EDITORIAL

Restless legs syndrome

The term restless legs syndrome (RLS) was first introduced by Karl A Ekbom, a Swedish neurologist and surgeon, in 1945, although the earliest description of restless legs associated with sleep disabilities possibly came from Sir Thomas Willis, an English physician, in 1672.^{1 2} More recently, abnormal involuntary movements during sleep such as nocturnal myoclonus (subsequently termed periodic limb movements during sleep (PLMS)) have been reported to be associated with RLS.^{3 4}

Epidemiology

Surveys in the white population suggest that adult prevalence figures of RLS may range between 5% and 15%.⁵⁻⁷ The prevalence seems to increase with age, although retrospective assessments indicate that onset of the syndrome may occur before the age of 20 in up to 43% of adult cases.^{8 9} The MEMO study, a population based survey of an elderly population, reported a higher prevalence of RLS in women, which however, did not change with age, unlike men.⁷ There are currently no data available on prevalence of RLS in other ethnic groups such as Asian or black populations. Periodic limb movements in sleep were first reported by Lugaresi *et al*, who showed polysomnographically recorded PLMS (more than five/hour) in up to 87.8% of patients with RLS.⁴ Prevalence estimates of PLMS are variable and range from 6% in the

general population to 58% in a subpopulation of subjects over 60 years old.¹⁰ It should be emphasised that PLMS occur in various sleep disorders and other neurological diseases and may increase with age, whereas RLS remains a clinical diagnosis by definition.¹¹

Pathophysiology and clinical associations

The underlying causes of RLS or PLMS remain unclear and as such various aetiologies including central and peripheral nervous systems, vascular, genetic, iatrogenic, and metabolic components have been proposed (table 1). The central dopaminergic system, particularly the striato-nigral system, has been implicated and this hypothesis has been supported by the beneficial effects of various dopaminergic agents in the treatment of RLS. Functional imaging studies with SPECT and PET techniques have shown reduced striatal D2 receptor binding using ¹²³I-IBZM and ¹¹C-raclopride, suggesting postsynaptic dopaminergic dysfunction in patients with RLS during sleep.^{12 13} Two of three ¹⁸F-DOPA PET studies have also shown a slight but significant decrease in striatal ¹⁸F-DOPA uptake in patients with PLMS-RLS compared with healthy controls.¹³⁻¹⁵ A state dependent decrease in cerebral blood flow in the caudate nuclei and increase in the anterior cingulate gyrus during increasing pain level has been reported in a patient with familial RLS.¹⁶ A high resolution fMRI

Table 1 Pathophysiological basis and conditions thought to be associated with restless legs syndrome (RLS)

Idiopathic RLS: RLS+PLM	Central dopaminergic dysfunction:	Presynaptic (caudate+putamen) Postsynaptic (D2)
RLS+SLD+PLM	Cerebellar and thalamic activation Diencephalodopaminergic dysfunction Red nucleus activation	
PLM+RLS	Spinal origin	Facilitation of spinal flexor reflexes
RLS	Metabolic	Low brain iron content
Familial	Genetic form	Positive family history
Secondary RLS: Renal failure and uraemia Iron deficiency anaemia Vitamin B12 deficiency Hypothyroidism Rheumatoid arthritis Sjogren's syndrome Diabetes mellitus		
Movement disorders:	Parkinsonism	Disease related Dyskinesia related
	Gilles de la Tourette's syndrome Attention deficit hyperactivity disorder	
Mood related:	Depression	
	Antidepressant related	
Peripheral neuropathy:	Sensory polyneuropathy	
	Hereditary motor sensory neuropathy (CMT 2)	
Pregnancy		

Table 2 Criteria for diagnosis of idiopathic restless legs syndrome (RLS)

Minimum diagnostic criteria	Additional features
Desire to move limbs, usually associated with para/dysaesthesia	Sleep disturbance
Motor restlessness	Periodic limb movements in sleep
Symptoms worse or exclusively present at rest: partial/temporary relief with activity	Neurological examination normal
Symptoms worse in the evening or at night	Chronic symptoms with exacerbations and remissions
	Positive family history

International Restless Legs Syndrome Study Group.¹¹

Response to dopaminergic agents, although often present, is not regarded as a criteria for diagnosis of idiopathic RLS.

study reported possible cerebral generators underlying sensory leg discomfort and PLMS in patients with RLS, there being bilateral cerebellar and contralateral thalamic activation during sensory leg discomfort, and additional activation of the red nucleus and brain stem during combined sensory leg discomfort and PLM.¹⁷

The relation between the occurrence of PLM and RLS is also unclear. Testing spinal flexor reflex excitability in patients with RLS, Bara-Jimenez *et al*¹⁸ suggested that PLMS and spinal flexor reflexes share a common spinal origin, and disinhibition of reticulospinal excitatory responses may lead to pathological recruitment of spinal motor neurons.^{17, 18} Spinal flexor reflexes seem to be under partial dopaminergic control and levodopa depresses both facilitatory and inhibitory flexor reflex afferents.¹⁹ Thus the concept that PLM may arise from loss of supraspinal inhibitory impulses resulting in enhanced spinal flexor reflex facilitation is consistent with the dopaminergic dysfunction hypothesis in RLS.

A metabolic basis of secondary RLS has been postulated and a common association of RLS is iron deficiency anaemia.²⁰ Studies of CSF concentrations of ferritin and transferrin in RLS have shown reduced CSF ferritin and increased transferrin concentrations in idiopathic RLS assuming a low brain iron content in RLS.²⁰ Serum iron concentrations exhibit circadian variation with up to a 50% drop in iron concentration at night when the symptoms of RLS are most obvious.²¹ Furthermore, iron is also required as a cofactor for hydroxylation of tyrosine hydroxylase, which is the rate limiting enzyme for dopamine production.²² Other metabolic correlates may be hypothyroidism²³ and diabetes mellitus.^{5, 24} Restless legs syndrome has also been reported to occur in up to 25% of patients with primary diagnosis of rheumatoid arthritis and Sjogren's syndrome although the association remains controversial.²⁵

The issue of coexistence of RLS and Parkinson's disease is controversial and currently being investigated. An increased PLM index has been reported in untreated patients with Parkinson's disease.²⁶ Misdiagnosis of RLS may occur due to nocturnal dyskinesias and akathisia in patients with Parkinson's disease treated with levodopa.

A genetic basis for RLS is supported by studies reporting a positive family history in 63%–92% of patients with idiopathic disease¹⁰ and an autosomal dominant pattern of inheritance has been suggested. No gene linkage to RLS has yet been found. Studies in kindreds of familial RLS suggest anticipation and variable penetrance.^{27, 28} The syndrome has also been found in patients with spinocerebellar ataxia (type 3) assuming a possible role of CAG repeat sequences in the SCA 3 gene.²⁹

Clinical features

Restless legs syndrome may present with a wide range of symptoms including unpleasant sensations between the ankle and knee, occasionally extending to involve the whole lower limb, or even the upper limbs. One study reported arm restlessness in 48.7% of patients with idiopathic RLS, particularly those with severe disease.³⁰ Thus misdiagnosis is common and in some cases diagnosis may be considerably delayed. To help early and accurate diagnosis, the

minimal criteria for diagnosis of RLS has been recommended by the international RLS study group (table 2).¹¹

Presenting features usually include sensory symptoms described as creeping, crawling, tingling, burning, or pain in the lower limbs associated with a compulsion to move the legs. Symptoms occur most commonly when lying or resting and commonly frustrate and interrupt sleep. There also seems to be a circadian pattern to symptoms, which are worse at night, independently of an association with sleep or rest.^{10, 15} Movement or voluntary actions such as pacing, shaking, or rubbing the limbs usually relieve symptoms temporarily, but add to sleep disturbance.³¹

Periodic limb movements in sleep, defined as repetitive flexing of lower limb joints (hip, knee or ankle) and dorsiflexion or fanning of toes, for periods of 0.5–5 seconds at intervals of 5–90 seconds³² is often associated with RLS. Daytime leg movements may also occur in severe RLS; these are also sometimes periodic in nature.

The differential diagnosis is broad and includes other conditions involving motor restlessness with sensory symptoms or disagreeable feelings in the legs. These include those with an inconsistent association with rest or sleep (panic attacks, akathisia, and painful legs and moving toes syndrome³³ and generalised restlessness similar to akathisia). The uncommon syndrome of painful legs and moving toes has a similar distribution but is not relieved by movement. "Vesper's curse" is a condition associated with congestive heart failure, in which engorgement of the lumbar veins at night brings about a transient stenosis of the lumbar cord causing nocturnal pain in the lower limbs extending to the lumbosacral region.³⁴ Sensory symptoms in the lower limbs may also be due to polyneuropathies, meralgia paraesthetica (compression of the lateral cutaneous nerve of the thigh), or muscle irritation due to cramps, conditions which may or may not include a desire to move the limbs. Sleep onset myoclonus and nocturnal myoclonus are other possibilities to consider in the differential diagnosis.

Diagnosis and investigation

POLYSOMNOGRAPHY

The frequency of the recorded PLMS correlates strongly although indirectly with RLS, and is a useful measure for diagnosing RLS and monitoring of treatment.⁹ PLM may be detected by EMG recordings, usually of the tibialis anterior muscle. PLM scoring should be done according to the American Sleep Disorder Association rules³²; per hour of sleep, a pathological value is defined as more than five PLM/hour of sleep. Evidence of arousal from EEG recordings is incorporated to form the PLM arousal index—the number of PLM events temporally associated with arousal/hour.

ACTIGRAPHY

Other objective assessments of increased lower limb motor activity include actigraphy and immobilisation tests. In actigraphy, muscle activity is monitored by a small portable meter, usually worn at the ankle. Although avoiding the need for laboratory studies and allowing monitoring in the

Table 3 Treatment strategies for restless legs syndrome (RLS)

Drugs	Dose range	Specific issues
Dopaminergic (usually first choice):		
Levodopa DCI	100–600 mg	Rebound/augmentation Evening or divided dose
Bromocriptine	7.5 mg (divided dose)	Poor tolerance
Pergolide	0.1–0.75 mg	Single or two evening doses
Ropinirole	0.5–4 mg	daily/twice daily
DHEC	10–40 mg	
Pramipexole	1.5 mg	Single evening dose
Cabergoline	1–4 mg	Useful for augmentation
Apomorphine	18–50 mg/12 h	Overnight sc infusion
Amantadine	100–400 mg	
Other drugs:		
Oxycodon	2.5–25 mg	
Propoxyphene	100–260 mg	
Clonazepam	0.5–2 mg evening dose	Drowsiness
Triazolam	0.125/0.25 mg	
Nitrazepam	2.5–10 mg	
Carbamazepine	100–600 mg	Single/divided doses
Gabapentin	300–2400 mg	Quick dose escalation
Clonidine	0.15–0.9 mg	
Baclofen	20–80 mg	Drowsiness/single dose
Only in iron deficient patients:		
Iron oxide	100–200 mg/dose	Intravenous
Iron sulphate	200 mg three times daily	Oral

patient's own home, most actigraphical devices do not differentiate between PLM and other involuntary movements associated with apnoea. Only few systems can be used for recording PLM specifically.³⁵

IMMOBILISATION TESTS

Immobilisation tests, in which patients attempt to maintain a seated posture without moving their legs (suggested immobilisation test (SIT)), are used experimentally as the only objective tests to provoke waking RLS symptoms by forced rest.³⁶ Another variant is the forced immobilisation test (FIT) during which the legs are physically restrained while anterior tibial EMGs record PLM. This test is no longer recommended by us due to the discomfort of the patients.

Treatment

Treatment strategies for RLS are diverse and mainly focus on dopaminergic therapy (table 3). However, published evidence of RLS therapy is compounded by issues surrounding (a) accuracy of diagnosis, (b) recruitment bias within study population, (c) lack of studies in multiethnic and younger subjects, (d) lack of parallel group studies.

Non-pharmacological measures include advice on improvement of sleep hygiene and avoidance of stimulants or aggravating drugs (for example, caffeine, alcohol, antihistamines, certain antidepressants). In physiological conditions such as pregnancy, symptoms may resolve after delivery. In iron deficiency anaemia iron supplementation should be given first.

LEVODOPA

Fifteen published studies (eight double blind and seven clinical series) in a relatively few patients (ranging from six to 32) using evening or divided dosing of standard levodopa at doses varying between 100 mg and 600 mg, indicate that levodopa therapy consistently reduces PLMS and nocturnal RLS symptoms in the early part of the night, possibly secondary to the short half life of levodopa.¹⁰ Open and controlled studies confirm the tolerability and subjective benefit of levodopa therapy. The major problem with levodopa therapy seems to be that of augmentation. Thereby, RLS symptoms occur earlier in the day after starting with levodopa treatment at night and RLS symptoms may also emerge in the trunk or upper limbs.³⁷

Rebound phenomena are rare and consist of a worsening of symptoms in the early morning after nocturnal levodopa application.³⁸

DOPAMINE AGONISTS

Virtually all dopamine agonists have been used for RLS because of problems related to long term levodopa therapy in RLS. Four double blind, one single blind, and nine open label trials involving various ergot and non-ergot agonists have been published so far. A double blind placebo controlled study using bromocriptine at a mean dose of 7.5 mg showed subjective benefit in 83.8% of cases, with decrease in PLMS.¹¹ Another clinical study comparing levodopa and bromocriptine suggested equivalent subjective improvement with both although tolerability seemed to be better with levodopa.³⁹ Two open label trials using pergolide (0.1–0.75 mg) given in the evening as a single dose or two doses showed a sustained effect through the night with improvement of RLS. These findings have been confirmed in two further double blind studies, one comparing pergolide (0.125–0.25 mg) and levodopa (250–500 mg), which showed better subjective improvement and a greater effect on PLMS (79% v 445%) with pergolide. Augmentation induced by levodopa was also reversed after treatment with pergolide.⁴⁰ Other studies, reported recently, include reports of beneficial effect on RLS with ropinirole (0.5–4 mg once/twice/day), dihydroergocriptine (10–40 mg in divided doses), pramipexole (1.5 mg as a single evening dose), cabergoline (1–4 mg as an evening dose) and apomorphine (nocturnal subcutaneous infusion 18–48 mg).^{41–43} Of these, pramipexole has been examined in a double blind fashion, with significant reduction of subjective restlessness and PLMS, although the sleep architecture remained unaltered. Cabergoline and ropinirole are currently undergoing double blind evaluation. Long term (mean 7.8. months) efficacy of pramipexole (0.25–0.75 mg) suggest continued efficacy of pramipexole during the follow up period.³⁰ Cabergoline, the longest acting dopamine agonist (half life 65 hours), has the advantage of being active when given once a day. Open label studies suggest that cabergoline is well tolerated in patients with severe RLS who have failed other therapies and also those with augmentation.^{41–42} Other dopaminergic drugs reported to be of benefit in RLS include orphenadrine, piribedil, and amantadine.⁴⁴

OPIATES

Opiates (laudanum) were used for the treatment of RLS in the 17th century and recently, opiates such as oxycodone¹¹ and propoxyphene have shown beneficial effects in four small studies (two double blind placebo controlled) diminishing both RLS and PLMS with symptomatic relief, reversible by the opiate antagonist naloxone.⁴⁵

BENZODIAZEPINES

Clonazepam has been most widely studied although others such as triazolam and nitrazepam have also been studied. Results of double blind crossover studies have been variable, reporting either no or modest benefit in leg symptoms and sleep. Overall, studies suggest that clonazepam can be helpful for treatment of RLS but considerable reservations remain owing to the small sample size of studies and the confounding effect of benzodiazepines on sleep variables.

ANTIEPILEPTIC DRUGS

Carbamazepine has been most widely studied, and recent studies have used gabapentin. Open label studies with gabapentin also showed subjective improvement of RLS symptoms between doses of 300 to 2000 mg/day. Thus

there seems to be some benefit from antiepileptic drugs, particularly with painful RLS although this may not include improvement of PLMS.

ADRENERGIC DRUGS

Those studied include propranolol and clonidine, which act to suppress noradrenergic activity. Clonidine at doses between 0.15–0.9 mg/day seems to be effective in suppressing RLS symptoms, including those due to uraemia as reported in one study.

BACLOFEN AND OTHER AGENTS

Drugs such as baclofen and clonidine are only rarely used because dopaminergic agents and opioids seem to reduce RLS symptoms sufficiently with less side effects.

Baclofen (20–80 mg/day) increased PLM but decreased arousals and improved sleep variables in a small placebo controlled study. Other agents that have been anecdotally reported to be of benefit in RLS include epidural morphine, folic acid, intravenous and oral iron, and avoidance of tricyclic and serotonin reuptake blocking antidepressant drugs.

Therapy of RLS in children, pregnant women, and elderly people is less well understood and needs further work.

In summary, restless legs syndrome is a common and often underrecognised condition with considerable morbidity, that can present either as primary disease or secondary to various medical conditions. A high index of suspicion is required for prompt diagnosis, counselling, and making sure that patients are able to avail themselves of a wide range of effective treatment strategies for improving RLS symptoms.

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