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Restless Legs Syndrome
An Update on Treatment Options

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Contents

Abstract

Restless legs syndrome (RLS) was first described in 1672 but it is only recently that this disorder has attracted attention in defining its phenotype, and identifying its aetiology, pathogenesis and pharmacological treatment. RLS can be divided into primary (idiopathic) and secondary forms. RLS is common, affecting 5–15% of the total population and manifesting at any age from childhood to late adulthood. Prevalence tends to increase with patient age and there may be geographic variation. There is a clear genetic contribution to primary RLS and evidence for dopaminergic dysfunction.

Although not all patients with RLS require medication, there can be a substantial reduction in the patient's quality of life related to pain, poor sleep and excessive daytime sleepiness. A variety of medications are now available for the symptomatic treatment of RLS. Dopaminergic therapy is currently the treatment of choice, usually initiated with a long-acting dopamine agonist, thereby avoiding some of the complications associated with levodopa. Anticonvulsants may be used as second-line treatment. Levodopa should be reserved for those patients who fail to respond to alternative medications because of the high risk of inducing augmentation. Hypnosedatives also have a role in RLS management. Patients with intractable RLS may require combination treatment. Several systemic disorders can cause RLS, and these should be identified and treated appropriately.

Although Sir Thomas Willis first described the clinical features of restless legs syndrome (RLS) in 1672,[1] attention has only recently focussed on this disorder since its 'rediscovery' by Ekbom[2] in 1945. RLS is now regarded as a specific disease entity and it benefits from international working group collaborations and a generally accepted definition. Epidemiological studies suggest that it is one of the commonest neurological disorders.

Despite all this, the general awareness of RLS among both physicians and patients is relatively low. This may well change in the near future. It is becoming clearer that RLS can cause substantial morbidity and, therefore, the relative 'disease burden' is high. Furthermore, drugs are now available for the symptomatic relief of RLS. Our understanding of the pathophysiology of this disorder is still at an early stage, although recent genetic and imaging studies have resulted in some important advances. This review focuses on the recent advances in RLS and specifically on treatment options.

1. Definition

The minimum diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG)[3] are:

- a distressing desire to move the legs, usually associated with uncomfortable para-dysaesthesiae;
- motor restlessness;
- symptoms should be brought on by rest (sitting or lying down) or worsen in rest, and there should be at least a partial but temporary relief with action; and
- symptoms worsen in the evening or at night.

Additional but not obligatory criteria are:

- involuntary limb movements while awake;
- periodic limb movements while asleep.

RLS can be divided into primary (idiopathic) and secondary forms. The primary form may be genetic (see section 4). There are multiple causes of secondary RLS (see table I).

The most common forms of secondary RLS are associated with iron deficiency anaemia, uraemia and diabetes mellitus. For instance, in one study of 69 patients with renal failure had evidence of periodic leg movements and 32% had features of RLS.[4] All patients were on haemodialysis. A further study utilising the IRLSSG criteria found 23% of haemodialysis patients fulfilled the criteria for RLS.[5]

Table I. Common causes of secondary restless legs syndrome

Iron deficiency
Uraemia
Diabetes mellitus
Pregnancy
Peripheral neuropathy

Certain drugs may also cause or exacerbate the features of RLS. These include the major neuropsychotherapeutic drugs, such as metoclopramide, lithium and the tricyclic antidepressant drugs.

2. Epidemiology

The estimated prevalence rate of RLS varies significantly between studies. There are also differences in distribution according to age and geography.

Ekbom[2] initially suggested a prevalence rate of 5% and an early study in Australia suggested a prevalence rate of 2.5%.[6] More recent studies utilising established diagnostic criteria for RLS have shown a prevalence rate distribution of between 5% and 15%. One large study from the US noted that 10% of individuals aged under 18 years, 3% aged between 18 and 29 years, 10% aged between 30 and 79 years, and 19% aged over 80 years fulfilled RLS diagnostic criteria.[7] A further large study based in Sweden including patients aged from 18–64 years found a prevalence rate of 5.8% among men[8] and 11.4% for women.[9] Another study from Germany found an overall prevalence rate of 9.8% among patients aged 65–83 years and the female to male ratio was 2 : 1.[10]

Interestingly, an epidemiological study based in Singapore found a very low prevalence rate of 0.1% among the Asian community aged over 21 years and 0.6% among those aged over 55 years.[11] In a study of Hong Kong Chinese patients with end-stage renal

failure on continuous ambulatory peritoneal dialysis, 62% of patients reported symptoms of RLS.[12]

Thus, there is a clear geographical distribution of primary RLS prevalence rates but this may not apply to secondary RLS.

3. Clinical Features and Diagnosis

The diagnosis of RLS can usually be based exclusively on the history from the patient. RLS is characterised by a desire to move the limbs and this usually results in relief of the paresthaesias/dysesthaesias. The movements are voluntary, although the patient feels 'compelled' to move. This induces motor restlessness which can include pacing the floor, leg stretching, marching on the spot, etc. Clinical features are the same for primary and secondary RLS.

The desire to move and the unpleasant sensations described above are usually present at rest, may be induced by rest and are worse during periods of inactivity. The onset of symptoms usually occurs after some minutes of rest and may, for instance, appear during car travel or at the theatre, etc. Therefore, the motor restlessness interferes with these activities and becomes worse the longer the period of inactivity lasts. The symptoms of RLS are worse during the evening and night, with a peak usually between midnight and 4am. Symptoms that occur when the patient retires to bed and before the onset of deep sleep may be particularly distressing because of the interference with sleep. Six am to noon is usually the time at which the patient is least bothered by his/her symptoms.

One of the most typical features of the clinical manifestation is the report by the patient of discomfort in the extremities. The patient may find this difficult to describe but usually constitutes a deep-seated discomfort within the extremities rather than a superficial sensation. The paresthaesias/dysesthaesias may be of a tingling, creeping, crawling, burning, aching or cramp-like nature. However, movement relieves the unpleasant sensations somewhat. The legs and, in particular, the calves are usually affected but the upper limbs can be affected in up to half of patients with primary RLS.[13] These abnormal sensations may fluctuate in time and in position, although they are characteristically worse in the evening and at night. The symptoms may be unilateral or bilateral.

Eighty percent of patients with RLS have periodic leg movements (PLM). These occur during sleep and most frequently affect the legs, but can affect both the legs and arms. They are repetitive, stereotypic and include extension of the big toe with fanning of the small toes accompanied by flexion at the ankles, knees and thighs. They are brief and recur at intervals of 5–90 seconds with a frequency of movement every 20–40 seconds. Although PLMs usually occur during sleep, they can occur while awake and comprise of jerks or twitches that may simulate myoclonus. They disappear on voluntary movement and are best observed if the patient is asked to remain entirely still. PLMs can cause significant disruption of sleep with decreased total sleep time and a consequent increase in daytime sleepiness. In one study, 95% of patients with RLS reported sleep problems.[14]

Neurological examination of patients with RLS is characteristically normal, although there may be evidence of other medical problems including, for instance, diabetic neuropathy. Electromyography and nerve conduction studies are typically normal. Blood investigations to exclude secondary causes of RLS should include a full blood count, iron studies and ferritin levels, renal function tests and fasting glucose level. Polysomnography is useful in the study of RLS but is not required for diagnosis. A sleep study will typically identify the PLMs during sleep. While these movements are not specific for RLS they are more common in patients with this disorder.

3.1 Differential Diagnosis

The differential diagnosis of RLS is wide but, most importantly, includes peripheral neuropathies and sleep disorders. A history from the patient of a period of PLMs during wakefulness or from the sleep partner of PLMs during sleep in the patient will clearly favour a diagnosis of RLS. Nevertheless, if any doubt remains, neurophysiological studies may be required to exclude the presence of a

neuropathy. The 'painful legs and moving toes' syndrome can also usually be distinguished from RLS on the basis of patient history. The sensory disturbance of this syndrome is more typical of pain and the abnormal movements are generally confined to the toes. There may be signs of cauda equina compression and a magnetic resonance imaging (MRI) scan of the lumbar spine may demonstrate significant thecal or nerve root compression.

Akathisia may sometimes be confused with RLS and these patients may have many of the typical sensory features of RLS, although these patients usually also have some associated extrapyramidal features. There is also usually a history of exposure to dopamine-blocking agents and these patients do not respond so well to dopaminergic therapy.

When sleep disturbance is a major feature of RLS, sleep disorders need to be excluded including, for instance, sleep apnoea. It is certainly possible for patients with sleep apnoea to have RLS as well and it will be necessary to undertake a polysomnography examination to identify these conditions when they coexist. Sometimes the PLMs in sleep may raise the possibility of a rapid eye movement (REM) sleep behaviour disorder, although a history of nightmares and vocalisation during sleep usually helps distinguish such patients.

4. Aetiology and Pathophysiology

RLS can manifest at any age from childhood to late adulthood. Mean age of onset for primary disease is around 27 years,[13] with 45% of patients experiencing the first symptom before age 20 years.[15] A positive family history is present in 55–92% of patients with primary RLS.[13,14,16-18] There is a high concordance rate of 83% for primary RLS in identical twin pairs.[19]

RLS has been reported in single families where it appears to follow an autosomal dominant pattern of inheritance with some features of anticipation.[20,21] Linkage to chromosome 12q has been described in one large French-Canadian family.[22] Linkage analysis for this and other families has excluded relevant candidates including genes for tyrosine hydroxylase, the dopamine transporter, dopamine receptors and GABA sub-unit receptors.[23] An additional locus for autosomal dominant restless legs syndrome has recently been identified on chromosome 14.[24]

The benefits of dopaminergic therapy (see section 5) in treating the symptoms of RLS have focused attention on the possible role of abnormal dopamine neurotransmitter mechanisms in this disorder. Patients with RLS have been investigated by single photon emission computed tomography (SPECT) and positron emission tomography (PET). However, the results have been variable. Some studies have demonstrated reduced uptake of radiolabelled ^{18}F-dopa in patients with RLS, whereas others have shown no difference between patients with RLS and controls.[25-28] Binding of raclopride to the dopamine D_2 receptor was found to be decreased in patients with RLS.[26] Cerebral blood flow was found to be decreased in the caudate nucleus in two patients with painful RLS.[29] One study found no difference in dopamine transporter binding in patients with RLS,[30] while another found a decrease.[31]

RLS can be found in patients with iron deficiency anaemia and RLS symptoms respond to oral iron therapy if ferritin levels are significantly decreased. Interestingly, ferritin levels are low in the cerebrospinal fluid of patients with RLS.[32] Iron is an important co-factor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. Iron levels exhibit a circadian rhythm in which there is a drop of iron concentrations at night, that is, when RLS symptoms are worst.[33] Furthermore, an MRI study has demonstrated reduced iron content in the substantia nigra and putamen of patients with RLS.[34] A recent report has described the neuropathology of seven brains from patients who had died with RLS. There was a significant decrease in iron and H-ferritin staining in the substantia nigra. There is also a decrease in transferrin receptor staining on dopaminergic cells.[35]

5. Treatment

The recognition of RLS has become more important since effective symptomatic treatments for this

Table II. Drugs used for restless legs syndrome

Drug	Initial dose (mg)	Usual daily dose range (mg)[a]	Common adverse effects
Dopamine agonists			
Ropinirole	0.25	0.5–8.0	Nausea, vomiting. At high dose ranges: confusion, hallucinations, sedation, peripheral oedema
Pramipexole	0.125	0.5–1.5	As above
Cabergoline	0.25	0.5–4.0	As above
Pergolide	0.025	0.5–1.0	As above
Levodopa			
Levodopa/Dopa-decarboxylase inhibitor	50	100–250	As above
Non-dopaminergic drugs			
Gabapentin	300	600–2400	Sedation
Carbamazepine	50	100–400	Sedation, skin rash
Clonazepam	0.5	0.5–2.0	Sedation
Oxycodone	2.5	2.5–25	Constipation, sedation
Dextropropoxyphene	100	200–400	Constipation, sedation

a Suggested dosage range only, some patients may require higher dosages.

disorder have become available (see table II). A patient with RLS does not automatically require treatment as the management is essentially symptomatic; the need for medication will depend upon how severely affected the patient is by RLS. Some patients require medication only for certain events, for example, air travel, theatre, etc., in which case a small dose of a dopaminergic agent is probably most appropriate. Other patients are significantly affected by their RLS and disturbed sleep, requiring daily treatment to improve their quality of life.

5.1 Levodopa

Levodopa has been used for RLS for over 20 years.[36] Several studies have subsequently confirmed the effectiveness of levodopa in RLS.[37-42]

A small dose of levodopa, for instance 50mg, with a dopa-decarboxylase inhibitor may be sufficient to provide the patient with substantial relief of the features of RLS (table II). The timing of the medication is important and is usually given an hour or two before bedtime. This results in a reduction in PLMs, improved sleep quality and decreased daytime sleepiness. Levodopa has a relatively short half-life and, therefore, the patient may wake from their sleep with symptoms of RLS. If so, a further dose of levodopa may be required. Alternatively, a controlled-release form of levodopa can be given before bedtime but this would usually need to be combined with a standard-release form, in order to provide effective treatment early during the sleeping period.[43]

An alternative strategy to prolong the action of levodopa would be to combine it with a catechol-*O*-methyltransferase inhibitor, such as entacapone 200mg.

Levodopa is well tolerated in patients with RLS, and dyskinesias do not develop as a result of levodopa use. Clinical efficacy is sustained[40] and, interestingly, prolonged use is not associated with any decrease in radiolabelled ^{18}F-dopa PET binding.[25] This argues against any inherent toxicity of levodopa on the nigrostriatal system.

However, there are significant problems with levodopa in RLS and these relate to the phenomena of rebound and augmentation. Rebound is the reappearance of symptoms when levodopa levels fall, that is, usually during the early hours of the morning. This is then usually followed by a symptom-free period during the day but then the re-emergence once more of some symptoms as night approaches. Rebound during the night can be managed with an additional dose of levodopa.

Augmentation is a more significant problem. This relates to the development of RLS features earlier during the day, more rapid onset of symptoms when at rest, together with increased severity and shorter symptomatic relief from dopaminergic therapy. Sometimes RLS can spread from the legs to the arms and trunk. Interestingly, there are some parallels between the onset of augmentation in patients with RLS and the development of motor complications in patients with Parkinson's disease.[44] The likelihood of augmentation appears to increase with the severity of RLS, and the duration and dosage of levodopa. It is estimated that 50–85% of patients receiving levodopa will develop augmentation. In the short term, augmentation may be managed by increasing the frequency of medication to cover the expanded symptomatic period. However, the period of response to drugs continues to shorten, and/or the symptoms spread to involve the upper limbs. Dopaminergic treatment may need to be withdrawn and alternative drugs substituted (see following sections).

The limitations of levodopa in terms of the development of rebound and augmentation have led to the search for alternative treatments using dopamine agonists.

5.2 Dopamine Agonists

Several dopamine agonists are used in RLS (see table II), and numerous studies have been undertaken to confirm their efficacy and safety in RLS patients.

In a placebo-controlled, double-blind crossover trial, bromocriptine resulted in a significant decrease in PLMs at a single evening dose of 7.5mg.[45] Further study in 1993 showed that bromocriptine had equipotency to levodopa for the relief of RLS symptoms but was better tolerated.[46]

Several studies have also demonstrated the effectiveness of pergolide in RLS.[47,48] This study showed that with pergolide doses between 0.1 and 0.75mg there was significant improvement in RLS symptoms during the day and night. Interestingly, patients who had developed augmentation with levodopa therapy also benefited. A further study has demonstrated the sustained effectiveness of pergolide at 1 year, although augmentation was seen in 6 of 22 patients (≈25%).[49]

Several studies have been undertaken looking at the effectiveness of pramipexole in patients with RLS.[50-52] The study by Montplaisir et al.[50] investigated use of pramipexole in ten patients with RLS in a double-blind, crossover fashion for 1 month. There was a significant reduction in PLMs during sleep and wakefulness. There was also improvement in leg discomfort. Up to 1.5mg per day was administered 1 hour before bedtime. Becker et al.[52] studied 16 patients with RLS who had previously failed to benefit with other dopaminergic therapies. A dosage of pramipexole 0.3 mg/day resulted in significant improvement in restlessness and PLMs.

Cabergoline is of particular interest for the treatment of RLS. Not only is it an effective dopamine agonist but it has a long half-life, which renders it particularly useful in managing night-time disorders such as RLS. One study has demonstrated improvements in RLS features cabergoline with 1–4mg as a single evening dose.[53] Patients who had already been treated with levodopa could be successfully transferred to cabergoline and this also led to some improvement in their augmentation.

Ropinirole has also proved effective in RLS at a dose of 1–8mg.[54-56] This dopamine agonist at a mean dose of 2.8mg produced a 58% improvement in a modified RLS questionnaire after approximately 4 months of use.[55]

One study has also demonstrated the effectiveness of apomorphine infusion, although the practical difficulties of administration is likely to limit the use of this drug in RLS.[57]

5.3 Non-Dopaminergic Therapy

A variety of non-dopaminergic therapies have been used in the treatment of patients with RLS (table II). These include benzodiazepines, anticonvulsants (e.g. carbamazepine and gabapentin), clonidine, iron and opioids.

Benzodiazepines are generally helpful in managing the symptoms of RLS. For instance, diazepam has been shown to improve symptoms in up to 75%

of patients at a dose of 10mg per night.[58,59] Clonazepam 0.5 and 2.5 mg/day has also been shown to be efficacious in small open-label studies.[60,61] However, controlled studies, albeit again relatively small, have not shown substantial benefit.[62,63] The difficulty with the use of benzodiazepines in RLS relates to their sedative properties which may 'hang over' into the day. Furthermore, there are concerns regarding the long-term use and the potential for dependency of patients using these drugs.

Two controlled studies have demonstrated the effectiveness of small doses (236mg or 600mg) of carbamazepine in patients with RLS.[64,65] These were relatively small studies and, although benefit was noted with this drug, there was also a substantial placebo response. Gabapentin 600–3600 mg/day has shown benefit in 50–90% of patients in open-label studies.[66-68] Two controlled studies using approximately 1800 mg/day of gabapentin showed both subjective improvement and objective improvement in PLMs in some patients.[69,70] Both these anticonvulsants are relatively well tolerated, although sedation is sometimes more of a problem with carbamazepine.

Clonidine at doses of between 0.075 and 0.9 mg/day have shown benefit in improving RLS in some[71,72] but not all studies.[73]

The iron deficiency associated with secondary RLS has led to the use of supplementary iron. Oral iron may be sufficient, particularly in those patients with iron deficiency and secondary RLS. Iron infusions are currently being attempted in patients refractory to other forms of therapy.

Several studies have reported the beneficial effect of opioids on the symptoms of RLS, including PLMs.[74] A variety of opioids have been used including oxycodone[74] and dextropropoxyphene.[75] A multicentre retrospective analysis of almost 500 patients with RLS showed that 23% had been on opioids, either alone or in combination with other drugs, at some point during the course of their management. A proportion of these patients had been taking their opioids for an average of 6 years. Polysomnography showed continued benefit and it appears that in some patients opioids offer an effective form of long-term treatment.[76]

6. Conclusion and Recommendations

RLS is an important disorder in terms of its high prevalence rate and significant morbidity in a proportion of patients. It is likely to be under-diagnosed at present and patients are often treated with a variety of therapies, many of which are ineffective. Not all patients require treatment but for those that do there is a range of therapies available for effective management. The sequence with which these are chosen may be determined by symptom severity and clinical response. An algorithm for the treatment of RLS is suggested (see figure 1).

It is becoming clear that the single most useful and well tolerated form of therapy are the dopaminergic drugs. In this context it seems most appropriate to begin therapy with a low-dose, once-daily dopamine agonist. This can be expected to result in

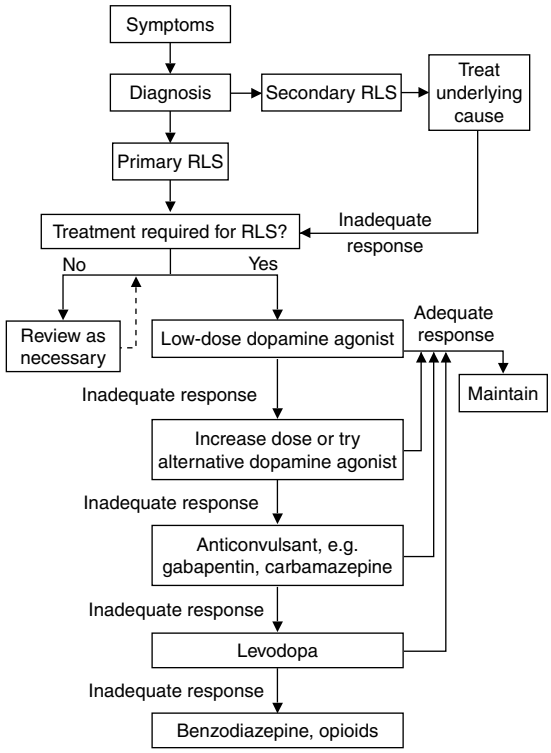

Fig. 1. Management algorithm for restless legs syndrome (RLS).

effective relief of symptoms with an, as yet, apparently low rate of augmentation or rebound. It is worth noting that some patients respond better to one agonist than another, and so switching from one to another may be appropriate in those who fail to respond to one dopamine agonist.

For those patients who cannot tolerate dopamine agonists or who require additional medication, carbamazepine, gabapentin or other non-opioid drugs should perhaps be considered as second-line treatment. Gabapentin is particularly useful for those with painful RLS. Because of its propensity to cause augmentation, it is perhaps only after this that levodopa should be considered for symptomatic management. Finally there are additional drugs such as the benzodiazepines or opioids which may be used for patients who fail to respond to dopaminergic and other treatments. Inevitably those with intractable RLS may require combination therapy, for example, a dopaminergic drug plus anticonvulsant or opioids.

The symptomatic management of patients with secondary RLS is the same as those with primary RLS, if treatment of the underlying disorder is not effective.

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