The restless l

time to recognize a very co

K Ray Chaudhuri
Regional Movement Disorders Unit, King's College Hospital, University Hospital Lewisham, Guy's, King's & St Thomas' School of Biomedical Medicine, King's College, London, UK; E-mail: Ray.chaudhuri@uhl.nhs.uk
Practical Neurology, 2003, **3**, 204–213

Restless legs causes restless nights, poor sleep, and tired days. (Drawn by Lucy Yates.)

egs syndrome
mmon movement disorder

INTRODUCTION

The Restless Legs Syndrome (RLS) is a common movement disorder with sensorimotor symptoms that are felt during quiet wakefulness and getting to sleep. Recently, Yoakum 1994 described it as the 'the most common disorder you've never heard of', a rather apt phrase. The term 'Restless Legs Syndrome' was first introduced in 1945 by Karl-Axel Ekbom, and it is known as Ekbom's syndrome (Ekbom 1945). The syndrome can present in primary or secondary care, is still under-recognized and is often regarded as a neurosis (Chaudhuri *et al*. 2001). In spite of being treatable, the RLS is generally poorly managed and often inappropriate drugs are prescribed.

HISTORY

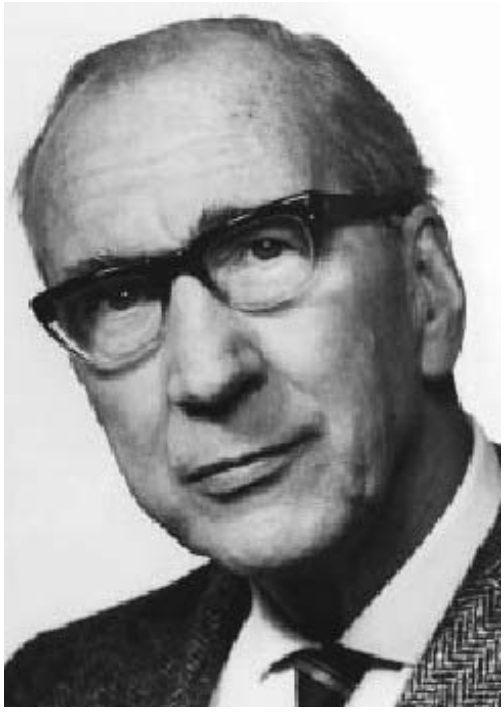
The earliest description of restless legs associated with sleep problems was probably by Sir Thomas Willis (1672), an English physician, in a chapter entitled 'Instructions for Curing the Watching-Evil':

> 'Wherefore to some, when being abed they betake themselves to sleep, presently in the arms and leggs, leapings and contractions to the tendons, and so great a restlessness and tossing of their members ensue, that the diseased are no more able to sleep, than if they were in a place of greatest torture'.

In the 19th century, Wittmaak 1861) used the term 'anxietas tibiarum' to describe a syndrome similar to the RLS, while in France the term 'impatience musculaire' was used.

HOW COMMON IS THE RESTLESS LEGS SYNDROME?

Epidemiological studies are limited by the lack of application of standard criteria and the intermittent nature of the symptoms. Pre-1995, Ekbom himself estimated a 5% prevalence in



Karl-Axel Ekbom, the Swedish neurologist and surgeon, who described, systematically characterized and named the Restless Legs Syndrome in 1945.

the general population (Ekbom 1960) while later studies reported figures from 1 to 29% (Strang 1967; Lavigne & Montplaisir 1994). Since 1995, studies have been better and surveys in white populations suggest an adult prevalence from 5 to 15% (Montplaisir *et al*. 1997; Rothdach *et al*. 2000; Ondo 2002). Based on these current estimates, there must be a few million sufferers in the UK alone. There are no prevalence figures for black populations. Low (5%), and even lower (0.1%), rates have been reported in Japanese and Singapore Chinese populations, respectively (Kageyama *et al*. 2000; Tan *et al*. 2001).

ASSOCIATIONS OF THE RESTLESS LEGS SYNDROME

Various associations have been made with the RLS, and the three key conditions are iron deficiency anaemia, pregnancy and uraemia/dialysis:

Iron deficiency anaemia

Mathews (1976) suggested that 43% of patients with iron deficiency may have 'leg restlessness'. Later studies have shown reduced CSF ferritin and raised transferrin levels in idiopathic RLS, suggesting a low brain iron content (Earley *et al*. 2000). Allen *et al*. (2001) used MRI in five RLS patients and five matched controls and reported that iron concentration was significantly lower in RLS patients, in the putamen and substantia nigra. There is circumstantial evidence that serum iron levels have a circadian variation with up to a 50% drop at night when the symptoms of RLS are most obvious (Garcia-Borreguero *et al*. 2002a).

Pregnancy

During pregnancy, RLS has been reported in 11–27% of women, usually during the third trimester (Goodman *et al*. 1988). The RLS often resolves following delivery.

Uraemia

20–57% of renal dialysis patients have the RSL (Winkelmann *et al*. 1996).

Other metabolic conditions

The RLS may be associated with hypothyroidism and diabetes mellitus. RLS has also been reported in up to 25% of patients with rheumatoid arthritis and Sjogren's syndrome although this association remains controversial (Ondo *et al*. 2000).

Peripheral neuropathy

The frequency of RLS in patients with large and small fibre neuropathies varies, ranging from 5 to 9%, not really more than in controls (Rutkove *et al*. 1996).

Periodic limb movements in sleep

Periodic limb movements in sleep were first reported by Lugaresi *et al*. in (1965). Polysomnographic studies have recorded more than five movements per hour in up to 88% of RLS patients (Montplaisir *et al*. 1997). Prevalence estimates of periodic limb movements range from 6% in the general population to 58% in a subpopulation of subjects over 60 years old (Henning *et al*. 1999). Periodic limb movements can occur in the lower and even upper limbs during quiet wakefulness as well. Periodic limb movements are also associated with insomnia/hypersomnia, the narcolepsy syndrome, REM behaviour disorder and neuroleptic use

Parkinson's disease

The association of the RLS with Parkinson's disease is controversial and studies are limited by the confounding effects of dopaminergic drugs, akathisia, dyskinesias and the non-motor symptoms of Parkinson's disease (Appiah-Kubi *et al*. 2002; Ondo *et al*. 2002).

PATHOPHYSIOLOGY

The underlying cause of both RLS and periodic limb movements during sleep is not known, although central dopaminergic or opioid dysfunction is the most likely (Rye 2002). A variety of other aetiologies including central and peripheral nervous system involvement, vascular, genetic, iatrogenic and metabolic components have been proposed (Chaudhuri *et al*. 2001). The pathophysiological basis of RLS is likely to originate from dysfunction of the dopaminergic and/or dopamine linked premotor circuits and the hypothalamic A11 dopamine cells, which converge and descend on the spinal flexor reflexes that are disinhibited as a result (Fig. 1). The final common pathway is influenced by many other supraspinal influences such as the reticulospinal, opioid and monoamine pathways. The evidence comes from Single Photon Emission Computed Tomogaphy and Positron Emission Tomography scanning studies although the reported results vary (Turjanski 1999; Eisenhsehr *et al*. 2001). The dopaminergic basis of the RLS is also supported by the often dramatic response

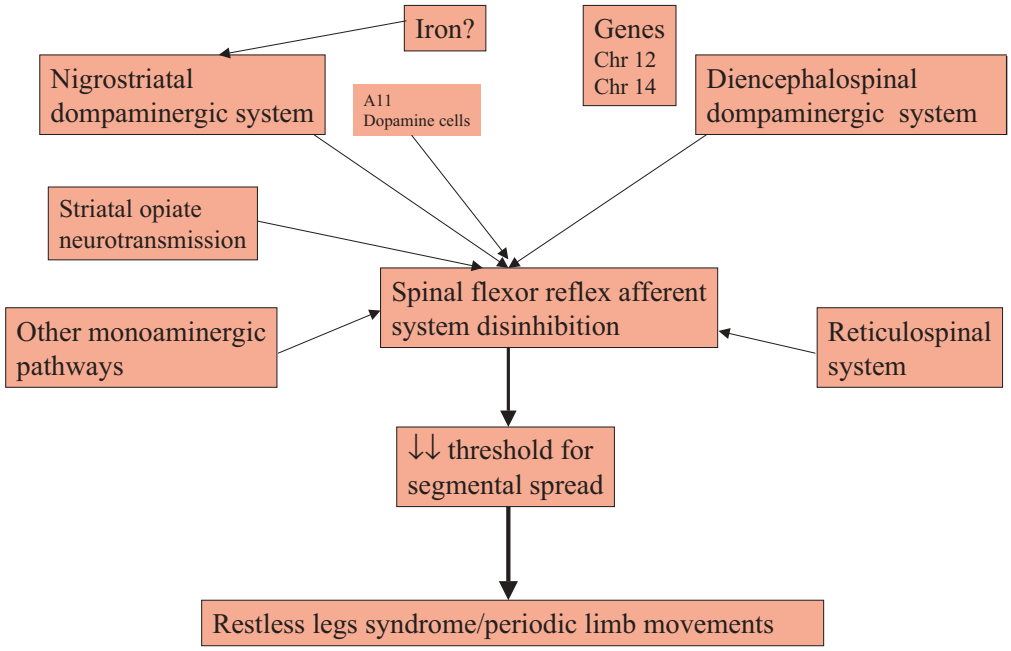


Figure 1 Possible pathophysiological basis of the Restless Legs Syndrome and periodic limb movements.

to dopaminergic drugs (see below) and recent reports of amelioration of the RLS and periodic limb movements in Parkinson's disease following pallidotomy and deep brain stimulation (Mandal *et al*. 2002; Rye & DeLong 1999)

THE GENETIC BASIS OF THE RESTLESS LEGS SYNDROME

The RLS has a strong genetic predisposition and Ekbom himself suggested autosomal dominant inheritance. 55% of cases with idiopathic RLS may have a family history of RLS (Winkelmann 2002) and first and second degree relatives have a significantly higher risk of the RLS compared with controls (Allen *et al*. 2002). RLS appears to follow a Mendelian autosomal dominant mode of inheritance (particularly in young onset cases) and 'anticipation' (earlier age of onset in later generations) has been proposed in some families (Trenkwalder *et al*. 1996).

Recently, Desautels *et al*. (2001) reported the first susceptibility locus for the RLS on chromosome 12q in a French–Canadian family. The genes involved may be the timeless gene and the gene encoding neurotensin, a neuropeptide thought to be a neuromodulator of dopaminergic neurotransmission. However, the true mode of inheritance in this family is autosomal recessive. Linkage to Chromosome 14 in two Italian families has also been reported (Bonati *et al*. 2003)

DIAGNOSIS, CLINICAL FEAURES AND DIFFERENTIAL DIAGNOSIS

The International Restless Legs Syndrome Study Group has proposed diagnostic criteria for the RLS (Walters 1995). Revised criteria were formulated during a consensus conference held at the National Institutes of Health in 2002 in Bethesda, Maryland, USA. There are four essential 'minimum' criteria that are all necessary for the diagnosis (see Table 1).

The key feature is the urge to move the limbs, accompanied or caused by uncomfortable, unpleasant sensations in the legs, and relief on activity. Any kind of sensation may be a manifestation of the RLS and a wide variety of descriptions have been used ranging from 'painful' or 'burning' to 'Elvis legs' (Table 2). The symptoms are bilateral although occasionally one leg may be more involved than the other. Sometimes the arms or other body parts are involved as well as the legs. This need to move, and the unpleasant sensations, are exclusively present or worsen during periods of rest or inactivity, such as lying or sitting, and are generally worse or exclusively present in the evening or at night in bed before going to sleep. The need to move, as well as the unpleasant sensations, is partially or totally relieved by movement such as walking or stretching, at least for as long as the activity continues. Arm restlessness has been reported in almost half the patients with idiopathic RLS in one series (Montplaisir *et al*. 2000).

Table 1 Essential criteria for the diagnosis of Restless Legs Syndrome

Minimum diagnostic criteria
Urge to move the limbs (previously motor restlessness)
Usually associated with para/dysaesthesia
Symptoms worse or exclusively present at rest
Partial/temporary relief with activity
Symptoms worse in the evening or at night
Additional features
Supportive features
Dopaminergic drug responsiveness
Periodic limb movements during sleep
Positive family history
Associated features
Chronic progressive course with periodic exacerbations
Normal neurological examination (except sometimes peripheral neuropathy)
Sleep disturbance

Table 2 Some descriptions used by patients with the restless legs syndrome

Like an electric current
Crazy legs
Like Coca-Cola bubbling through my veins
Aching in my bones
Pulling
Elvis legs
Tearing
Throbbing
Creepy crawly
Pain
Like a toothache in the legs
Growing pains
Itching bones

Table 3 The differential diagnosis of the restless legs syndrome

Nocturnal leg cramps
– but no relationship with rest, and no relief on activity
Akathisia
– excessive movements, without specific sensory complaints, any time of day, neuroleptic use
Peripheral neuropathy
– not usually associated with motor restlessness or helped by movement
Vascular disease such as varicose veins or deep vein thrombosis
Painful legs and moving toes syndrome
Nocturnal dyskinesias in Parkinson's disease
Sleep onset myoclonus/hypnic jerks
Attention Deficit Hyperactivity Disorder in children

Misdiagnosis is common and in some cases the true diagnosis may be considerably delayed. The symptoms commonly cause severe sleep disruption and although the movements or voluntary actions, such as pacing up and down, shaking or rubbing the limbs, usually relieve the symptoms temporarily, this all adds to the sleep disturbance. Failure to recognize the implications of the RLS, and so not offering any effective treatment, may make some patents severely depressed and even suicidal.

Phenotypically the RLS is divided into young (< 45 year) and late onset (> 45 years) groups. Young onset RLS is usually familial and more likely to be progressive, while the latter is milder and more often associated with low blood ferritin levels.

The differential diagnosis includes other conditions of motor restlessness with sensory symptoms or disagreeable feelings in the legs (Table 3). In practice, the most common confounders of the diagnosis of the RLS are nocturnal leg cramps, and akathisia where there is an inner restlessness, and an urge to move, but here the lower limb movements are faster, there is no circadian rhythm, there is often a history of neuroleptic/dopaminergic use, and there are no or few sensory symptoms. The uncommon syndrome of painful legs and moving toes has a similar anatomical distribution to the RLS but is not relieved by movement. 'Vesper's curse', a condition associated with congestive heart failure, is characterized by engorgement of the lumbar veins at night, which brings about a transient stenosis of the lower spinal canal causing nocturnal pain in the lower limbs extending to the lumbosacral region.

INVESTIGATIONS

The RLS is diagnosed clinically and so a thorough clinical history from the patient and partner is essential. Most cases do not need specific laboratory investigations. The three main and partially reversible causes of RLS are iron deficiency anaemia, pregnancy and renal disease (usually advanced renal failure). The symptoms of the RLS may rarely be a secondary feature of the following primary conditions:

- peripheral neuropathy, e.g. Charcot-Marie-Tooth disease (axonal form) (Hereditary Motor Sensory Neuropathy)
- rheumatoid arthritis
- diabetes mellitus
- hypothyroidism
- Parkinson's disease

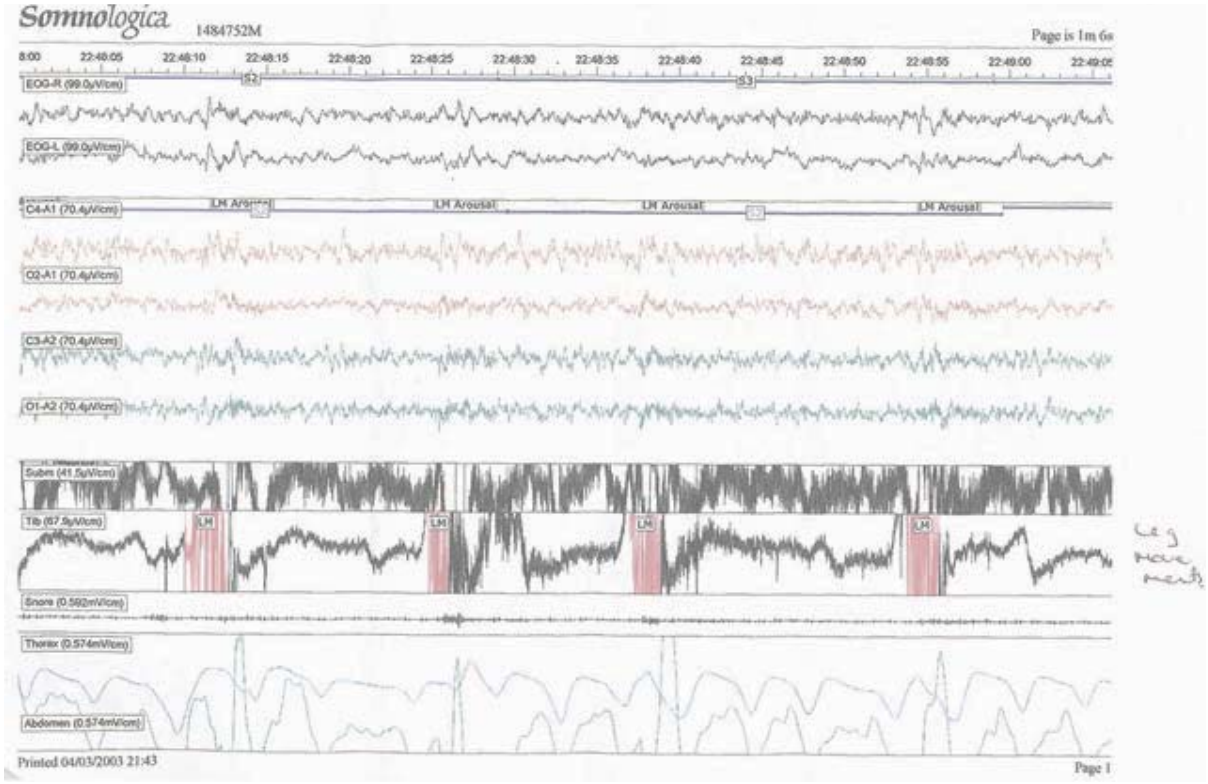


Figure 2 Polysomnography showing severe periodic limb movements (LM) during sleep. (Courtesy Adrian Williams, St Thomas' Hospital, London.

- attention deficit disorders
- spinocerebellar ataxia (types 2 and 3).

Thus patients should have tests to exclude iron deficiency anaemia (including blood ferritin level), renal function tests and blood glucose. Ferritin is the primary storage unit for iron and correlates inversely with RLS severity; blood levels below 45 μg/L need treatment with iron supplementation.

Some patients with severe RLS and insomnia may require sleep tests using polysomnography. Periodic limb movements during sleep (detected by EMG recordings, usually of tibialis anterior) correlate strongly although indirectly with the RLS, and this is useful both for diagnosis and monitoring treatment (Fig. 2). Periodic leg movements are defined as repetitive flexing of the lower limb joints (hip, knee or ankle) and occasionally the upper limb, and dorsiflexion or fanning of toes, for periods of 0.5–5 s at intervals of 5–90 s during sleep (Atlas Task Force of the American Sleep Disorders Association 1993). The degree of leg movement is classified according to the frequency of periodic limb movements, and more than five per hour of sleep is thought to be pathological. The periodic limb movement arousal index is also useful and indicates the number of events temporally associated with arousal per hour (as shown by concomitant EEG recordings).

TREATMENT OF THE RESTLESS LEGS SYNDROME

Not all patients with RLS need pharmacological treatment. Proper diagnosis, 'telling' and reassurance are important and may be enough. However, anecdotal observations suggest that about 20–25% of patients are affected severely enough to need specific treatment. The factors influencing treatment decisions are:

- The age of the patient (e.g. worry about adverse effects of benzodiazepines in the elderly).
- Symptom severity frequency and regularity of symptoms (some patients have significant symptoms only from time to time).
- Comorbidity (such as cardiac disease) and pregnancy.

Various treatment strategies are available but often there is a dramatic initial response to levodopa or dopamine agonists; the latter are currently regarded as first line treatment (Fig. 3). Although there is a considerable body of evidence supporting dopaminergic therapy, it is confounded by issues surrounding accuracy of diagnosis, recruitment bias within study

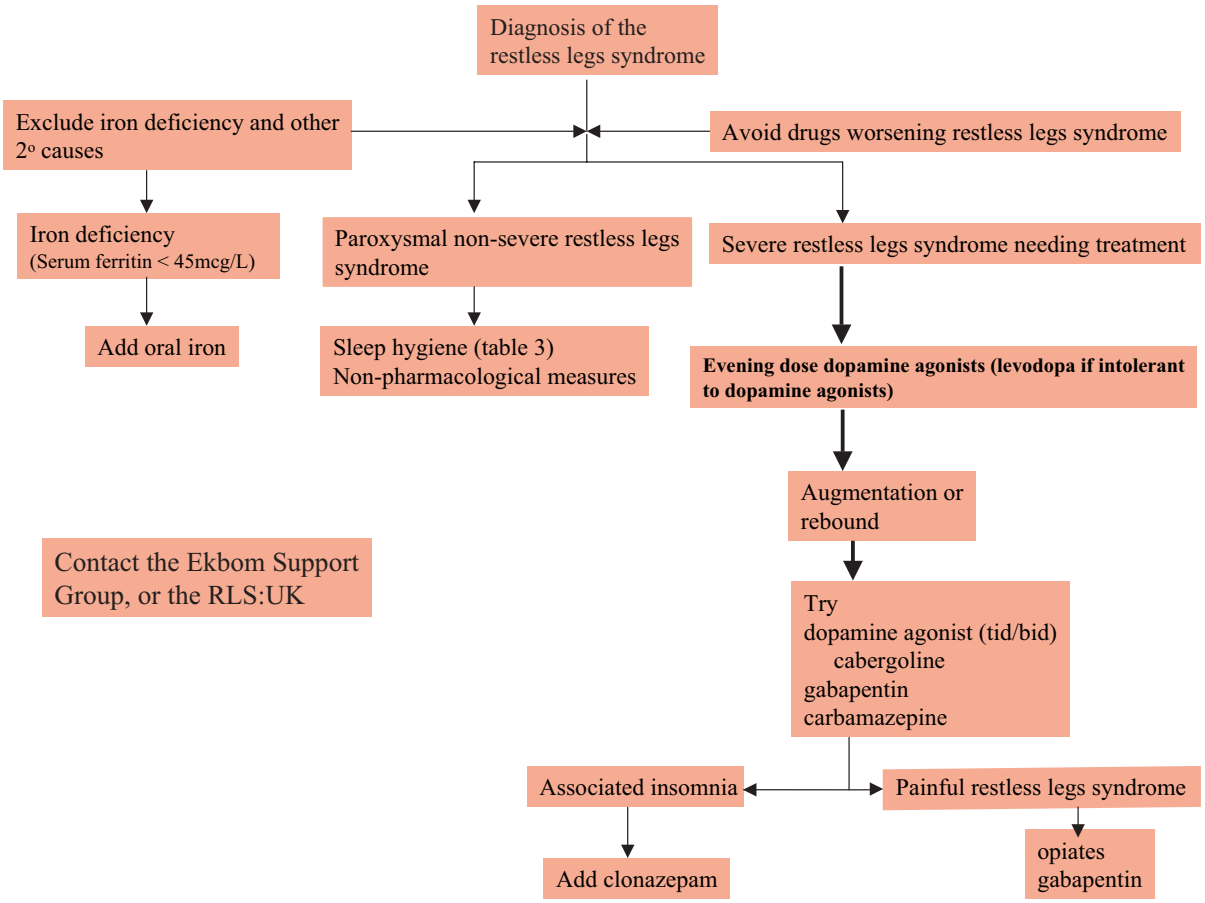


Figure 3 A suggested flow chart for treatment of the Restless Legs Syndrome (RLS). Severity of RLS can be assessed by subjective questioning and a RLS severity rating scale (Allen et al. 2002). As first line, any dopamine agonist may be used but to date there are no reports of augmentation with ropinirole or cabergoline use. Our own experience suggest that cabergoline may be useful in cases with augmentation.

Table 4 Sleep hygiene for the restless legs syndrome

Quiet, comfortable and cool sleeping environment
Avoiding tea/coffee before bedtime
Avoiding diuretics before bedtime
Some people find it helps to sleep late and rise late

populations, small numbers of patients studied, and lack of parallel group and head to head comparative studies of different treatments.

In many patients, non-pharmacological measures such as advice on sleep hygiene (Table 4) and avoidance of stimulants or aggravating drugs at night is sufficient (e.g. antidepressants, calcium antagonists, antiemetics except domperidone, high intake of caffeine, phenytoin and alcohol). In iron deficiency anaemia characterized by low ferritin states, iron supplementation should be tried first.

During an attack of RLS the following activities can be helpful:

- Walking and stretching, hot or cold bath, relaxation exercises (biofeedback or yoga).
- An engaging discussion or activity during sitting to distract the mind.
- Massaging affected limbs.

Levodopa

Currently, there are 15 published studies, in relatively small numbers of patients, using a single evening or divided dose of levodopa with a decarboxylase inhibitor, at doses varying

between 100 and 600 mg as a single dose in the evening. This consistently reduces periodic limb movements during sleep and RLS symptoms in the early part of the night but less so later in the night (Henning *et al*. 1999). Unfortunately, up to 80% of patients on levodopa may develop augmentation – the symptoms occur progressively earlier in the day and spread beyond the legs to the upper limbs (Allen & Earley 1996). Another problem is rebound – worsening of symptoms in the early morning. Controlled release formulations at night may offer a theoretical advantage and Sharif (2002) has described the successful treatment of a patient with severe secondary RLS (due to uraemia) with controlled release levodopa three times a day supplemented by entacapone, a catechol-o-methyl transferase inhibitor.

Dopamine agonists

Levodopa and bromocriptine provide equivalent subjective improvement, although tolerability appears to be better with levodopa, and virtually all the other dopamine agonists are effective for the treatment of the RLS (Stiasny *et al*. 2000a). Two open label trials using pergolide given in the evening as a single (0.1–0.75 mg), or twice daily (0.05 mg × 2) dose, showed a sustained effect through the night (Stiasny *et al*. 2000a). These observations have been confirmed in two further double-blind studies, one of which compared pergolide (0.125–0.25 mg single evening dose) with levodopa (250–500 mg single evening dose) – pergolide had a significantly greater effect on periodic limb movements during sleep. Augmentation induced by levodopa was also reversed after treatment with pergolide although augmentation has been reported with pergolide itself – in about 20% of patients (Earley and Allen 1996; Henning *et al*. 1999; Wetter *et al*. 1999; Stiasny *et al*. 2000a). Other studies reported recently show a beneficial effect with ropinirole (0.5–4 mg divided once or twice per day), pramipexole (1.5 mg single evening dose) although augmentation has been reported in 8% of patients (Ferini-Strambi 2002), cabergoline (1–4 mg evening dose), rotigotine transdermal patch (1.125–4.5 mg at night time) and apomorphine (nocturnal subcutaneous infusion 18–48 mg) (Reuter *et al*. 1999; Montplaisir *et al*. 2000; Saletu *et al*. 2000; Stiasny *et al*. 2000b; Appiah-Kubi *et al*. 2002; Stiasny *et al*. 2002). These all produce a significant reduction of subjective restlessness and periodic limb movements. As yet there are few long-term follow up studies but one reported continued efficacy of pramipexole (0.25–0.75 mg evening dose) during follow up for about 8 months (Montplaisir *et al*. 2000). Cabergoline has the longest half-life of all the dopamine agonists with the advantage of being active for 24 h, and so can be given once a day. Open label studies suggest that cabergoline is well tolerated in severe RLS patients who have failed other therapies, and also those with augmentation (Stiasny *et al*. 2000b; Appiah-Kubi *et al*. 2002). Other dopaminergic drugs reported to be of benefit include orphenadrine, piribedil, dihydroergocriptine and amantadine.

Open label studies suggest that cabergoline is well tolerated in severe RLS patients who have failed other therapies, and also those with augmentation

Opiates

Historically, opiates (laudanum) were used for treatment of the RLS in the 17th century. Recently, opiates such as oxycodone and propoxyphene have shown beneficial effects in four small studies, diminishing both the RLS and periodic limb movements, and the symptomatic relief is reversed by the opiate antagonist naloxone (Henning *et al*. 1999). Opiates may have a special role in the RLS associated with pain (asthenia crurum dolorosa).

Anti-epileptic drugs

Gabapentin and carbamazepine have been the most widely evaluated in open label and double-blind studies. Recently, Garcia-Borreguero *et al*. (2002b) reported that gabapentin was effective in a double-blind crossover polysomnography-controlled study. At doses up to 1850 mg/day, gabapentin improved periodic limb movements, sleep architecture and pain scores. At 6 weeks, no augmentation was observed.

Benzodiazepines

Clonazepam, triazolam and nitrazepam have all been tried but the 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 the RLS but considerable reservations remain owing to the small sample size of the studies and the confounding effect of benzodiazepines on sleep architecture. Additional (to levodopa or dopamine agonists) dosing of a benzodiazepine may help when insomnia is associated with the RLS.

Adrenergic drugs

Those studied include propranolol and clonidine, which act to suppress noradrenergic activity. Clonidine at doses between 0.15 and 0.9 mg/day may be effective in suppressing RLS symptoms.

Baclofen

Bbaclofen (20–80 mg/day in three divided doses) is rarely used because dopaminergic agents and opioids seem to reduce RLS symptoms sufficiently and have a better adverse effect profile

Iron

Iron administration is likely to be helpful for iron deficient patients with the RLS and is indicated with serum ferritin levels below 45 µg/L. The ideal means of administration is not known and oral treatment may take several months to be effective. Intravenous iron may be poorly tolerated.

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

CONCLUSIONS

The RLS is probably the most common movement disorder and affects sleep as well as daytime function. In the UK, it often continues to be regarded as a psychosomatic disorder and patients are told 'to put up with it' in spite of the availability of very effective treatments. In practice, it is not unusual to see RLS patients whose diagnosis has been delayed by years, and lack of appropriate treatment has rendered patients severely sleep deprived and depressed, even to the point of suicide. It is time therefore to reverse the notion that RLS is 'the most common disorder you have never heard of'.

If you wish to receive more information regarding the RLS or want to put patients in contact with Ekbom Support Group or the RLS:UK please visit http://www.welcome.to/ekbom, or E-mail: ray.chaudhuri@uhl.nhs.uk regarding RLS:UK. Also contact http://www.restlesslegs.org.uk.

ACKNOWLEDGEMENTS

Dr A Williams (for Fig.2), Mrs Eileen Gill, Miss Lucy Yates (artwork).

REFERENCES

Allen RP, Barker PB, Wehrl F, Song HK & Earley CJ (2001) MRI measurement of brain iron in patients with restless legs syndrome. *Neurology*, **56**, 263–5.

Allen RP & Earley CJ (1996) Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep*, **19**, 205–13.

Allen R, Kushida CA, Atkinson MJ & RLS QOL Consortium (2002) Factor analysis of the International Restless Legs Syndrome Study Group's scale for restless legs severity. *Sleep Medicine*, in press.

Appiah-Kubi L, Pal S & Chaudhuri KR (2002) Restless legs syndrome (RLS), Parkinson's disease and sustained dopaminergic therapy for RLS. *Sleep Medicine*, **3**, S51–S55.

Atlas Task Force of the American Sleep Disorders Association (1993) Recording and scoring of leg movements. *Sleep*, **16**, 748–59.

Chaudhuri K, Ray Appiah-Kubi L & Trenkwalder C (2001) Restless legs syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **71**, 143–6.

Bonati MT, Ferini-Strambi L, Aridon P *et al*. (2003) Autosominal dominant restless legs syndrome maps on chromosome 149. *Brain*, **126**, 1485–92.

Desautels A, Turecki G, Montplaisir J *et al*. (2001) Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. *American Journal of Human Genetics*, **69**, 1266–70.

Earley CJ & Allen RP (1996) Pergolide and carbidopa/levodopa treatment of the restless legs syndrome and periodic leg movements in sleep in a consecutive series of patients. *Sleep Medicine*, **3**, (Suppl.1) 523–525.

Earley CJ, Connor JR, Beard JL *et al*. (2000) Abnormalities in CSF concentrations of ferritin and transferring in restless legs syndrome. *Neurology*, **54**, 1698–700.

Eisenhsehr I, Wetter TC, Linke R *et al*. (2001) Normal IPT and IBZM SPECT in drug naïve and levodopa treated idiopathic restless legs syndrome. *Neurology*, **57**, 1307–9.

Ekbom KA (1945) Restless Legs Syndrome. *Acta Medica Scandinavica*, **158**, 4–122.
Ekbom KA (1960) Restless legs syndrome. *Neurology*, **10**, 868–73.
Ferini-Strambi L (2002) Restless legs syndrome augmentation and pramipexole treatment. *Sleep Medicine*, **3**, S23–S25.
Garcia-Borreguero D, Larrosa O & de la Llave Y (2002a) Circadian aspects in the pathophysiology of the restless legs syndrome. *Sleep Medicine*, **3**, S17–S21.
Garcia-Borreguero D, Larrosa O, Verger K *et al.* (2002b) Effects of gabapentin on restless legs syndrome. Results of a double blind, crossover study with polysomnographic control on 24 patients. *Movement Disorders*, **17**, S233 (abstract P748).
Goodman JDS, Brodie C & Ayida GA (1988) Restless legs syndrome in pregnancy. *British Medical Journal*, **297**, 1101–2.
Henning W, Allen R, Earley C, Kushida C, Picchieti D & Silber M (1999) The treatment of restless legs syndrome and periodic limb movement disorder. *Sleep*, **22**, 970–99.
Kageyama T, Kabuto M, Nitta H *et al.* (2000) Prevalences of periodic limb movements of sleep and restless legs syndrome among Japanese adults. *Psychiatry and Clinical Neuroscience*, **54**, 296–8.
Lavigne GJ & Montplaisir JY (1994) Restless legs syndrome and sleep bruxism. prevalence and association among Canadians. *Sleep*, **17**, 739–43.
Lugaresi E, Coccagna G, Tassinari CA & Ambrosetto C (1965) Polygraphic data on motor phenomena in the restless legs syndrome. *Rivista Di Neurologia*, **35**, 550–61.
Mandal S, Appiah-Kubi L, Porter MC & Chaudhuri KR (2002) A clinical observaional study of restless legs syndrome in Parkinson's disease. *Movement Disorder*, **17**, S229.
Mathews WB (1976) Iron deficiency and restless legs syndrome. *British Medical Journal*, **1**, 898.
Montplaisir J, Boucher S, Poirier G *et al.* (1997) Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Movement Disorders*, **12**, 61–5.
Montplaisir J, Denesle R & Petit D (2000) Pramipexole in the treatment of restless legs syndrome: a follow up study. *European Journal of Neurology*, **7**, 27–31.
Ondo W (2002) Epidemiology of restless legs syndrome. *Sleep Medicine*, **3**, S13–S15.
Ondo WG, Vuong K & Jankovic J (2002) Exploring the relationship between Parkinson's disease and restless legs syndrome. *Archives Neurology*, **59**, 421–4.
Ondo WG, Vuong KV & Wang Q (2000) Restless legs syndrome in monozygotic twins: clinical correlates. *Neurology*, **55**, 1404–6.
Reuter I, Ellis CM & Ray Chaudhuri K (1999) Nocturnal subcutaneous apomorphine infusion in Parkinson's Disease and restless legs syndrome. *Acta Neurologica Scandinavica*, **100**, 163–7.
Rothdach AJ, Trenkwalder C, Haberstock J, Keil U & Berger K (2000) Prevalence and risk factors of RLS in an elderly population. The MEMO study. *Neurology*, **54**, 1064–8.
Rutkove SB, Matheson JK & Logigian EL (1996) Restless legs syndrome in patients with polyneuropathy. *Muscle and Nerve*, **19**, 670–2.
Rye DB (2002) Modulation of normal and pathologic motoneuron activity during sleep. Insights from the neurology clinic, Parkinson's disease, and comments on parkinsonian-related sleepiness. *Sleep Medicine*, **3**, S43–S49.
Rye DB & DeLong M (1999) Amelioration of sensory limb discomfort of restless legs syndrome by pallidotomy. *Annals Neurology*, **46**, 800–1.
Saletu M, Anderer P, Saletu B *et al.* (2000) Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. *Neuropsychobiology*, **41**, 190–9.
Sharif AA (2002) Entacapone in restless legs syndrome. *Movement Disorders*, **17**, 421 (Abstract).
Stiasny K, Moller JC, Bodenschartz R *et al.* (2002) Rotigotine CDS (Constant Delivery System) in the treatment of moderate to advanced stages of restless legs syndrome – a double blind placebo-controlled study. *Movement Disorders*, **17**, S241 (abstract P776).
Stiasny K, Robbecke J, Schuler P & Oertel WH (2000b) Treatment of idiopathic restless legs syndrome (RLS) with the D2-agonist cabergoline – an open clinical trial. *Sleep*, **23**, 349–54.
Stiasny K, Wetter TC, Trenkwalder C & Oertel WH (2000a) Restless legs syndrome and its treatment by dopamine agonists. *Parkinsonism and Related Disorders*, **7**, 21–5.
Strang PG (1967) The symptoms of restless legs. *Medical Journal of Australia*, **1**, 1211–3.
Tan EK, Seah A, See SJ *et al.* (2001) Restless legs syndrome in an Asian population: a study in Singapore. *Movement Disorders*, **16**, 577–9.
Trenkwalder C, Seidel VC, Gasser T & Oertel WH (1996) Clinical symptoms and possible anticipation in a large kindred of familial restless legs syndrome. *Movement Disorders*, **11**, 389–94.
Turjanski N, Lees AJ & Brooks DJ (1999) Striatal dopaminergic function in restless legs syndrome: 18F–dopa and 11C-raclopride PET studies. *Neurology*, **52**, 932–937 .
van de Vijver D, Petri H & Sampson T (2002) The epidemiology of diagnosed restless legs syndrome in primary care in the United Kingdom. *Movement Disorders*, **17**, S 243 (abstract P783).
Walters AS (1995) Toward a better definition of restless legs syndrome. The International Restless Legs Syndrome Study Group. *Movement Disorders*, **10**, 634–42.
Wetter TC, Stiasny K, Winkelmann J *et al.* (1999) A randomised controlled study of pergolide in patients with restless legs syndrome. *Neurology*, **52**, 944–50.
Willis T (1672) *De anima brutorum*. London: Wells and Scott.
Winkelmann J (2002) The genetics of restless legs syndrome. *Sleep Medicine*, **3**, S9–S12.
Winkelmann JW, Chertow GM & Lazarus JM (1996) Restless legs syndrome in end stage renal disease. *American Journal of Kidney Disease*, **28**, 372–8.
Wittmaak T (1861) Pathologie und Therapie des Sensibilitäts-Neurosen. *Lehrbuch der Nervenkrankheiten, Teil 1: Pathologie und Therapie der sensiblen Neurosen*. Leipzig: E. Schäfer.
Yoakum R (1994) Night walkers: do your legs seem to have a life of their own? Your torment has a name. *Modern Maturity*, **55**, 82–4.