

Diagnosis and management of restless legs syndrome

INTERVIEW

2

**Restless legs syndrome:
an underdiagnosed, treatable
disease affecting patients' quality
of life**

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CASE REPORT

4

**A 54-year-old female patient with
severe pain and tingling in her legs
for over 20 years**

POSTER PRESENTATION

6

**Piribedil is effective in
restless legs syndrome**

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EDITORIAL

Restless legs syndrome (RLS), or Ekbom's syndrome, is a neurological disease that not only affects the extremities during waking hours, but also causes sleep disturbances and consequent daytime fatigue, profoundly affecting patients' quality of life. Because RLS is linked to dopamine deficiency, it frequently occurs in patients with Parkinson's disease.

In this issue, Dr Claudia Trenkwalder, an expert on RLS, reviews the salient features of the disease including its diagnosis, prevalence and pathophysiology, and the relevance of dopaminergic agents. She also presents a clinical case report that illustrates the ease with which RLS can be diagnosed, and the benefits that therapy with dopamine agonists can produce in improving the quality of life of patients with the disease.

Finally, clinical data from Dr Virgilio Evidente are presented that demonstrate the efficacy of Trivastal® (piribedil), a D₂/D₃ dopamine agonist, in the long-term treatment of the disabling motor symptoms of RLS.

We hope that the practical information about RLS in this issue will encourage physicians to consider the diagnosis of RLS more frequently, in the knowledge that treatment options are available to improve the quality of life of affected patients.

INTERVIEW



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Restless legs syndrome

Q1 Restless Legs Syndrome (RLS), whilst common and treatable, is frequently underdiagnosed. Could you define the aetiology, prevalence and symptoms of this condition?

The symptoms of RLS are very typical, and the minimum criteria for diagnosis are the presence of all four of the following clinical features:¹

- desire to move the limbs, usually associated with paresthesia or dysesthesia
- motor restlessness
- symptoms that are worse or are present exclusively at rest (i.e. lying down, sitting), with at least partial and temporary relief obtained by activity
- symptoms that are worse in the evenings or at night.

Additional features include:

- sleep disturbance and its consequences
- involuntary movements (periodic limb movements in sleep [PLMS], involuntary limb movements while awake and at rest)
- chronic condition (at any age, but increased severity after middle age)

- family history
- primary RLS – lack of neurological abnormalities
- secondary RLS – peripheral neuropathy, radiculopathy and other neurological disorders.

Another commonly observed feature is sleep disturbance characterized by PLMS, which is present in more than 80% of patients with RLS. Involuntary movements may also occur occasionally during wakefulness. Affected patients complain of unpleasant sensations that are felt mainly in the evenings, which limit their social life.

RLS is a disorder that occurs frequently, with prevalence rates within the general population of between 5% and 10%.² The rate may be up to 15% in the elderly, particularly in elderly women.³ The results of recent epidemiological studies are expected to confirm the high prevalence of patients who meet the minimum diagnostic criteria outlined above (K Berger *et al.*, personal communication). RLS occurs in 19.5% of patients with Parkinson's disease.⁴

The aetiology of RLS remains unclear, but many authors believe that it may be caused

by a central nervous system (CNS) disorder, with CNS hyperexcitability, or a metabolic disorder involving dopamine, iron, or the opioid system. In patients with Parkinson's disease, the occurrence of RLS cannot be attributed to dopamine deficiency in the neurons of the substantia nigra. It may arise, instead, from an alteration in the uptake of dopamine or its binding to receptors. It is generally accepted that RLS is predominantly a genetic disorder, with a probable autosomal-dominant mode of transmission.

Q2 **The International RLS Study Group, of which you are a member, has defined the clinical features of RLS. Could you elaborate on their recommendations?**

The clinical features of RLS defined by the International RLS Study Group are outlined above in the first paragraph. These criteria¹ should be the basis of all clinical diagnoses of RLS, so that we are able to make comparisons between different patient populations experiencing these symptoms. There are additional clinical features that occur frequently, of which sleep disturbances are very important. More than 90% of RLS patients suffer from some kind of sleep disorder, i.e. increased sleep latency, frequent awakenings or (subjectively assessed) reduced quality of sleep. PLMS cause frequent awakenings, resulting in sleep disturbances; some patients also report periodic involuntary leg movements during wakefulness.

Q3 **How do the clinical features of RLS differ from those of other conditions with neurological symptoms, e.g. nocturnal leg cramps, akathisia (syndrome of motor restlessness), peripheral neuropathy, and vascular diseases such as deep venous thrombosis?**

Differential diagnosis of RLS includes other conditions involving motor restlessness and sensory symptoms of the legs, such as rare movement disorders (e.g. painful legs and moving toes, generalized restlessness similar to akathisia, and sensory forms of polyneuropathies). Akathisia can easily be ruled out on the basis of the patient's drug history, and signs of body rocking as well as marching on the spot that are associated with this syndrome. Some symptoms of RLS can be similar to those in vascular diseases such as deep venous thrombosis. Persistence of these symptoms after surgery, and the almost complete relief obtained by motor activity, point to a diagnosis of RLS rather than other peripheral venous or neuropathic diseases. For differential diagnosis of RLS, one has also to consider other nocturnally occurring phenomena, such as leg cramps, startled movements during sleep and motor symptoms associated with epilepsy or respiratory problems.

Q4 **What therapeutic agents are recommended for the treatment of RLS?**

Experts agree that dopaminergic agents are the drugs of first

choice for the treatment of RLS. Levodopa, in combination with a dopa-decarboxylase inhibitor (DDCI), has been proven by several blinded and non-blinded trials to be very efficacious.⁵ Dopamine agonists such as pergolide, cabergoline, pramipexole, ropinirol and piribedil can also be used.⁶⁻⁹ Opioids, benzodiazepines and anticonvulsants may be considered in patients for whom dopaminergic drugs are contraindicated or inadequate.

Q5 **Recent reports indicate that dopamine agonists are efficacious for the treatment of moderate to severe RLS. What are the main considerations when instituting treatment with these agents?**

Treatment with dopamine agonists can be initiated in patients with moderate to severe RLS, especially if daytime symptoms occur before treatment is started. Our experience has shown that levodopa therapy can lead to the worsening of daytime symptoms, with the occurrence of a phenomenon called 'augmentation',¹⁰ manifested by an increase in and earlier onset of daytime symptoms, i.e. in the early afternoon or at lunchtime. Recent studies indicate that augmentation of symptoms does not occur during treatment with dopamine agonists.^{6,8} Treatment with dopamine agonists is instituted on the premise that the dose will be given daily, starting with a low dose followed by a titration period, and should be considered for patients requiring daily treatment.

Q6 What effect do dopamine agonists have on the quality of life of treated patients?

Quality of life may improve tremendously in RLS patients treated with dopamine agonists. We know of patients who were

unable to have any social life in the evenings due to RLS, and in whom treatment with dopamine agonists led to the complete disappearance of RLS symptoms.⁷ Data showing improved quality of life are available from short-term studies as well as studies

followed-up for periods of 12 months or 2 years.⁸ Treated patients may achieve significantly enhanced quality of life during the daytime as well as improved quality of sleep. Long-term studies will show if these effects are likely to be maintained.

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CASE REPORT

A 54-year-old female patient came to the movement disorder clinic because she had been suffering from severe pain and tingling in the legs for more than 20 years. The symptoms had deteriorated dramatically in the previous 3 years, so that she was unable to fall asleep without walking around or showering her legs with warm and cold water. She reported that the symptoms had worsened after she had been ill

with a fever, and had had to stay in bed for 1 week. During the preceding year, her symptoms had been starting in the late afternoon around 5 p.m. She was unable to sit and watch TV in the evenings, or to go to the cinema or theatre, because of her restlessness. She had to stand up and walk during the evenings. She was usually quite tired during the day because she had a total of only 4 or 5 hours

of sleep during the night. She had to get up early in the mornings, although this would have been the best time for her to sleep.

The patient reported that her mother had suffered from similar symptoms, and she remembered her mother wandering around all night long when the patient still lived at home. A sister had mentioned experiencing painful tingling in

one leg after lumbar surgery, and was now continuing to have sleeping problems.

Further neurological investigations indicated a normal status, with measurement of nerve conduction velocity revealing no evidence of polyneuropathy. Iron, ferritin, creatinine, and other blood and serum values were normal. The only concomitant disease was mild arterial hypertension. Laboratory tests were carried out to exclude secondary forms of restless legs syndrome (RLS) associated with iron deficiency anaemia or uraemia.

During a polysomnographic examination, a severe periodic limb movement syndrome was detected, with more than 500 PLMS (periodic limb movements in sleep) during the night, which was associated with frequent awakenings. There was no evidence of respiratory disturbances.

A diagnosis of typical familial RLS was made as the patient met all four minimum criteria for RLS, associated with restlessness and sensory leg discomfort, and the symptoms had a clear circadian pattern that started in the late afternoons. She was treated with dopamine agonists. This treatment was chosen because of the severity of symptoms in the evenings and late afternoons, and to avoid augmentation of the symptoms during daytime. Treatment with levodopa might provoke more daytime symptoms in a patient who has already experienced RLS problems during the day. The patient remained almost symptom free under this treatment, but continued to require domperidone to cope with side effects, especially nausea. During a follow-up period of 3 months, the patient tolerated the dopamine agonist and was able to reduce the dosage of domperidone. The symptoms improved at times, so that we were able to reduce the

dosage during vacations. After 1 year of treatment, the patient started to experience symptoms in the early mornings, around 3 and 4 a.m. and therefore we increased the dosage, which restored her sleep in the second half of the night once more. The duration of sleep improved markedly from 4 hours to 6 hours during weekdays and sometimes longer at weekends.

Her sister disclosed that she is also suffering from RLS, with symptoms that had gradually increased in severity after lumbar spine surgery. However, she refuses to take any medication at present, preferring to cope with the symptoms by physical activity if she wakes during the night.

Dopamine agonists, in general, may be used for the treatment of RLS. A recent study¹ showed that piribedil produced moderate control of symptoms in 85% of patients and complete control in 62% of patients.

Summary

A case report of a 54-year-old female patient, who had experienced severe pain and tingling in her legs for over 20 years, is presented. The symptoms had worsened following a febrile illness. There was a positive familial history. Polysomnographic examination revealed severe periodic limb movement syndrome, with more than 500 PLMS during the night, which was associated with frequent awakenings. A diagnosis of RLS was made and the patient responded to treatment with dopamine agonists. The patient became almost symptom free, and the duration of sleep improved markedly. After 1 year, the dosage of dopamine agonist was adjusted to maintain control of early morning symptoms.

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PIRIBEDIL IS EFFECTIVE IN RESTLESS LEGS SYNDROME

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Adapted from a poster presented at the 10th Meeting of the European Neurological Society. 18–22 June 2000; Jerusalem, Israel.

BACKGROUND

Restless legs syndrome (RLS) is a common condition characterized by paresthesia or dysesthesia, a desire to move the limbs, motor restlessness and periodic limb movements. These symptoms appear or are exacerbated during the night resulting in sleep disturbance,¹ and cause significant physical disability and emotional stress to affected patients. The exact aetiology of idiopathic RLS is unknown. However, the favourable response of RLS that occurs with anti-parkinsonian medications suggests that dopaminergic dysfunction may be involved.² Levodopa, which is particularly effective in RLS, may be associated with augmentation and rebound of clinical symptoms. Better alternative therapy may be offered by dopamine agonists.

Piribedil is a direct-acting, selective D₂/D₃ dopamine receptor agonist with proven effectiveness in both early and advanced stages of Parkinson's disease (PD). Its therapeutic effects in patients with RLS have not yet been studied.

STUDY OBJECTIVE

The purpose of this study was to describe the therapeutic effects of piribedil in 12 patients with RLS.

METHODS

Patients

Twelve consecutive RLS patients (6 male, 6 female) were treated with piribedil (Trivastal® retard 50), with or without domperidone (10–20 mg) pre-treatment to prevent nausea and vomiting. This open label trial was started in February 1999, and the patients were followed up to May 2000.

Efficacy evaluations

Patients were rated using an RLS scale (0–10) (Table 1) pre- and post-treatment with piribedil. The patient's subjective assessment of improvement was also graded

TABLE 1. RLS rating scale (maximum score = 10)

Occurrence of unpleasant restless leg sensations at night, which are relieved by leg movements

- 0: never
- 1: rarely (< 1 per month)
- 2: occasionally (< 1 per week)
- 3: often (at least 1 per week)
- 4: almost every night

Level of distress caused by these sensations

- 0: nil
- 1: mild
- 2: moderate
- 3: severe

Duration of these sensations

- 0: 0–few seconds
- 1: <30 minutes
- 2: >30 minutes
- 3: >1 hour

from 0% (no response) to 100% (complete resolution of symptoms) using an ordinal scale.

Statistical analyses

Pre- and post-treatment RLS scores were compared using the Wilcoxon signed rank test. The association between the subjective improvement and RLS score was assessed using Spearman's rank correlation. The relationship between subjective improvement or RLS scores and the presence of neuropathy or PD was ascertained using the Mann-Whitney U-test.

RESULTS

Patients

The mean age of the patients was 66.5 years; 67% had idiopathic RLS, whereas 33% had neuropathy (Table 2); 33% had PD. One patient had uraemia (on regular dialysis); none of the patients had iron deficiency.

There were six de novo cases of RLS (no past or current treatment for RLS). Three patients had received levodopa preparations for the treatment of PD, with inadequate effect on the RLS symptoms; two had received clonazepam, and one was on zolpidem with continuation of significant symptoms.

TABLE 2. Patients' baseline characteristics (n = 12)

<i>Age in years</i>	
Mean:	66.5
Range:	39–87
<i>RLS score</i>	
Mean:	9.92
Number with score of 10:	11 (92%)
Number with de novo RLS:	6 (46.8%)
Number with idiopathic RLS:	8 (67%)
Number with neuropathy:	4 (33%)
Number with Parkinson's disease:	4 (33%)

Efficacy

Ten of the 12 patients (83%) responded to piribedil, with a mean subjective improvement of 78.3%; eight had 100% response (Table 3). The RLS score decreased significantly from 9.92 pre-treatment to 3.25 post-treatment (p = 0.0003). There was a strong correlation

TABLE 3. Efficacy of piribedil for the treatment of RLS (n = 12)

<i>Subjective evaluation</i>	
Number of treatment responders:	10 (83%)
Mean degree of improvement (range):	78.3% (0–100%)
Number of patients with 100% improvement:	8 (67%)
<i>Mean RLS score</i>	
Baseline:	9.92
Post-treatment:	3.25*
* The improvement in mean RLS score following treatment is significant (p = 0.0003)	

between subjective improvement and RLS score (r = 0.953; p < 0.001). There was, however, no association between RLS scores and neuropathy (p = 0.697) or PD (p = 0.614), or between subjective improvement and neuropathy (p = 0.935) or PD (p = 1.0).

Duration of response

Duration of response for the 10 treatment responders ranged from 1 to 12 months (mean 6.2 months). Two responders stopped the drug (one after 1 month of treatment, the other after 5 months), despite positive results without side effects, and decided to try alternative forms of treatment; one stopped due to side effects (palpitations and chest pain); one stopped responding to piribedil after 15 months of therapy, and was switched to alternative medications; six (60%) continued to benefit from the drug.

Effective dosage

The effective dose ranged from 25 to 350 mg/day (mean dose: 110 mg/day); 9/10 patients responded to low dose piribedil (≤150 mg/day), whereas 1/10 (with severe uraemia and neuropathy) needed a dose of 350 mg/day.

Side effects

- 2/12 patients stopped the drug due to side effects.
- 1/12 (a nonresponder) experienced sleepiness and mental clouding at a dose of 50 mg/day and stopped the drug.
- 1/12 (a responder) stopped the drug after 9 months of therapy due to palpitations and chest pain despite a low dose of piribedil (50 mg/day).
- None experienced nausea or vomiting with piribedil when pretreated with domperidone (10–20 mg before every dose of piribedil).

CONCLUSIONS

- Piribedil is an effective treatment, even at low dosages, for RLS.
- Piribedil is, in general, well-tolerated by the majority of patients.
- Piribedil may be effective for the long-term RLS therapy.
- A double-blind placebo-controlled study is warranted.

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