The restless legs syndrome: is it more than that?

The restless legs syndrome is not only common and frequently unrecognized but research has revealed that the limb symptoms are only part of the clinical picture. Abnormalities of dopamine availability in the CNS have been demonstrated and suggest new approaches to treatment.

Very little attention has been paid to restless legs syndrome although it is one of the commonest disorders affecting the general population. This anomaly is partly because many subjects feel that it is just 'how they are', and other family members often have similar symptoms which they have considered to be normal. Second, the leg symptoms are often not linked to the difficulties in sleeping and other daytime problems such as fatigue. Third, health-care practitioners often fail to recognize restless legs syndrome because there is nothing abnormal to find on examination and the symptoms are often absent at the time of the consultation since they characteristically only appear in the evening and at night. Restless legs syndrome falls between the conventional medical specialties and has not been taken up by any one group of professionals.

This 'invisibility' of restless legs syndrome has a long history. The first description appears to have been by Thomas Willis in his famous textbook *The London Practice of Physic* originally published in Latin in 1672 and translated into English (Willis, 1685). Boissier de Sauvages (1763) described the condition as 'anxietas tibiarum' in his classification of medical disorders and Wittmack in 1861, Beard in 1880, Tourette in 1898 and Bing in 1913 all emphasized the hysterical or neurasthenia-like nature of the condition (Konofal et al, 2009). Oppenheim (1923) first recognized it as a neurological disorder but, despite several further case reports, it was not until the work of the Swedish neurologist Karl-Axel Ekbom (1945) that the clinical picture was accurately described. He recognized the core features of an ill-defined sensation within the legs coming on in the evening or early in the night with an urge to move the legs and transient relief from moving or rubbing the legs. Ekbom coined the term 'restless legs syndrome' but the disorder is still often known as the Ekbom syndrome.

Prevalence and impact on quality of life

The prevalence of restless legs syndrome depends on how it is defined but it appears to be commoner in western than at least some Asian communities such as Japan and Singapore. A questionnaire study of 15 391 subjects aged over 18 years in the USA and Europe showed that 11.2% of subjects had symptoms of restless legs syndrome at least weekly, and in 5% at least twice each week. They were moderately or severely distressing in 2.7% but only 6.2% were diagnosed with restless legs syndrome (Allen et al, 2005). In a similar study of 23 052 subjects in primary care 88.4% had sleep-related symptoms but only 12.9%, even in the severest group, were diagnosed with restless legs syndrome (Hening et al, 2004).

The restless legs syndrome becomes slightly more common with age and probably has a similar prevalence in males and females apart from the effects of pregnancy. It is commoner during pregnancy, particularly towards the end of gestation, and its prevalence afterwards increases with the number of pregnancies. There is a family history of restless legs syndrome in over one third of subjects and in these individuals restless legs syndrome usually begins at a younger age.

The SF36 score, which is a generic quality of life assessment, is significantly lower in those with restless legs syndrome than in normal subjects (Abetz et al, 2004; Hening et al, 2004; Allen et al, 2005) and restless legs syndrome is associated with poor general health (Winkelman et al, 2006). The costs of loss of productivity at work, medication and other costs related to impaired health pose a significant financial burden on society (Dodel et al, 2010). In addition the presence of severe restless legs syndrome appears to be linked to a shorter life expectancy (Mallon et al, 2008).

Clinical features

These fall into several groups:

Sensory symptoms

Restless legs syndrome causes disagreeable sensory symptoms particularly in the legs but occasionally in the rest of the body, especially the arms. These are felt inside the limbs and there is usually a sensation of movement or tension which is hard to describe. Words such as creeping, stretching, tingling, itching as well as warm and painful are often used to describe it. These sensations only occur at rest, particularly while sitting, for instance

Dr JM Shneerson *is Director of the Respiratory Support and Sleep Centre, Papworth Hospital, Cambridge CB23 3RE*

as a car or train passenger or in the cinema. They usually come on in the evening and persist during the first half of the night but if they are severe, they may be present during the afternoon or even the morning as well. They are worse if the subject is tired and improve if he or she is distracted. They are temporarily relieved by movement such as walking, by stretching the limbs, and by massage or cooling the legs.

Motor abnormalities

Like the sensory symptoms, these are more pronounced in the evening and the first half of the night. There is an urge to move the legs which may be irresistible and is often manifested by an inability to sit for any length of time even, for instance, to eat an evening meal, and by walking around in the evening and on waking during the night. The limbs may also jerk involuntarily.

The movements usually involve extension of the big toe and flexion of the ankle, knee and hip and are usually bilateral. They occur at regular intervals both while awake and during sleep (periodic limb movements in sleep). They are most common in stages 1 and 2 non-rapid eye movement sleep and are usually absent in rapid eye movement sleep except, for instance, in narcolepsy.

Insomnia

Around 10% of patients referred to sleep centres with insomnia have restless legs syndrome. There is a difficulty initiating and maintaining sleep in the first half of the night when arousals from restless legs syndrome overcome the drive to enter or remain in sleep. The total sleep time may be markedly reduced, often to only 3–5 hours.

Fatigue

Despite the marked sleep restriction, patients primarily suffer a sensation of physical and mental fatigue rather than excessive sleepiness. This fatigue is almost indistinguishable from that of other disorders such as coeliac disease, chronic fatigue syndrome and fibromyalgia, in each of which restless legs syndrome is also more common than in the general population. The lack of sleepiness during the day is paralleled by a sensation of being wide awake, as if 'wired', at night. Those with restless legs syndrome are able to maintain wakefulness during the day better than similarly sleep-deprived normal subjects (Gamaldo et al, 2009), suggesting that there is a hyper-arousal state in restless legs syndrome.

Mood disorders

Anxiety and depression are more common in restless legs syndrome than in the general population (Picchietti and Winkelman, 2005; Winkelman et al, 2005; Celle et al, 2010). In addition restless legs syndrome is often worsened by antidepressant medication. There is also a possible link between restless legs syndrome and impaired verbal fluency (Winkelman et al, 2005).

Cardiovascular complications

The Sleep/Heart Health Study showed that, after allowing for confounding variables, restless legs syndrome was associated with an increased risk of coronary arterial and cerebrovascular disease in middle-aged and elderly subjects, particularly when restless legs syndrome symptoms were at least moderately severe (Winkelman et al, 2008). The risk of an ischaemic stroke is increased (Elwood et al, 2006) and there is an increased risk of systemic hypertension (Billars et al, 2007).

Pathophysiology

The limb movements in restless legs syndrome are similar to the spinal flexor response which leads to withdrawal of the limb and which is an antinociceptive reflex. This reflex is released from higher centre inhibition in restless legs syndrome. There is also an increase in the startle reaction to noise in keeping with disinhibition of reticulospinal pathways (Frauscher et al, 2007). Abnormalities in the extrapyramidal pathways probably influence the dorsal and ventral horns in the spinal cord. Peripheral nerve disorders also lead to restless legs syndrome through altering sensory processing in the spinal cord.

The regular periodicity of the limb movements may result from central pattern generators in the spinal cord being released from their normal inhibition or alternatively the oscillator for these periodic movements could be more directly connected with the basal ganglia.

Sympathetic activity is also increased leading to peripheral vasoconstriction (Walters and Rye, 2009). There is a greater increase in blood pressure and heart rate with arousals from sleep with limb movements than normal (Siddiqui et al, 2007). This exaggerated heart rate response can be abolished by dopamine agonists which might thereby reduce the risk of cardiovascular disease (Manconi et al, 2011).

Neurochemistry and the role of iron

Although a range of neurotransmitters, particularly opioids, are involved in the generation of restless legs syndrome, functional neuroimaging and other studies have demonstrated abnormalities particularly of dopaminergic function in the thalamus, red nucleus and other areas of the brainstem.

Iron is required for the synthesis of tyrosine hydroxylase which is a rate-limiting enzyme in dopamine production. The restless legs syndrome may be caused by iron deficiency but the links to this are complex (Allen and Earley, 2007). It may be triggered not only by systemic iron deficiency (or iron overload in haemochromatosis when iron presumably is less available than

normal) but also as a result of faults in the blood–brain barrier for iron transfer, abnormalities of iron circadian rhythms, and of CNS iron regulation. Abnormalities in the transferritin receptor in the blood–brain barrier have been demonstrated and the normal nocturnal fall in CSF ferritin concentration is exaggerated in people with restless legs syndrome (Earley et al, 2005). This presumably leads to a fall in dopamine synthesis at this time. In addition, iron, which is mainly stored in astrocytes in normal subjects, is concentrated in oligodendrocytes in patients with restless legs syndrome where it is probably less available to neurones for dopamine synthesis.

Interestingly one of the abnormal genes implicated in the generation of restless legs syndrome, BTBD9, regulates iron homeostasis whereas other abnormal genes, such as MEIS1, are linked to abnormalities of development of spinal cord sensory motor processing (Stefansson et al, 2007).

Causes of restless legs syndrome

Restless legs syndrome is conventionally divided into primary and secondary types according to whether or not there is a predominantly familial, presumably largely genetic, factor or an identifiable external cause. These two types cannot be clearly distinguished, although in general there is a significant familial component in at least half of subjects. In these, restless legs syndrome tends to arise at a younger age and to be more slowly progressive and less closely related to iron deficiency. However, around 10% of patients with restless legs syndrome have iron deficiency and conversely probably 40–50% of people with severe iron deficiency will develop restless legs syndrome.

Restless legs syndrome is a common feature of severe renal disease, particularly when this is treated with haemodialysis (Araujo et al, 2010), and a variety of neurological disorders including spinal cord lesions, peripheral nerve disorders and multiple sclerosis (Manconi et al, 2008). It has been thought to be related to Parkinson's disease which also has a dopaminergic origin. The possible slightly increased prevalence in this disorder is probably the result of iron deficiency in this elderly population and possibly related to augmentation and rebound from short-acting dopaminergic agents used in the treatment of Parkinson's disease.

A wide range of drugs may cause or worsen restless legs syndrome (*Table 1*). Abstention from caffeine and, in some subjects, reduction in alcohol intake can also lead to significant improvement in symptoms.

Differential diagnosis

The nature of the leg symptoms, their occurrence in the evening and early in the night, the need to move the legs, and the relief of symptoms by movement are characteristic of restless legs syndrome. Physical examination usually reveals no abnormality unless there is a contributory cause such as a peripheral neuropathy. Investigations such as actigraphy and polysomnography are only required if there is an atypical presentation, if other sleep disorders such as obstructive sleep apnoeas may be contributing to the symptoms, or if there is a failure to respond to drug treatment.

The disorders which are most commonly confused with restless legs syndrome are:

1. Peripheral neuropathies – these cause more constant sensations throughout the day which are not relieved by movement. However, peripheral neuropathies predispose to the development of restless legs syndrome and often co-exist with it
2. Akathisia – this is usually caused by psychotic, antidepressant or dopamine agonist drugs or their withdrawal. There is an urge to move the whole body in response to an inner feeling of restlessness. There is no diurnal rhythm to these symptoms and no specific sensory symptoms in the limbs
3. Attention deficit hyperactivity disorder – this causes restlessness without a diurnal variation. Sensory symptoms in the legs are absent. Interestingly around 20% of children with attention deficit hyperactivity disorder have restless legs syndrome which may contribute to or even possibly cause the attention deficit hyperactivity disorder features
4. Nocturnal cramps – these cause localized pain and tenseness within the muscle which is distinguishable from the more diffuse sensations of restless legs syndrome
5. Positional discomfort – sensory symptoms and the need to move are located only in the limb that has been in an unusual position and it is only this position which triggers the symptoms
6. Voluntary limb vibration – this common condition, which may run in families, is characterized by higher frequency movements or 'bouncing' of the legs, which are under voluntary control. They are usually associated with relaxation or occasionally with relief from stress. There are no sensory symptoms in the limbs and no diurnal variation.

Table 1. Drugs causing restless legs syndrome

Glucocorticoids
Monoamine oxidase inhibitors
Tricyclic and selective serotonin re-uptake inhibitor antidepressants
Lithium
Antipsychotics
Antihistamines
Calcium-channel blockers
Dopamine antagonists
Withdrawal from anticonvulsants and hypnotics

Treatment

Treat the cause

Any underlying cause such as iron deficiency should be treated. The serum ferritin level should be maintained above 50 μg/litre.

Lifestyle measures

Relief from the limb symptoms of restless legs syndrome may be obtained by moving the legs or massaging them and in some patients even by hitting the limbs. Subjects often keep their feet cool before going to bed and outside the bedclothes at night. Mental distraction and avoiding tiredness often help. Some people prefer to go to bed later when they can initiate sleep more quickly but this may lead to sleep restriction if a normal wake-up time has to be observed.

Drug therapy

Dopaminergic agents

These are the most effective group of drugs. Only low doses are required. These are taken mainly before sleep but additional doses may be required earlier in the evening and occasionally during the day as well. The restless legs syndrome symptoms often 'rebound' during the night with short-acting drugs. These may also lead to 'augmentation' in which the symptoms become apparent earlier in the day, often more severely, and in parts of the body which were previously unaffected (Garcia-Bourreguero et al, 2007). Although augmentation may respond to a slight increase in dopaminergic therapy, it is usually better to change to a longer acting dopaminergic drug or to discontinue or reduce the dose and add a different type of agent.

Two similar licensed dopaminergic drugs for restless legs syndrome in the UK are ropinirole, usually given as 0.25–4 mg daily, and pramipexole 0.125–0.75 mg daily (Bogan, 2008; Merlino et al, 2008). These drugs both have their maximum effect around 1½ hours after oral intake and usually control the symptoms throughout the night. A longer acting licensed preparation is the rotigotine patch 1–3 mg daily (Trenkwalder et al, 2008). This is as effective and has the advantages of controlling symptoms throughout the day as well as at night and of having a very low rate of augmentation.

Opiates

Drugs such as codeine, dihydrocodeine and tramadol are often used, particularly at night in view of their sedative action. Occasionally more potent opiates such as oxycodone or even methadone or morphine may be required for those with very severe symptoms which are unresponsive to other treatments.

Anticonvulsants

The most commonly used are gabapentin and pregabalin, usually in conjunction with a dopaminergic drug or opiates (Fulda and Wetter, 2005).

Benzodiazepines

Most experience has been obtained with clonazepam but related drugs such as zopiclone may be as effective. Their main advantage is to relieve insomnia caused by restless legs syndrome. They are usually used in conjunction with dopaminergic and other drugs.

KEY POINTS

- Restless legs syndrome is common but frequently unrecognized.
- Restless legs syndrome is characterized by unpleasant sensations inside the limbs in the evenings which are worse at rest, relieved by exercise and associated with an urge to move the legs which may be irresistible.
- Restless legs syndrome often leads to difficulty initiating sleep, daytime fatigue, anxiety and depression and is a risk factor for hypertension and cardiovascular events.
- Many of the features of restless legs syndrome are caused by abnormalities of dopamine availability in the CNS at night.
- Iron is required for dopamine synthesis and both systemic deficiency and a lack of availability of iron in the CNS can cause restless legs syndrome.
- Restless legs syndrome may be secondary to a neurological disorder, pregnancy, renal failure or triggered by a wide range of drugs.
- Dopaminergic agents are the most effective treatment but opiates, anticonvulsants and benzodiazepines may also be useful.

Conclusions

The classical sensory and motor symptoms in the legs, which are worse in the evenings, associated with an urge to move the legs and relieved by movement, are now recognized to be only part of restless legs syndrome. This also leads to insomnia, daytime fatigue, anxiety and depression, and increases the risk of hypertension and cardiovascular events. The hyperarousal state both at night and during the day and an increase in sympathetic activity appear to underlie most of these features.

Dopamine is one of the main arousal neurotransmitters in the CNS and is central to the control of movements. There appears to be a localized nocturnal lack of availability of dopamine within the CNS causing the limb symptoms but perhaps more widespread compensatory overproduction or release elsewhere which may be responsible for the hyperarousal and increased sympathetic activity. The cognitive and autonomic effects of restless legs syndrome are less well recognized but may be as important as its classical motor and sensory features. **BJHM**

Conflict of interest: Dr JM Shneerson has been a member of advisory boards for GSK, Boehringer Ingelheim and UCB Pharma Ltd.

Abetz L, Allen R, Follet A, Washburn T, Earley C, Kirsch J, Knight H (2004) Evaluating the quality of life of patients with restless legs syndrome. *Clin Therap* **6:** 925–35

Allen RP, Earley CJ (2007) The role of iron in restless legs syndrome. *Mov Disord* **22:** S440–S448

Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L (2005) Restless legs syndrome prevalence and

impact. *Arch Intern Med* **165:** 1286–92
Araujo SMHA, Sales de Bruin VM, Nepomuceno LA, Maximo ML, de Francesco Daher E, Ferrer DPC, Carvelhedo de Bruin PF (2010) Restless legs syndrome in end-stage renal disease: Clinical characteristics and associated comorbidities. *Sleep Med* **11:** 785–90
Billars L, Hicks A, Bliwise D et al (2007) Hypertension risk and PLMS in restless legs syndrome. *Sleep* **30:** A297–8
Bogan RK (2008) Ropinirole treatment for restless legs syndrome. *Expert Opin Pharmacother* **29:** 611–23
Boissier de Sauvages F (1763) *Nosologia methodica. Tomi tertii pars prima.* Freres De Tournes, Amsterdam
Celle S, Roche F, Kerleroux J et al (2010) Prevalence and clinical correlates of restless legs syndrome in an elderly French population: the synapse study. *J Gerontol A Biol Sci Med Sci* **65:** 167–73
Dodel R, Happe S, Peglau I et al (2010) Health economic burden of patients with restless legs syndrome in a German ambulatory setting. *Pharmacoeconomics* **28:** 381–93
Earley CJ, Connor JR, Beard JL, Clardy SL, Allen RP (2005) Ferritin levels in the cerebrospinal fluid and restless legs syndrome: effects of different clinical phenotypes. *Sleep* **28:** 1069–75
Ekbom KA (1945) Restless legs. *Acta Med Scand* **158**(Suppl): 1–123
Elwood P, Hack M, Pickering J, Hughes J, Gallacher J (2006) Sleep disturbance, stroke and heart disease events: evidence from the Caerphilly cohort. *J Epidemiol Commun Health* **60:** 69–73
Frauscher B, Loscher WN, Hogl B, Poewe W, Kofler M (2007) Auditory startle reaction is disinhibited in idiopathic restless legs syndrome. *Sleep* **30:** 489–93
Fulda S, Wetter TC (2005) Emerging drugs for restless legs syndrome. *Expert Opin Emerg Drugs* **10:** 537–52
Gamaldo C, Benbrook AR, Allen RP, Oguntimein O, Earley CJ (2009) Evaluating daytime alertness in individuals with Restless Legs Syndrome (RLS) compared to sleep restricted controls. *Sleep Med* **10:** 134–8
Garcia-Borreguero D, Allen RP, Kohnen R et al (2007) Diagnostic standards for dopaminergic augmentation of restless legs syndrome: Report from a World Association of Sleep Medicine – International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. *Sleep Med* **8:** 520–30
Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L (2004) Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med* **4**(5): 237–46
Konofal E, Karroum E, Montplaisir J, Derenne J-P, Arnulf I (2009) Two early descriptions of restless legs syndrome and periodic limb movements by Boissier de Sauvages (1763) and Gilles de la Tourette (1898). *Sleep Med* **10:** 586–91
Mallon L, Broman J-E, Hetta J (2008) Restless legs symptoms with sleepiness in relation to mortality: 20-year follow-up study of a middle aged Swedish population. *Psychiatry Clin Neurosci* **62:** 457–63
Manconi M, Ferini-Strambi L, Filippi M et al (2008) Multicenter case-control study on restless legs syndrome in multiple sclerosis: the REMS study. *Sleep* **31:** 944–52
Manconi M, Ferri R, Zucconi M, Clemens S, Rundo F, Oldani A, Ferini-Strambi L (2011) Effects of acute dopamine-agonist treatment in restless legs syndrome on heart rate variability during sleep. *Sleep Med* **12:** 47–55
Merlino G, Serafini A, Robiony F, Valente M, Gigli GL (2008) Clinical experience with pramipexole in the treatment of restless legs syndrome. *Expert Opin Drug Metabol* **4:** 225–35
Oppenheim H (1923) *Lehrbuch der Nervenkrankheiten.* 7th edn. S Karger, Berlin: 1774
Picchietti D, Winkelman JW (2005) Restless legs syndrome, periodic limb movements in sleep, and depression. *Sleep* **28:** 891–8
Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, Walters AS (2007) Rise of blood pressure with periodic limb movements in sleep and wakefulness. *Clin Neurophysiol* **118:** 1923–30
Stefansson H, Rye DB, Hicks A et al (2007) A genetic risk factor for periodic limb movements in sleep. *N Engl J Med* **357:** 639–47
Trenkwalder C, Benes H, Poewe W (2008) Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomized, double-blind, placebo-controlled trial. *Lancet Neurol* **7:** 595–604
Walters A, Rye D (2009) Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep* **32:** 589–97
Willis T (1685) *The London Practice of Physic.* Bassett and Crooke, London
Winkelman J, Prager M, Lieb R et al (2005) 'Anxietas Tibiarum'. Depression and anxiety disorders in patients with restless legs syndrome. *J Neurol* **252:** 67–71
Winkelman JW, Finn L, Young T (2006) Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep Med* **7:** 545–52
Winkelman JW, Shahar E, Sharief I, Gottleib DJ (2008) Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology* **70:** 35–42