the diagnosis

1. Family history
2. Response to dopaminergic therapy
3. Periodic limb movements during wakefulness or sleep

pattern may be lost in severe cases and it is modified by shift work, medication and sleep disorders.

Supportive clinical features

Over 50% of patients have a family history of restless legs syndrome. The pattern is consistent with an autosomal dominant mode of inheritance.

In 80% of patients, repetitive flexing movements of the legs (occasionally the arms), and dorsiflexion and fanning of the toes, for 0.5–5 seconds every 5–90 seconds, occur during sleep or wakefulness. While common, these movements are not required for the diagnosis of restless legs syndrome, nor are they specific to the condition, occurring normally and in a number of other conditions.

Associated features

Over 90% of patients have insomnia – usually trouble initiating or maintaining sleep. The neurological examination is usually normal although there may be signs of neuropathy in some secondary cases. There is an association between restless legs syndrome and cardiovascular disease.[3] Clinical examination is mainly directed at identifying causes of secondary restless legs syndrome (Table 1).

Investigations

Laboratory testing is fairly limited unless a secondary cause is suspected from the history or examination. Measuring iron and ferritin is particularly important as low stores may precipitate and aggravate restless legs syndrome. Recently, measures of ferritin in the cerebrospinal fluid and MRI scans showing reduced iron in the red nucleus and striatum suggest that iron stores in the brain are reduced.[4]

Nerve conduction studies are indicated if the clinical evaluation suggests a neuropathy. They are of doubtful use otherwise, particularly if there is a family history.

Sleep studies for the formal evaluation of sleep quality or periodic limb movements during sleep are neither generally feasible or usually required. They may be considered if excessive daytime somnolence suggests significant sleep disruption.

Table 1

Classification of restless legs syndrome

Primary	Secondary
'Idiopathic'	Iron deficiency
	Pregnancy, especially in third trimester, resolving with delivery
	Uraemia
	Peripheral neuropathies generally, and specifically Charcot-Marie-Tooth type 2 and familial amyloid neuropathy
	Diabetes
	Rheumatoid arthritis
	Vitamin B_{12}/folate deficiency
	Spinocerebellar ataxia, especially type 3
	? Parkinson's disease
	Drugs:
	antiemetics, e.g. metoclopramide
	some anticonvulsants, e.g. phenytoin
	antipsychotic agents, e.g. phenothiazines and haloperidol
	occasionally tricyclic antidepressants, selective serotonin reuptake inhibitors, lithium

Differential diagnosis

Peripheral arterial disease, arthritis and bursitis are easily distinguished by examination. Most painful conditions are not instantly ameliorated by activity.

Restless legs syndrome should be distinguished from akathisia.* The clinical setting may help, for example exposure to an offending drug (such as an antipsychotic or metoclopramide) in akathisia. Patients with restless legs syndrome emphasise the provocative nature of rest and sleep, identify the sensory disturbance as the cause of motor restlessness and have greater relief from activity. On the other hand, repetitive stereotyped movements, like body rocking, are more likely in akathisia, in which such overt motor behaviour is usually evident during the examination. The absence of symptoms while lying down generally excludes a diagnosis of restless legs syndrome.

The association with Parkinson's disease is not established by well-designed studies, but both conditions respond to dopaminergic drugs and are associated with periodic limb movements during sleep. The pathology of Parkinson's disease, however, is quite different.

Treatment

Any underlying causes should be identified and treated. Mild symptoms may respond to good sleep hygiene (Table 2) or simple analgesics. More severe symptoms may need to be managed with dopaminergic drugs, opioids or benzodiazepines. Most trials have used levodopa and dopamine agonists, but other drugs such as amantadine, selegiline and anticonvulsants also have reported efficacy. Initially at least, 90% of patients report relief with levodopa or dopamine agonists. Generally the doses are much smaller than those used in Parkinson's disease.

Opioids or benzodiazepines have a role in drug treatment of occasional symptoms as long as the patient and doctor understand the potential for dependence and withdrawal

* Akathisia: a feeling of inner restlessness which makes the person unable to sit still.

Table 2

Good sleep hygiene

Sleep/wake activity regulation	Establish regular sleep times
	Avoid oversleeping
	Avoid excessive napping (limit to afternoon 'powernap' of 10–15 minutes)
	Exercise regularly (at least six hours before bedtime)
Sleep setting and influences	Avoid bright light exposure in late evening or night, but bright light after rising may be helpful
	Avoid heavy meals within three hours of bedtime
	Sleep in a quiet, dark room (remove TV, stereo)
	Use a suitable mattress and pillow for comfort and support
	Reserve bedroom for sleep and intimacy
	Avoid alerting and stressful ruminations before bedtime (doing jigsaws may help)
	Avoid caffeine after lunch
	Reduce excessive alcohol intake
	Avoid tobacco, especially after dinner
Sleep promoting adjuvants	Have a light snack or warm bath before bed
	Engage in quiet activities before sleep e.g. reading

and restrict their use to only a few days in the month. Of the benzodiazepines, most published experience concerns treatment with clonazepam. This has a modest benefit, but may also be complicated by sedation and confusion. Opioids may be useful when dopaminergic drugs are poorly tolerated or are unhelpful. The advantages of opioids are long half-life and the absence of augmentation as an adverse effect. Another alternative is gabapentin, especially when pain is prominent. The class of drugs shown to be ineffective are anticholinergics; antidepressants with anticholinergic effects may worsen restless legs syndrome.

As the condition often fluctuates over time, the mildly affected patient may be able to use medication intermittently. Continuous treatment should be reserved for more severely affected individuals. Generally, idiopathic restless legs syndrome does not resolve.

Dopamine agonists

Low-dose dopamine agonists are largely replacing levodopa as first-line treatment for restless legs syndrome because of ease of management and better efficacy. Cabergoline has the advantage of a very long half-life and had superior efficacy to levodopa in the first large randomised controlled trial comparing two dopaminergic therapies in restless legs syndrome.[5] Of the newer non-ergot derived dopamine agonists, ropinirole has been the most extensively studied[6], followed by pramipexole.[7] If there are significant daytime symptoms, patients may need multiple doses or long-acting preparations. As a general rule, doses should start low and be increased gradually to avoid adverse effects. It is important to keep doses low as there is no extra benefit from the higher doses used in Parkinson's disease, and because of the risk of augmentation with higher doses.

Adverse effects

Several problems may be encountered usually within 3–4 months of starting a dopaminergic drug. The phenomenon of augmentation complicates treatment in up to 80% of patients, as early as 3–4 weeks into treatment. In augmentation, the symptoms are shifted to an earlier time in the day, may be more severe and more easily provoked and may spread to previously uninvolved limbs. Pain and sleeplessness cause severe anxiety and so augmentation is important to recognise. Raising the dose aggravates augmentation, but it resolves on withdrawal of the drug. Risk factors for augmentation are taking the dose well before symptom onset, and doses of levodopa above 200 mg per day. It is primarily a problem with levodopa, but has also been reported with pergolide. So far, it seems that augmentation is less of a problem with cabergoline and non-ergot dopamine agonists. If augmentation occurs, it is best to switch to or between dopamine agonists, or temporarily use opioids while the dose of the dopaminergic drug is lowered.

Another problem is rebound, in which the symptoms of restless legs syndrome reappear after the drug has worn off. This is similar to 'wearing off' in Parkinson's disease and manifests as early morning or late night symptoms. Rebound is related to the half-life of the drug, so it is best to use a long-acting preparation, multiple dosing or switch to cabergoline.

Concerns have arisen over the use of ergot-derived dopamine

agonists (such as cabergoline and pergolide) in the treatment of Parkinson's disease because of the serious complication of restrictive cardiac valvulopathy.[8] The risk could be smaller with bromocriptine and with the lower doses used in restless legs syndrome, but good studies are lacking. Great caution should therefore be used when prescribing cabergoline or pergolide. If they are necessary, regular (six-monthly) echocardiography is recommended, although we still do not know if the valvulopathy is reversible. The non-ergot derived dopamine agonists (such as ropinirole and pramipexole) have not yet been implicated in valvulopathy. There have been no direct comparative studies between cabergoline, pramipexole and ropinirole, therefore no claim for greater efficacy can be made for any of these drugs.

Common adverse effects of dopamine agonists, particularly at the start of treatment, are nausea and dizziness (due to postural hypotension). Impulse control disorders including pathological gambling and hypersexuality are increasingly being recognised. Another concern is pathological daytime somnolence occurring as 'sleep attacks' which may cause motor vehicle accidents. While these adverse effects seem dose related, they may occur with the relatively low doses used in restless legs syndrome, so awareness and caution are necessary.

Opioid treatment may be complicated by sedation and constipation. It has the potential for abuse, dependency and withdrawal, so occasional use is preferable. Caution should be exercised in prolonged treatment.

Conclusion

Restless legs syndrome is a common but under-recognised disorder. For patients with mild symptoms, no drug treatment may be necessary. For patients with severe symptoms, dopamine agonists are the first-line treatment when a drug is needed. Some patients can be managed with intermittent therapy.

References

1. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101-19.
2. Willis T. The practice of physick. Two discourses concerning the soul of brutes. Samuel Pordage (trans. 1683). London: T Dring, C Harper and J Leigh; 1684.
3. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology 2008;70:35-42.
4. Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003;61:304-9.
5. Trenkwalder C, Benes H, Grote L, Happe S, Hogl B, Mathis J, et al; CALDIR study group. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Mov Disord 2007;22:696-703.
6. Trenkwalder C. The weight of evidence for ropinirole in restless legs syndrome. Eur J Neurol 2006;13 Suppl 3:21-30.
7. McCormack PL, Siddiqui MA. Pramipexole: in restless legs syndrome. CNS Drugs 2007;21:429-37; discussion 438-40.
8. Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet Neurol 2007;6:826-9.

Further reading

Headrick S, Adsett M, Lander C. Medicinal mishap: Cabergoline-induced valvulopathy. Aust Prescr 2008;31:21.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false

(answers on page 111)

1. Anticholinergic drugs are an effective therapy for restless legs syndrome.
2. If symptoms of restless legs syndrome come on earlier in the day during treatment with a dopaminergic drug, the dose should be increased.