

## Review Article

# The restless legs syndrome

W.R.G. Gibb and A.J. Lees

*National Hospitals for Nervous Diseases, Maida Vale, London W9 1TL, UK.*

The first description of the restless legs syndrome (RLS) is attributed to Thomas Willis in the 'London Practice of Physick' of 1685 (Ekbom, 1960). Here he wrote 'wherefore to some, when being a bed they betake themselves to sleep, presently in the arms and leggs, leapings and contractions of their tendons, and so great a restlessness and tossings of their members ensue, that the diseased are no more able to sleep than if they were in a place of the greatest torture'. In 1861 Whittmaack used the term *anxietas tibiaram* to describe nocturnal discomfort of the legs, which he considered was a common symptom of hysteria (Ekbom, 1945). The same phenomenon was called 'impatience musculaire' in the French literature (Ekbom, 1944; Bonduelle, 1952) and the leg jitters by Allison (1943).

Ekbom's earliest descriptions of the RLS distinguished a common form which he called 'asthenia crurum paraesthetica' from a painful variant 'asthenia crurum dolorosa' (Ekbom, 1946). He identified the first of these in 34 cases. Paraesthesia with deep calf and shin discomfort started only when the legs were at rest and necessitated that they were moved to provide relief. He postulated that pregnancy was an aetiological factor and in some patients he diagnosed prostatitis, testosterone deficiency and the burning feet syndrome due to malnutrition. Ask-Upmark noted the disorder as a late effect of gastrectomy (Ask-Upmark & Meurling, 1955) and on the basis of anecdotal evidence of postural dependence of symptoms, suggested the cause was vascular congestion of the spinal cord (Ask-Upmark, 1959). Some authors doubted the existence of a distinct syndrome; Purdon-Martin (1946) believed the symptoms were due to acroparaesthesia and Masland (1947) that they were a manifestation of myokymia.

By 1960 Ekbom had studied 175 people whom he had identified with restlessness of the legs. He found that 5% of normal psychiatrically stable individuals were disturbed by restless sensations, but also believed it was symptomatic of anaemia, certain infectious

diseases, diabetes, cold exposure or those taking phenothiazine drugs (Ekbom, 1945, 1950, 1960). A diabetic patient whose symptoms vanished on the side of a recent leg amputation was presented as evidence for a peripheral origin (Ekbom, 1961) and Bornstein (1961) speculated about abnormal connections with the reticular system.

In recent years neuroleptic-induced akathisia has been compared with idiopathic RLS. Akathisia was originally described in its uncommon idiopathic form by Haskovec (1901) and later in relation to Parkinson syndromes (Sicard, 1923) and drugs such as promethazine (Sigwald *et al.*, 1947) and the phenothiazines (Steck, 1954). It is characterized by a state of mental and motor restlessness which is accompanied by an irresistible compulsion to physically move about. Restlessness of the legs is common and similar to that occurring in idiopathic RLS, but inner restlessness of the mind and body is peculiar to akathisia. Confusion between these two conditions explains why promethazine and prochlorperazine have been considered both cause and ineffective remedy of RLS.

## Epidemiology

Aches, pains and restless sensations in the legs and body are at some time an almost universal experience. RLS may form an extreme example of these affections, or could be a different entity. In either case, studies should define the clinical criteria for diagnosis. Suggested criteria are presented in Table I. As a result of failure to apply definitions, comparable studies of the same phenomenon are not reported.

Surveys of 500 and 320 people identified 5% (Ekbom, 1960) and 2.5% (Strang, 1967), respectively, with symptoms of restless legs. It was reported at ages from 7–82 years and in children considered to be in the guise of growing pains (Allison, 1943). In a recent survey of surgical out-patients personally questioned by the investigators, 8/54 (15%) complained of unpleasant sensations in the legs associated with an inability to keep them still (Braude & Barnes, 1982). Such a high prevalence is doubted by the authors of a

Correspondence: W.R.G. Gibb, M.B., M.R.C.P.

Accepted: 2 October 1985

**Table I** Diagnostic criteria

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1. Discomfort of both legs of a peculiar restless quality.
  2. Aching and tension in calf muscles.
  3. A desire to shift the legs because of the uncomfortable restless sensation.
- Other features:  
 movement of legs provides partial or complete relief for a variable period;  
 relief by walking is most effective;  
 symptoms are worse in the evenings;  
 occurs in discrete episodes lasting days, weeks or months.
- Exclusion criteria:  
 other neurological symptoms or the presence of neurological signs;  
 local causes in the legs:  
 dopamine antagonist or depleting drugs;  
 Parkinsons syndromes.
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questionnaire based survey of 452 patients of whom less than 20 complained of restless legs (Feest & Read, 1982). When these 20 were interviewed their symptoms were considered non-specific. There is probably no major sex difference (Morgan, 1967; Sandyk, 1983), the recent incorporation of twice as many women as men in a study of carbamazepine, may reflect the method of selection of patients. This study was based in general practice (Telstad *et al.*, 1984). Early studies noted that 1/3 to 1/2 of patients reported affected relatives (Ekbohm, 1945; Morgan, 1967) and there are examples of familial occurrence (Bornstein, 1961; Boghen *et al.*, 1975; Boghen & Peyronnard, 1976).

It is recognized that healthy individuals can be affected, but there have been many suggestions of possible causes. These include pica (Ekbohm, 1966), late pregnancy, folate-deficiency in pregnancy (Botez & Lambert, 1977), iron deficiency anaemia, blood loss (Morgan, 1967), chronic bronchitis, cancer (Ekbohm, 1960), neuropathies (Harriman *et al.*, 1979; Gorman *et al.*, 1965, Heinze *et al.*, 1967), venous insufficiency, Parkinson's disease (Morgan, 1967), barbiturate withdrawal (Gorman *et al.*, 1965), caffeine (Ekbohm, 1966),  $\beta$ -blockers (Morgan 1975), phenothiazines (Harriman *et al.*, 1979), anxiety and depression (Morgan, 1967; Gorman *et al.*, 1965). Morgan considered many patients had symptoms considered to be of psychosomatic origin such as tension headaches, dyspepsia or proctalgia fugax (Morgan, 1975). Ekbohm found an incidence of 11% in late pregnancy, 24% in iron deficiency anaemia (Ekbohm, 1960) and 12.6% after gastrectomy (Ekbohm, 1966). The aetiological role of neuropathies has not been clarified although it is described in uraemia (Callaghan, 1966; Thomas *et al.*, 1971), in alcoholic and diabetic patients (Gorman *et al.*, 1965) and in painful amyloid neuropathy (Heinze *et al.*, 1967). Recently, one renal unit has stated that as many as 15–20% of their patients on dialysis have appropriate symptoms (Read *et al.*, 1981).

In Parkinson syndrome Ekbohm found that 3 of 28 patients had restless legs and Strang found a 7% incidence among 600 patients, but presumably none were drug-induced (Strang, 1967). According to Strang (1967) and Sicard (1923) untreated Parkinson's disease can be associated with both idiopathic restless legs syndrome and akathisia, although their prevalences are unknown.

### Pathogenesis

A peripheral aetiology has often been considered likely. This assumption is based on the peripheral nature of the complaints and the absence of a closely associated neurological disorder or indication of a central neurochemical abnormality. However, structural abnormalities in peripheral nerve or muscle have not been found to support this concept. The adverse effects of anaemia or local ischaemia and the beneficial effects of movement, vasodilatation and fever (Ekbohm, 1960) once supported the belief that the disorder was provoked by an excessive accumulation of metabolites.

In a number of patients with leg discomfort and restlessness, nocturnal myoclonic jerks of the limbs occur excessively frequently during sleep or relaxation (Frankel *et al.*, 1974; Callaghan, 1966; Thanh *et al.*, 1975). Long recognized as a benign phenomenon Oswald (1959) noted nocturnal myoclonic jerks were often linked to an arousal stimulus, suggesting that afferent impulses from the legs influenced a susceptible reticular activating system. During relaxation and the onset of sleep an imbalance between inhibitory and excitatory mechanisms in the reticular system allows it to become susceptible to afferent sensory input. This input precipitates a discharge of motor neurones down reticulospinal paths.

The recently discovered diencephalo-spinal dopaminergic system could conceivably be involved in the pathogenesis of restless legs, in neuroleptic-induced akathisia or in the pathology of Parkinson's disease (Lindvall *et al.*, 1983b). It is feasible that there is an abnormal modulation of sensory information in the dorsal horn involving dopaminergic, noradrenergic or serotonergic neurones. The possibility of alterations in muscle tone or abnormal activity at muscle stretch receptors also remains.

Akathisia, in contrast, is usually considered to be of central origin because of its association with known neurochemical alterations in Parkinson syndrome, neuroleptic therapy and its strong subjective component. Here the most plausible theory implicates the meso-cortical dopamine system (Marsden & Jenner, 1980; an hypothesis involving the cortex being particularly desirable in view of the accompanying mental agitation.

## Clinical features

An unusually prominent aching discomfort is located deep in the calf and is associated with restlessness of the legs and an irresistible urge to move them. Feelings of heaviness, tension, stiffness, dullness, local heat and cold, mounting tension, itching, stabbing and paraesthesiae occur (Callaghan, 1966) and these occasionally spread to thighs, feet and arms (Morgan, 1967). The discomfort lies in muscles and occasionally bones and is usually bilateral. Ekbom quoted the descriptive words used by his patients; fidgets, jumps, horrors, creeps, kicks, toothache, crawling and creeping. The disorder is intermittent but characteristically begins during relaxation in the evenings or in bed (Ask-Upmark, 1955) and is often worse on lying or sitting (Braude & Barnes, 1982). Relief is obtained by skin rubbing, massage, standing, stretching, or general leg movements, but walking is often the only effective measure. Improvement often takes some minutes to start, and full relief is often not obtained or quickly returns on stopping. It can occur each evening for weeks or months before resolving, so that evenings are disturbed and insomnia may result (Nordlander, 1953). Unlike akathisia the phenomenon is more often confined to the evening and night or appears to be aggravated by recumbency, whereas in mild to moderate akathisia patients often feel most at ease when lying.

## Differential diagnosis

Restless legs syndrome is a distinct disorder which must be distinguished from spastic paraparesis, extrapyramidal rigidity, neuropathies or vascular or neurogenic claudication. Hudson described five cases of a chronic neuromuscular condition, which comprised muscular aching and sometimes burning pain with fasciculations, cramps, fatigue and paraesthesia (Hudson *et al.*, 1978). It affected legs, trunk and arms and symptoms were enhanced by physical activity and relieved by rest.

In 1971 Spillane *et al.* described six patients with pain in the feet and legs with involuntary movements of the toes. Nathan (1978) reported four more cases, suggesting that major peripheral nerve or root damage was an important aetiological factor. It is also described after minor local trauma to the feet in the absence of features of causalgia (Schott, 1981). It had been assumed to be a peripheral disorder, possibly due to a spreading irritative disorder in the lower cord, but evidence for a central origin has been reported (Schoenen *et al.*, 1984). The association of involuntary spasms and myoclonus with Sudeck's atrophy, following trauma, is thought to be due to a peripheral mechanism (Marsden *et al.*, 1984).

## Treatment

The assorted medications advocated for restless legs reflect the high placebo response and spontaneous remission rates. This further emphasizes the need for strict diagnostic criteria, double-blind and cross over trials.

The hypothesis of metabolite accumulation due to reduced blood flow at rest was supported by the apparent benefit obtained from inositol niacinate, tolazoline and nitroglycerin (Ekbom, 1960; Allison, 1943; Murray, 1967). Recently 660 patients were entered by 147 GPs into a study which showed benefit from oxerutins (Pulvertaft, 1983). Out of four criteria—aching or heavy legs, night cramps, restless legs at night and paraesthesiae—only two were required for entry to the study.

Massage, raising the legs, use of a vibrator, sedatives, narcotics, analgesics, ascorbic acid, aldehydes, dextrans, heparin, anticholinergics and quinine have been advocated, although Bornstein (1961) considered fluctuations in symptoms occurred independently of these treatments. In those with iron deficiency anaemia (Ekbom, 1960) iron injections usually provided temporary relief (Thomas *et al.*, 1971). The use of iron has been extended to those who are not anaemic (Nordlander, 1953). Oral iron therapy (Matthews, 1976) and folate supplements, particularly in pregnant patients, have been advocated (Botez & Lambert, 1977).

Promethazine and phenothiazines were both noted to exacerbate symptoms (Morgan, 1967; Murray, 1967) but chlorpromazine (50–100 mg nocte) has been recommended (Sandyk, 1983).  $\beta$ -blockers have also been described as cause and treatment (Strang, 1967). The association with myoclonus prompted report of benefit from 5-hydroxytryptophan (Menon & Kling, 1983), and that with Parkinson's disease from levodopa or bromocriptine (Akpinar, 1982).

The anticonvulsant drugs phenytoin and carbamazepine have been used. A study of 6 patients showed that 3 gained marginal improvement in severity ratings and preference for carbamazepine (Lindvall *et al.*, 1983). Recently a double-blind study (Telstad *et al.*, 1984) reported that placebo and carbamazepine were effective in reducing sleep disturbance and in having therapeutic effect. Carbamazepine (mean dose 236 mg) was more effective than placebo. The importance of placebo response was emphasized, but criteria for entry to the study were not presented. Widespread use of carbamazepine may be associated with cases of idiosyncratic leucopenia and exfoliative dermatitis.

The benzodiazepines have been advocated ever since diazepam (Strang, 1967; Feest & Read, 1982; Sandyk, 1983) and chlordiazepoxide (Strang, 1967) were used. The use of clonazepam was also prompted

by the association of RLS with myoclonus and effective relief reported in five patients (Matthews, 1979). When a group of 15 renal unit patients were given 0.5 mg at 18.00 h and 0.5 mg half an hour before bed, symptoms were totally abolished in 6, although 8 others needed larger doses (Read *et al.*, 1981). In low doses that are not sedative (0.5 mg in evenings), it is often very effective.

## Conclusions

The restless legs syndrome (RLS) consists of a specific

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