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. 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.

Epidemiology
Surveys in the white population suggest that adult prevalence figures of RLS may range between 5% and 15%. 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. 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. 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. 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. 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.

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 striatoniigral 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. 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. 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. A high resolution fMRI

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

<table>
<thead>
<tr>
<th>Idiopathic RLS: RLS+PLM</th>
<th>Central dopaminergic dysfunction:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLS+SLD+PLM</td>
<td>Cerebellar and thalamic activation</td>
</tr>
<tr>
<td>PLM+RLS</td>
<td>Diencephalodopaminergic dysfunction</td>
</tr>
<tr>
<td>RLS</td>
<td>Red nucleus activation</td>
</tr>
<tr>
<td>Familial</td>
<td>Spinal origin</td>
</tr>
<tr>
<td></td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td>Genetic form</td>
</tr>
</tbody>
</table>

| Secondary RLS: Renal failure and uraemia | Parkinsonism |
|                                          | Disease related |
| Iron deficiency anaemia                  | Gilles de la Tourette’s syndrome |
| Vitamin B12 deficiency                   | Attention deficit hyperactivity disorder |
| Hypothyroid                              | Depression |
| Rheumatoid arthritis                     | Antidepressant related |
| Sjogren’s syndrome                       | Sensory neuropathy |
| Diabetes mellitus                        | Hereditary motor sensory neuropathy (CMT 2) |

| Movement disorders: | |
|---------------------| |
| Attention deficit hyperactivity disorder | |

| Mood related: | |
|--------------| |
| Depression   | |
| Antidepressant related | |

| Peripheral neuropathy: | |
|-----------------------| |
| Sensory neuropathy    | |
| Hereditary motor sensory neuropathy (CMT 2) | |
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 al18 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 anemia.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.14 Restless legs syndrome has also been reported to occur in up to 25% of patients with primary diagnosis of rheumatoid arthritis and Sjögren’s syndrome although the association remains controversial.24

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.25 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 disease26 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 ankle clonus in 48.7% of patients with idiopathic RLS.30 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

### 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 rules8; 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 2 Criteria for diagnosis of idiopathic restless legs syndrome (RLS)

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

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.
and nocturnal RLS symptoms in the early part of the night, indicate that levodopa therapy consistently reduces PLMS to 32) using evening or divided dosing of standard clinical series) in a relatively few patients (ranging from six to 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 44%) with pergolide. Augmentation induced by levodopa was also reversed after treatment with pergolide. 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). Of these, pramipexole has been examined in a double blind fashion, with significant reduction of subjective restless 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. 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. Other dopaminergic drugs reported to be of benefit in RLS include orphenadrine, piribedil, and amantadine. 

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 RLS symptoms by forced rest. 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. 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.

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

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. Another clinical study comparing levodopa and bromocriptine suggested equivalent subjective improvement with both although tolerability seemed to be better with levodopa. 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 44%) with pergolide. Augmentation induced by levodopa was also reversed after treatment with pergolide.

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). Of these, pramipexole has been examined in a double blind fashion, with significant reduction of subjective restless 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. 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. Other dopaminergic drugs reported to be of benefit in RLS include orphenadrine, piribedil, and amantadine.

OPIATES

Opiates (laudanum) were used for the treatment of RLS in the 17th century and recently, opiates such as oxycodone 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.

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 uremia 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 trycyclic 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.

K RAY CHAUDHURI
The Movement Disorders Unit, Department of Neurology, University Department of Clinical Neurosciences, King’s College Hospital, London, UK

K RAY CHAUDHURI
University Hospital of Lewisham, London, UK

L S APPIAH-KUBI
Gray’s, King’s, and St Thomas’ Medical School, London, UK

C TRENKWALDER
Department of Clinical Neurophysiology, University of Goettingen, Germany

Correspondence to: Dr K Ray Chaudhuri, Movement Disorders Unit, Mapother House, King’s College Hospital, Denmark Hill, London SE5 9RS, UK ray.chaudhuri@kingshc.nhs.uk


www.jnnp.com
Restless legs syndrome

K RAY CHAUDHURI, K RAY CHAUDHURI, L S APPIAH-KUBI and C TRENKWALDER

J Neurol Neurosurg Psychiatry 2001 71: 143-146
doi: 10.1136/jnnp.71.2.143

Updated information and services can be found at:
http://jnnp.bmj.com/content/71/2/143

These include:

References
This article cites 38 articles, 9 of which you can access for free at:
http://jnnp.bmj.com/content/71/2/143#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/