Overview of restless legs syndrome

Khaled Amar

Restless legs syndrome is a common movement and sleep disorder, which can significantly reduce quality of life. Restless legs syndrome is probably related to dopamine imbalance and may have a primary or secondary aetiology. It is greatly underdiagnosed, yet potentially treatable.

Restless legs syndrome (RLS) was originally described by David Willis in 1685. It was only in the 1940s, however, when RLS was described by Ekbom in a series of medical articles, that RLS came into prominence again, known as Ekbom's syndrome (Ekbom, 1945).

The prevalence of RLS in the population varies from 2–15%, depending on the population examined, criteria used for diagnosis and whether milder cases are included. In the USA, Phillips et al (2000) examined the prevalence of RLS in 1803 subjects of 18 years of age and older using a questionnaire administered over the telephone. They reported that the prevalence of RLS increased with age from 3% in those aged 18–29 years to 19% in those 80 years and over, with an overall prevalence of 10%. The presence of RLS symptoms correlated with diminished general and mental health.

Rothdach et al (2000), investigating a German population who ranged from 65–83 years of age, examined 469 participants with a mean age of 73 years. They reported an overall prevalence of RLS of 9.8%. There was a higher incidence of depression and lower self-reported mental health scores in the subjects with RLS.

CLINICAL PICTURE AND DIAGNOSTIC CRITERIA

RLS is characterized by an uncomfortable sensation in the lower limbs accompanied by an urge to move the legs, which momentarily helps relief the discomfort. These symptoms are usually worse in the evening or at night. The discomfort in the lower limbs varies in description from numbness to actual pain (*Table 1*). Patients frequently give a history of being unable to lie still in bed and of having an urge to move, rub, massage or kick their legs, or even pace the floor. Although the syndrome is characterized by involvement of the legs, a recent study revealed that approximately half of RLS patients also have restlessness of the arms, although this tended to occur in patients with more severe disease (Michaud et al, 2000).

Approximately 80% of patients with RLS have periodic limb movements of sleep (PLMS). PLMS, originally called 'nocturnal myoclonus', are rhythmic stereotyped movements of the lower limbs during sleep and are best diagnosed with polysomnography. During these movements, there is dorsiflexion of the big toe and the foot, and there may be flexion of the knee and hip joints. These occur regularly every 20–60 seconds during non-rapid eye movement (REM) sleep. PLMS may be noticed by bed partners and are associated with microarousal from sleep, resulting in a reduced quality of sleep (Montplaisir et al, 1997). Because of the reduced sleep quality, RLS patients frequently experience daytime sleepiness, fatigue and poor concentration, which further reduce quality of life.

The diagnosis of RLS relies on the presence of characteristic symptoms and the absence of physical signs on examination, except in patients with secondary RLS. Diagnostic criteria of RLS were proposed by the International Restless Legs Syndrome Study Group and are

TABLE 1.
Terms used to describe the sensation of restless legs syndrome

Aching
Numbness
Hotness
Creeping/crawling
Burning
Pain
Itching
Pulling
Restless

Dr Khaled Amar is Consultant Physician in General Medicine and Medicine for the Elderly, Royal Bournemouth Hospital, Bournemouth BH7 7DW

outlined in *Table 2* (Walters and International RLS Study Group, 1995).

CLASSIFICATION AND PATHOGENESIS OF RLS

RLS can be classified as either primary or secondary. Although primary RLS can start at any age, it starts in around one third of patients before the age of 20 years, with a positive family history reported in 50% of patients. Circa half of the patients with a positive family history have an autosomal dominant mode of inheritance. There is, however, variability in penetrance and evidence of anticipation in some families, indicating that multiple genes, rather than a single gene, may be involved (Lazzarini et al, 1999).

Secondary RLS may accompany a number of conditions including peripheral neuropathy, diabetes, pregnancy, spinal cord lesions or uraemia. There are also reports of RLS being secondary to iron, vitamin B_{12}, folate or magnesium deficiency. Some secondary causes of RLS, such as diabetes and vitamin deficiencies, may induce the symptoms of RLS by causing peripheral neuropathy.

TABLE 2.
Diagnostic criteria of restless legs syndrome

A compelling urge to move the limbs associated with paraesthesia
Motor restlessness
Symptoms are worst during rest
Variable and temporary relief by activity
Symptoms are worse in the evening and at night

Walters and International RLS Study Group (1995)

TABLE 3.
Differential diagnosis of restless legs syndrome

Condition	Difference from restless legs syndrome
Peripheral neuropathy	Pain or paraesthesia is the main problem
	No diurnal variation
	No relief from movement or exercise
	Signs of peripheral neuropathy
Leg cramps	Sudden onset of severe muscle pain
	Usually unilateral
Akathisia	Stereotyped motor restlessness
	Sensory symptoms usually absent
	No diurnal variation
	Exposure to neuroleptic drugs
Painful legs and moving toes syndrome	A rare condition characterized by pain in the legs and toes associated with dystonic movements of the toes
	Abnormal electromyograph

Although in the past, patients with primary RLS showed no pathological abnormalities of nerves, more recent studies have shown that some of these patients have electrophysiological evidence of a peripheral neuropathy (Polydefkis et al, 2000).

Although the exact cause of RLS is not understood, there is increasing evidence that a central dopaminergic abnormality may play an important role in its pathogenesis. For example, levodopa and dopamine agonists frequently relieve the symptoms of RLS, while dopamine agonists usually have the opposite effect. Also, opiates have been shown to be of benefit in alleviating the symptoms of RLS, but this therapeutic benefit is blocked by the dopamine antagonist pimozide (Montplaisir et al, 1991).

Iron deficiency is also thought to figure at some point in the pathogenesis of RLS. There is evidence of reduced CSF ferritin and increased CSF transferrin levels as well as reduced regional brain iron levels in patients with RLS (Earley et al, 1999; Allen et al, 2001). There is also a correlation between low serum ferritin and the severity of RLS symptoms (Sun et al, 1998). The role of iron deficiency in the pathogenesis of RLS may be through a central dopaminergic abnormality as iron plays an important part in the synthesis of dopamine.

DIFFERENTIAL DIAGNOSIS OF RLS

The differential diagnosis of RLS is outlined in *Table 3*.

INVESTIGATIONS

It must be emphasized again that the diagnosis of RLS is a clinical diagnosis and that it relies on the characteristic history and the absence of abnormal clinical signs on examination, except in patients with secondary RLS. Polysomnography, which is mostly available in research institutes, can detect PLMS and microarousals in the majority of patients with RLS. Nerve conduction studies are also normal except for patients with RLS secondary to a peripheral neuropathy. Brain computed tomography and magnetic resonance imaging scans are normal. Functional magnetic resonance imaging and position emission tomography scanning were reported to show subtle abnormalities in striatal dopaminergic transmission (Routtinen et al, 2000), but this is disputed by other investigators (Trenkwalder et al, 1999).

MANAGEMENT

Many patients with RLS have only mild symptoms, which can be managed with reassurance and explanation of the cause of their symptoms.

It is also common for patients with RLS to have periods of spontaneous remission of their symptoms. Secondary causes of RLS, such as iron or vitamin deficiencies, uraemia, diabetes or precipitating drugs, such as dopamine antagonists, need to be considered and managed appropriately.

Drug treatment is usually necessary in RLS patients with moderate or severe disease where dopaminergic drugs are the mainstay treatment. Levodopa combined with a peripheral decarboxylase inhibitor, such as co-beneldopa or co-careldopa, given as a single dose at night before the onset of symptoms, has been shown to be effective (Benes et al, 1999). A small proportion of patients, however, develop augmentation of their symptoms, with symptoms becoming more severe and starting earlier in the day. A number of dopamine agonists, including pergolide, ropinirole, cabergoline and pramipexole, usually given in a single small dose at bedtime, have been shown to be effective and well tolerated (Montplaisir et al, 1999; Stiasny et al, 2000).

Non-dopaminergic drugs that are helpful in controlling the symptoms of RLS include benzodiazepines, opiates, carbamazepine and gabapentin. Benzodiazepines have been used for many years, and clonazepam can be particularly useful in controlling PLMS and any associated REM behaviour disorder (Boghen, 1981). Carbamazepine and gabapentin may be particularly useful in controlling burning pain, such as that accompanying peripheral neuropathy in RLS (Mellick and Mellick, 1995). Moderately strong opiates, such as codeine or tramadol, have also been shown to be useful (Lauerma and Markkula, 1999). The empirical use of iron tablets in all RLS patients, rather than those who are iron deficient, was not found to be beneficial and is therefore not justified (Davis et al, 2000).

Further information and advice can be obtained from the RLS foundation based in Rochester in the United States, or from their website (www.rls.org).

CONCLUSIONS

RLS is a common movement and sleep disorder, reducing the sufferer's quality of life. Although a number of drugs, particularly dopaminergic drugs, are useful in controlling the symptoms of RLS, there is no uniformly effective treatment. Further research is necessary to improve our understanding of the pathogenesis of RLS, particularly the exact role played by iron deficiency, the relationship to other central dopaminergic disorders, such as Parkinson's disease, and factors leading to spontaneous remission. HM

Conflict of interest: none

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KEY POINTS

- Restless legs syndrome is a common condition, which is greatly underreported.
- Restless legs syndrome may be primary or secondary to other conditions, such as uraemia or peripheral neuropathy.
- Restless legs syndrome manifests clinically by an uncomfortable sensation of the lower limbs, which is usually worse in the evening and which is relieved by active movement.
- Restless legs syndrome is probably related to central dopamine dysfunction.
- Restless legs syndrome symptoms frequently respond favourably to dopaminergic drugs.