

Diagnosis and Management of Restless Legs Syndrome

Introduction

Restless Legs Syndrome (RLS) was first described in 1672 and rediscovered by KA Ekbom in 1945¹ who extensively studied this disorder and contributed important findings which are still relevant today. The international RLS Study Group (IRLSSG) published a set of criteria to establish a diagnosis of this frequent sensorimotor disorder.^{2,3}

Clinical features, definition and diagnosis of RLS

RLS is a neurological sleep disorder characterised by an almost irresistible urge to move the limbs which is most often but not necessarily accompanied by uncomfortable sensations in the legs. RLS symptoms are evoked by rest and are worse in the evening or night. The arms may also be involved. RLS occurs predominantly in the evening or during the night and has a profound impact on sleep. In addition to difficulty initiating sleep, many RLS patients have problems maintaining sleep with frequent awakenings or short arousals resulting in poor sleep efficiency.

Diagnostic criteria for RLS are characterised by four essential criteria (Table 1). To make a definite diagnosis of RLS, all four diagnostic criteria must be established.

The following supportive features have been established which are not necessary to make the diagnosis of RLS but which may, especially in doubtful cases, help to diagnose or exclude RLS.

Positive family history

A positive family history is present in more than 50% of RLS patients.

Positive response to dopaminergic treatment

Several controlled studies have shown that most patients with RLS have a positive therapeutic response to dopaminergic drugs. Based on clinical experience, more than 90% of patients report a relief of their symptoms when treated with these agents.

Periodic limb movements in sleep (PLMS)

PLMS are reported to occur in 80 to 90% of patients with RLS. However, PLMS also commonly occur in other disorders and in the elderly. A PLMS index (number of PLMS per hour of sleep) of greater than 5 is considered pathologic, although data supporting this feature is very limited. The occurrence of PLM during nocturnal periods of wakefulness (PLMW) is considered to be more specific for RLS. Thus the presence of a high number of PLM is supportive for RLS but the absence of PLM does not exclude RLS.

In addition to the essential and supportive criteria the progressive clinical course with intermittent symptoms in the beginning, the presence and character of sleep disturbances and the normal physical examination in primary cases are other features of RLS that may be helpful for diagnosis.³

Epidemiology

The prevalence of RLS in the general population lies between 5 and 10%, women are affected twice as often as men.⁴ Most individuals suffer from primary RLS which shows a familial association in more than 50%. An autosomal-dominant mode of inheritance has been shown.⁵ Genome-wide studies have been conducted to map genes that play a role in the vulnerability to RLS. So far linkage was found to a locus on chromosome 12q,⁶ 14q^{7,8} and 9p.⁹ While most RLS cases may be idiopathic, RLS is often linked to other medical or neurological disorders. The most important associations of RLS are with end-stage renal disease or iron deficiency. RLS may also develop during pregnancy or intensify secondary to treatment with various drugs such as dopamine antagonists, typical and atypical neuroleptics, metoclopramide, or antidepressants such as tri- and tetracyclic antidepressants, serotonin reuptake inhibitors and lithium. Although supporting data are limited, peripheral neuropathies may be associated with RLS.¹⁰

Treatment

Pharmacological therapy should be limited to those patients who meet the specific diagnostic criteria and suffer from clinically relevant RLS symptoms. Several factors like the frequency and severity of symptoms, the temporal appearance of symptoms, the kind of sleep disturbances and the degree to which RLS interferes with the quality of life influence treatment strategies. Dopaminergic agents are considered the first-line treatment in RLS,¹¹ after secondary RLS associated with low iron or ferritin levels has been excluded. Even raising ferritin levels from the lower normal range frequently improves RLS symptoms.

L-dopa

L-dopa/benserazide (Restex® and Restex® retard) was the first drug licensed for RLS in September 2000 in two European countries, Germany and Switzerland. Doses of 50/12.5 to 100/25mg standard L-dopa / DDI improve RLS symptoms about one hour after drug intake resulting in an improved quality of sleep. In correlation to the plasma half-life of L-dopa (1–2 hours) the beneficial effect decreases and RLS may persist in the second half of the night. If so, an additional application of slow release L-dopa/DDI (100/25mg given in combination with standard L-dopa/benserazide one hour prior to or at bed time) is recommended. In general, L-dopa is best used in patients with mild RLS. In patients with sporadic RLS, L-dopa can be given on demand. Tablets are generally taken at bedtime, perhaps supplemented by a dose earlier in the day to control evening or daytime symptoms.

In more severely affected patients RLS symptoms may not be adequately controlled for the whole night even with the combination of standard and sustained release preparations.



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Professor Wolfgang Oertel is Director of the Department of Neurology at the University of Marburg. He has been opinion leader in the diagnosis and treatment of RLS for more than 15 years and was founder of the RLS research group in Germany. He was principal investigator in placebo-controlled national and multinational clinical trials in RLS and involved in the conception and design of studies for EMEA or FDA approval. He is speaker of the German RLS Patient Register, which was founded by the German Ministry for Education and Research (BMBF).

Table 1: Essential diagnostic criteria of the International RLS Study Group [76]

1. *An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs).*
2. *The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting.*
3. *The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.*
4. *The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).*

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Table 2: Characteristics of dopaminergic agents in the treatment of RLS

	Half-life (hrs.)	Initial dosage	Titration	Dosage in RLS	Max. dosage
<i>l</i>-dopa/benserazide	1-2	50/12.5 – 100/25mg	50-100mg / day	50–300mg	400mg
α -dihydroergocriptine	10-15	5mg	5mg / 3 days	10–40mg	80mg
Bromocriptine	3-8	1.25mg	1.25mg / week	2.5–5mg	7.5mg
Cabergoline	> 65	0.5mg	0.5mg / week	0.5–2mg	4mg
Lisuride	2–3	0.1mg	0.1mg / week	0.–2mg	4mg
Pergolide	7–16	0.05mg	0.05mg / 3 days	0.1–0.75mg	1.5
Pramipexole-HCl* (non-ergot)	8–12	0.125mg	0.125mg / 3 days	0.125–0.5mg	1.5mg
Ropinirole (non-ergot)	3–10	0.25mg	0.25mg / 3 days	0.5–4mg	8mg
Rotigotine (non-ergot)	(5 hrs.) constant plasma levels due to patch application	1.25mg (2.5cm ²) or 2.5mg (5cm ²)	1.25mg / day above 4.5mg; 2.25mg / day	1.25–4.5mg (2.5–10 cm ²)	9mg

* in some European countries declared as free base 0.088mg pramipexole = 0.125mg pramipexole-HCl
bold = at least two randomised, placebo-controlled clinical trials with a sufficient number of patients

Dopamine agonists

Due to their longer half-life dopamine agonists are preferred especially in patients with advanced daily RLS. Given once in the evening in dosages usually much lower than in Parkinson's disease dopamine agonists cover sensory and motor symptoms of RLS throughout the night and some dopamine agonists even during the day. As a consequence sleep and quality of life markedly improves in most patients. Convincing data are available for the dopamine agonists cabergoline, pergolide, ropinirole, pramipexole, and the dopamine agonist patch rotigotine. For details on the characteristics of dopaminergic agents in the treatment of RLS see Table 2.

Opioids

Opioids have shown to be effective in RLS and their analgesic or sedative effect may be of advantage in individual patients, but data from placebo-controlled trials are very limited and only available for oxycodone. Opioids may be highly effective particularly in advanced RLS and should not be withheld from appropriate patients because of fear of potential development of tolerance or dependence. If opioids are used, treatment regimens like in chronic pain syndromes should be applied. Severely affected patients may particularly profit from opioid patch applications.

Gabapentin

Gabapentin may be an alternative choice, particularly in less intense RLS, RLS in combination with a painful peripheral neuropathy or an unrelated chronic pain syndrome. Gabapentin should be used as once- or twice-daily doses in the late afternoon or evening or before sleep. A controlled trial has shown that mean doses of 1800mg/d are needed for efficacy. The anticonvulsants carbamazepin and valproic acid seem to be less effective in RLS than gabapentin.

Benzodiazepines

Benzodiazepines are sometimes employed for residual insomnia but should be used with caution in particular in older patients. Better alternatives are zaleplon, zolpidem or zopiclone.

In some patients combination therapies with dopaminergic agents, opioids, anticonvulsants or benzodiazepines may be a necessary but not formally studied option.

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