

## RESTLESS LEGS SYNDROME: CLINICAL OVERVIEW AND TREATMENT

### Huzursuz bacak sendromu: Klinik özellikler ve tedavi

Murat AKSU<sup>1</sup>

**Abstract:** Eventhough restless legs syndrome (RLS) was first described more than 300 years ago, it is a common, sometimes disabling and often misdiagnosed condition. Two clinical forms of RLS were described: primary and secondary. The primary form is mostly familial. The main causes of secondary RLS are uremia, neuropathy and iron deficiency. Periodic limb movements of sleep (PLMS) are repetitive, often stereotyped movements that recur at intervals of 15-40 seconds during sleep. Between 70-80 % of RLS patients also have PLMS. RLS and PLMS therapy is generally symptomatic. Cures are only possible with the secondary form where the primary illness can be cured. The drug treatments of RLS and PLMS include dopa and dopa agonists, benzodiazepines and opiates. In our experience L-Dopa and pergolide are the most effective treatments.

**Key Words:** Restless legs syndrome, Movement, Sleep disorders

Restless Legs Syndrome (RLS) is a common, sometimes disabling and often misdiagnosed condition that is not completely understood. It is known that the clinical features of RLS were first described by Willis more than 300 years ago (1). Ekbom provided the first modern scientific definition for the syndrome from the 1940s on (2-6). More recently, the clinical features of RLS were defined by the International RLS Study Group (1). Minimal diagnostic features are, a desire to move the limbs usually associated with paresthesias/dysesthesias, motor restlessness, symptoms most severe or exclusively present at rest with at least partial relief by activity, and symptoms worst during evening and / or night hours.

Erciyes Üniversitesi Tıp Fakültesi 38039 KAYSERİ  
Nöroloji. Y.Doç.Dr.

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**Özet:** Huzursuz Bacak Sendromu (HBS) sık görülmesine ve 300 yıl önce ilk kez tanımlanmış olmasına karşın sıklıkla tanı güçlüğü olan bir durumdur. HBS'nun primer ve sekonder olmak üzere iki klinik formu tanımlanmıştır. Primer formu çoğunlukla aileseldir. Sekonder formu ise en sık olarak üremi, nöropati ve demir eksikliğine bağlıdır. Uykudaki periyodik bacak hareketleri, uykuda 15-40 saniyede bir olan, yineleyici, sıklıkla stereotipik hareketlerdir. HBS olan hastaların % 70-80' inde görülür. HBS ve uykuda periyodik bacak hareketleri tedavisi genelde semptomatiktir. Sadece sekonder olgularda, neden olan hastalığın tedavisi ile tam kür sağlanabilir. HBS ve uykuda periyodik bacak hareketlerinin ilaçla tedavisinde dopa ve dopa agonistleri, benzodiazepinler ve opiatlar kullanılır. Ancak bizim deneyimimize göre L-Dopa ve pergolide en etkili ilaçlardır.

**Anahtar Kelimeler:** Huzursuz bacak sendromu, Hareket, Uyku bozuklukları

Early studies found that approximately one third of RLS was familial (6). However if subgroups in the various studies are combined, more recent studies report 64 %, 63 %, and 62.5 % of probands had a positive family history of RLS (7-9) These forms of the disease are mostly called idiopathic RLS.

Therefore, a secondary form of RLS was described. Considerations for the more common forms of secondary RLS are as follows:

Uremic RLS is present in 20-57 % or more of patients with renal failure (10-13). Trenkwalder et al. (14) compared clinical and polysomnographic features of idiopathic and uremic RLS and reported no differences in sensory symptoms but noted increased dyskinesias while awake and periodic limb movements during sleep (PLMS) in uremic patients. RLS has been associated with increased mortality in the dialysis population (15).

Other causes of secondary RLS are various forms of neuropathy i.e. diabetic, alcoholic, amyloid, motor neuron disease, poliomyelitis and radiculopathy (9,16-20). The general epidemiology of neuropathic RLS is unknown. O'Hare et al (19) evaluated 800 diabetic patients for neuropathic features and reported that only 8.8% complained of RLS; this was not significantly different from the control group. Rutkove et al (20) more recently reported that only 5 % of neuropathic patients meet clinical criteria for RLS. Actually, the exact role of neuropathy in the genesis of RLS is unknown. Ianoccone et al (18) has suggested that all cases of RLS may be the result of peripheral neuropathy too subtle to be detected by standard electrophysiology testing.

A possible association between RLS symptoms and iron deficiency has long been recognized. Ekbom (2) reported that about 25 % of his RLS patients were iron deficient, an association corroborated by other early series (21,22). One study reported that 43 (% 80) iron deficient patients reported symptoms of RLS (23). Alen stated that reduced ferritin is a risk factor for those who first develop RLS symptoms at an older age and for those without a positive family history (personal communication). This would support iron deficiency's role as a true secondary form of RLS rather than a mitigating agent.

RLS has been associated with rheumatoid arthritis in two separate series and RLS symptoms were reported in 25-30 % of patients with rheumatoid arthritis (24,25). Another study, comparing sleep disturbances between patients with rheumatoid arthritis and Sjögren's syndrome reported that only 2 % of rheumatoid arthritis patients reported restless legs (26).

Pregnancy is considered as a serious cause of RLS. RLS frequency during pregnancy ranges from 11 to 27 % (27-29).

Numerous other conditions have been anecdotally associated with RLS. Some of these include Parkinson's disease (30,31), attention deficit disorder (32), hypothyroidism (33), obstructive sleep apnea (34), chronic respiratory insufficiency

(35), acute intermittent porphyria (36), spinal anaesthesia (37), Tourette's syndrome (38), congestive heart failure (39) and myelopathy (40).

Approximately 70 to 80 % of patients with RLS also have PLMS (41,42). PLMS are repetitive, often stereotyped movements that recur at intervals of 15-40 seconds during sleep (43). Periodic limb movements should be a sequence of at least four muscle contractions, each lasting 0.5-5 seconds and recurring at intervals of 5-90 seconds (44). They usually involve the legs and the movements seem quite similar to triple flexion movements of the hips, knees and ankles (45). PLMS also has the circadian pattern i.e. it is more prominent in the first half of the night.

## TREATMENT OF RLS AND PLMS

Restless Legs Syndrome (RLS) and Periodic Limb Movements of Sleep (PLMS) therapy generally is symptomatic and temporarily suppresses the symptoms during sleep. Cures are only possible in secondary cases where the primary illness can be cured.

Over the years, several medications have been proposed to treat RLS and PLMS. The drug treatment of RLS and PLMS includes dopa and dopa agonists, benzodiazepines and opiates.

### Dopa and Dopa Agonists

The treatment currently favored by many treating specialists for both RLS and PLMS is the use of dopaminergic agents. Those include precursors (e.g., L-dopa), agonists (e.g., bromocriptine, pergolide) and facilitating agents (e.g., selegiline hydrochloride). Low doses of dopamine provide an excellent treatment for the RLS (46,47,48). Dopaminergic treatment is also effective for reducing the leg movements of patients with PLMS (49). However two major problems with L-dopa have been reported: First the short half-life of L-dopa (50) and second, a significant augmentation of restlessness symptoms (51).

A single night time (25/100 mg and 50/100 mg) carbidopa/l-dopa normalize the PLMS for the first three hours of sleep (49), but for sleep through the rest of night, the patients who took the low dose may need a second dose. A rebound in leg activity in later sleep with carbidopa/levodopa has been reported (46).

The dopamine agonists bromocriptine and pergolide have been shown to prove effective treatments for RLS (52,53). Pergolide had at least three advantages over bromocriptine. First, pergolide has a longer duration of efficacy than bromocriptine; second, bromocriptine failed to relieve the symptoms as well as levodopa; and third, pergolide costs less than bromocriptine (52).

Pergolide is also effective in PLMS. In a double blind, randomized crossover study of 0.125 mg pergolide at bed time versus 250 mg L-Dopa+carbidopa, patients receiving pergolide showed almost complete PLMS relief and compared to L-Dopa, showed a significant increase in total sleep time (54). The data from the sleep polygraphically controlled long term follow-up (averagely 517 treatment days) study on pergolide, showed that after long term pergolide therapy, the RLS and PLMS did not increase (55).

Because of these reports indicating an excellent response to pergolide, it could be argued that pergolide, rather than carbidopa/levodopa, should be the medication of first choice.

The other medication, which is used for the treatment of RLS and PLMS is selegiline, a medication known to inhibit monoamine oxydase type B, probably has a positive therapeutic effect, decreasing the frequency of PLMS at night (56).

### **Opiates**

Opiates such as propoxyphene, methadone (57), oxycodone (58), codeine (58,59), penthazocine and propoxyphene (58,59) were found remarkably effective in a small number of patients. The most

effective of these drugs is propoxyphene. More recently it was shown that the primary benefit of propoxyphene on sleep was decrease in arousal, rather than an actual decrease in PLM (59). The danger of addiction associated with opiate use considerably limits its clinical utility.

### **Benzodiazepines**

Several benzodiazepines, including alprozolam, clonazepam, nitrazepam, temazepam and triazolam have been used to treat RLS and PLMS (60-67). Among these, clonazepam is by far the most studied benzodiazepine. Clonazepam administered before bedtime is effective in patients with RLS (60), but it may cause unacceptable daytime drowsiness (46). Shorter half-life benzodiazepines such as temazepam may preclude this effect (64).

Clonazepam, temazepam and triazolam were also found effective in PLMS. Although none of these have been found effective in reducing periodic limb movements, they did reduce the number of arousals and awakenings associated with leg jerks and also increased total sleep time and sleep efficiency (64,65).

### **Other Pharmacological Treatments**

Several other drugs such as carbamezapine, baclofen, clonidine, gabapentin, imiprapine, propranolol hydrochloride and L-tryptophan were found effective in PLMS or RLS in uncontrolled studies.

The therapeutic effect of carbamezapine in RLS was shown in several studies (68,69). Younger patients with a short history and severe symptoms of RLS had the best response to carbamezapine (69). However, carbamezapine has no effect in PLMS (70).

Baclofen, a gamma aminobutyric acid II mimetic with a known depressant effects on spinal excitatory transmission, increases the total number of PLMS; it shortens the mean intervent duration but decreases

the amplitude of the EMG discharge without significantly changing its duration (71).

Clonidine, an adrenergic agonist (72); gabapentin, a well tolerated anticonvulsant and structurally related to gamma aminobutyric acid (73,74); and propranolol hydrochloride, a beta blocker (75) have all been reported to ameliorate symptoms of RLS.

L- tryptophan and serotonin (76) and imiprapine (77) were also found effective in treating PLMS in some reports.

There are some nonpharmacological treatments in PLMS and RLS. The most important one of these is transcutaneous electric nerve stimulation (TENS). TENS before the onset of sleep may be of benefit (78).

In conclusion, there are currently several treatments for RLS and PLMS. In our experience, L-dopa and pergolide are the most effective treatments.

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