CHAPTER 10

RESTLESS LEGS SYNDROME

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DEFINITION AND CLINICAL FEATURES

The restless legs syndrome (RLS) is a neurologic disorder that is characterized by unpleasant dysesthetic or paresthetic sensations in the legs that occur at rest especially at bedtime (night). The dysesthesias may be described as pins and needles, an internal itch, or drawing, creeping, crawling sensations in the calves and legs. These symptoms cause an irresistible urge to move.[1] Movement of the legs or walking often yields prompt relief. Due to the night time symptoms it is common that patients with RLS have delayed sleep onset, leading to insomnia and chronic mild sleep loss.[2]

RLS is primarily a clinical diagnosis.[3-5] The minimal criteria for diagnosis are presented in Table 1. The first, a desire to move the extremities, often associated with paresthesias or dysesthesias, is usually experienced as "deep seated" and does not affect the skin. The calves are the most frequently affected area, but it can be felt in the thighs and feet as well. Some patients actually only describe this as a need to move the legs without paresthesias. Another criteria, motor restlessness, occurs during wakefulness where patients move to relieve the discomfort in the legs. The movements are voluntary, but the compelling urge to move is involuntary. Third, is a worsening of the signs and symptoms at rest with at least temporary relief by activity. Patients often turn to pacing, leg stretches, marching, body rocking, tossing and turning in bed, or hot/cold baths to counteract the leg sensations. Finally, there is a worsening of the symptoms at night. This seems to be secondary to an independent circadian factor where the sensations are worse at night and are absent or less disturbing in the morning.[6,7]

The past 2 decades have shown a substantial increased interest in RLS research groups. In the last 10 years in particular there has been a significant amount of research on RLS in regard to prevalence, etiologies, pathophysiology, and treatment. This has led to a better understanding of this condition. This paper will review the most recent insights of the pathogenesis, epidemiology, associated features, and treatment options.

Table 1

CLINICAL CHARACTERISTICS OF RLS NECESSARY FOR DIAGNOSIS (MINIMAL CRITERIA)

1. Desire to move the limbs usually associated with paresthesias/dysesthesias.
2. Motor restlessness.
3. Symptoms are worse at rest (i.e., lying, sitting) with at least temporary relief by activity.
4. Symptoms are worse in the evening or night.

PATHOGENESIS

The pathogenesis of RLS is better understood in the 21st century although the exact neurophysiologic aspects of idiopathic RLS are still in question. In most instances, the cause of RLS is unknown. This is generally referred to as idiopathic RLS. Clinical surveys of idiopathic RLS patients have shown that up to 60% of the patients report a positive family history.[8] An autosomal dominant mode of inheritance is suggested, and is sometimes present.[9] Some genetic studies have lead to a few possible areas that may predispose patients to this disorder. In particular, genes encoding for the GABA A receptor subunits, the gene for the alpha 1 receptor of the glycine receptor and genes involved in dopaminergic transmission and metabolism have been analyzed but no significant consensus has been reported.[8]

Research seems to suggest that the endogenous dopaminergic system seems to be intimately involved in the pathogenesis of RLS.[3] Studies reveal that dopaminergic drugs suppress the signs and symptoms of RLS, while dopamine antagonists (e.g., Pimozide) reactivated the symptoms and reversed the beneficial effect of the agonists.[10]

Further support for the dopaminergic role in RLS can be inferred from 3 clinical features of RLS. First, the circadian pattern to the RLS symptoms corresponds with the diurnal variation in human

dopamine levels.[6,7] Second, an increased frequency of RLS with age corresponds to the general decrease in the dopaminergic system with aging.[3] Finally, iron deficiency, although not a common cause, is an important, treatable cause or exacerbating factor of RLS.[1,11] Iron supplementation has improved RLS symptoms in those with an iron deficiency.[12-14] The relevance of iron to RLS may be its role as a cofactor for tyrosine hydroxylase, which is the rate limiting enzyme for the production of dopamine.

The most commonly excepted causes of secondary RLS are iron deficiency anemia,[11-14] pregnancy,[15-17] end stage renal disease (uremia),[18,19] and polyneuropathy.[20,21] Iron deficiency as a secondary cause of RLS has been reported to be more common in patients with late onset RLS.[12] Iron deficiency anemia is more common with age. O'Keffe found a 22% incidence of iron deficiency (serum ferritin <50 ng/ml) in RLS patients before the age of 50 and a 39% incidence between 50 to 64 and finally a 58% incidence in patients greater than 64-years-old.[13] If serum ferritin levels are low, iron supplementation has been shown to help the symptoms of RLS.[14]

Pregnant women have at least a 2- to 3-times higher risk of experiencing RLS than the general population. Epidemiologic studies have shown a prevalence of 11-27% of RLS during pregnancy. Usually the symptoms are worse during the third trimester. The cause of the association between pregnancy and RLS is unknown. The most common hypotheses are: metabolic alterations in regard to iron or folate deficiency; increasing hormones late in pregnancy and the changing motor habits and psychological state of pregnant women.[15-17]

Other testimonials have linked vascular insufficiency,[22] COPD,[20] lumbar spinal stenosis,[20] different peripheral polyneuropathies,[19] radiculopathies,[3] caffeine abuse,[23] partial gastrectomy,[21] rheumatoid arthritis,[25] Mg deficiency,[26] diabetes[21] and Parkinson's disease[27] as causes of secondary RLS.

EPIDEMIOLOGY

In 1960, Ekbom[1] estimated that RLS affected 5% of the population, but further reports consider this figure to be too low. Research notes RLS has a prevalence ranging from 2.5 to 15% of the general population.[28-30] The largest population questionnaire of 23,052 patients had at a 9.6% rate of RLS symptoms at least weekly. Of these patients, 88.4% had some form of sleep related symptom. Most patients complained of insomnia due to the RLS.[29] There is a female predominance. Women are twice as often affected as men.[31] Determining the exact frequency is difficult because symptomatology varies in intensity from patient to patient, and only severe cases seek medical attention. RLS may begin at any age and it may or may not occur on a daily basis. The most severely affected patients are middle-aged or older with increasing severity in the elderly.[5,13] RLS may be static or progressive and is generally chronic, although remissions may occur.

ASSOCIATED CLINICAL FEATURES OF RLS

Other features commonly seen in RLS include sleep disturbances, periodic limb movements of sleep and similar involuntary movements while awake. With sleep disturbances, many patients note a difficulty initiating sleep, maintaining sleep, daytime fatigue or exhaustion and, less commonly, and excessive daytime somnolence.

Approximately 80% of patients with RLS also experience stereotyped repetitive movements once asleep, a condition known as periodic limb movements of sleep (PLMS).[10] PLMS, (nocturnal myoclonus), usually affects the legs alone, or the legs more than the arms. They are typically characterized by stereotypic, periodic movements occurring in long "trains" during sleep. The patient exhibits dorsiflexion of the hallux and ankle with fanning of the small toes, accompanied by the flexion of the knee and hip (Babinski-like movement).[32] The movements may be recorded by electromyographic studies made from both tibialis anterior muscles. They are slower than a true myoclonic jerk (<250 ms) and are noted to recur every 5 to 90 seconds with a duration of 0.5 to 5 seconds per movement. These movements usually occur in the first and second stages of sleep, may be unilateral or bilateral, and the appearance can be variable.[10]

Periodic movements, while awake, are very similar in appearance to the PLMS, however, the movements disappear on voluntary movement. The patients use the voluntary movement to suppress the involuntary activity. Therefore, many times these movements may be hidden until forced immobilization tests are performed.[33]

LABORATORY FINDINGS

Laboratory studies may help document any associated causes of RLS. In most patients, complete blood counts and iron, ferritin, folate and vitamin B12 levels are normal.[22] However, the labs are useful to rule out anemia. The most critical laboratory test would be a serum ferritin < 50 ng/ml.[13] Other secondary causes of the disease may be documented as well. For example, abnormal EMG and NCV studies may be evident secondary to peripheral neuropathy (diabetes, etc.) or radiculopathies.[20,21] Idiopathic RLS usually has a normal neurological examination with normal EMG and NCV studies.[3]

Polysomnography can help support the diagnosis of RLS by documenting sleep disturbances as well as periodic limb movements of sleep (PLMS). The usual polysomnographic features show a delay in sleep onset, or may less often show prolonged arousals usually associated with subjective restless leg complaints. In some patients, frequent quasiperiodic movements during wakefulness are observed that become more stereotyped and periodic as sleep is achieved, at which point PLMS may emerge.[22]

DIFFERENTIAL DIAGNOSIS

In most cases the differentiation of RLS from other conditions is straight-forward. One of the more problematic differentiations is that between RLS and small fiber peripheral neuropathies, such as those occurring in diabetes.[10] This is the patient population in our practices that is critical to appropriately diagnose especially since there is a higher incidence of RLS in diabetics.[19] These patients may have similar symptoms to RLS, however, they usually persist during walking when the RLS symptoms would subside.

Another condition in the differential diagnosis of RLS is known as neuroleptic-induced akathisia (NIA). This is a motor restlessness induced by dopamine receptor blocking antipsychotic agents. NIA differs from RLS in the following ways: movements are usually induced by an inner restlessness rather than leg paresthesias, symptoms are not necessarily worse at rest or at night, patients may even prefer the lying position, finding the symptoms are much better than when they are standing or sitting, PLMS and sleep disturbances are less common, body rocking is the typical movement described in NIA, and a history of neuroleptic intake would be present.[34]

Other conditions in the differential diagnosis include peripheral vascular disease (PVD), and simple cramps. Patients with PVD may experience rest pain and night cramps secondary to vascular insufficiency, and can be easily differentiated from RLS with an appropriate physical examination. Simple cramps are a frequent phenomenon in normal as well as pathologic conditions. There are spontaneous night cramps, cramps occurring while awake without apparent stimulus, or cramps occurring as a result of a voluntary effort. There is usually an altered physiologic balance associated with cramping. Cramps may be terminated with forceful stretching of the contracted muscle or by activation of the antagonist muscles. Simple cramping usually results in a palpable muscle contraction (i.e., Charlie horse) noted by the patients that helps distinguish simple cramps from RLS.[10]

TREATMENT

A practical approach to management involves a stepwise plan. Nonpharmacologic treatments center on avoiding alcohol, caffeine, tobacco, and stress. Various pharmacologic agents have been proposed for the treatment of RLS and PLMS. Dopaminergic agents have become the most commonly prescribed medicines for the treatment of RLS. These include dopamine precursors (L-dopa) and dopamine agonists (pergolide, pramipexole, cabergoline and ropinirole). L-dopa itself always is used in conjunction with dopa decarboxylase inhibitor such as carbidopa.[12] The efficacy of these dopaminergic agents have been reported in several studies.[35-41] It is important to note that L-dopa/carbidopa may require a second dose in the middle of the night secondary to its short half-life.[36] Although treatment with levodopa alleviates the symptoms, many RLS patients develop rebound (occurrence of symptoms during the night) or augmentation (occurrence of symptoms before levodopa dosing in the evening). Augmentation has been shown to occur in as many as 82% of the patients treated with levodopa, limiting the usefulness of this agent. The direct dopamine receptor agonists are longer acting drugs that require only a single nighttime dose. These have replaced levodopa/carbidopa as the most effective treatment for RLS. Success rates between 70 to 100%

have been described with these dopamine agonists.[41] At the time this article was written, the only FDA approved agent for RLS is ropinirole.[38-40] Other dopamine agonists are trying to get approval and can be tried off-label.[41]

Bogan et al showed ropinirole was a successful, well-tolerated dopaminergic medication in a double-blind, placebo-controlled, flexible dose study showing a statistically significant decrease in RLS symptoms and subjective measures of sleep, quality of life and anxiety.[39] A similar double-blind, randomized, placebo-controlled study by Walters et al showed similar outcomes 2 years previously.[38] Allen et al showed ropinirole decreases PLMS and improves sleep parameters in patients with RLS.[40] There have been no reports of augmentation with ropinirole. Patients usually need to take their medication 1 to 3 hours prior to bedtime for it to be effective. The dose of ropinirole starts low and is titrated up to a level of efficacy. The usual start dose is 0.25 mg at night titrating up as high as 4 mg/ day based on response to the therapy. The author usually sees improvement in patients with a dose of 1 mg.

Normal adverse events associated with dopaminergic medications have been reported.[38-41] These usually include somnolence, nausea/ vomiting, dizziness, and fatigue. There is a report in the dental literature of increased dental disease in patients on dopaminergic medications due to the decrease in saliva production from the RLS medications.[42]

Benzodiazepines were among the medications first reported to be useful for treating PLMS and RLS. Clonazepam has always been the favored benzodiazepine, and when administered before bedtime has been shown to be effective.[43] However, excessive daytime drowsiness has been reported suggesting that a shorter half-life benzodiazepine may be necessary, such as Temazepam or Triazolam.[44]

Opiates such as oxycodone, propoxyphene, and codeine have been effective in the treatment, however, potential for abuse, problems with constipation and the development of intolerance have made physicians more reluctant to prescribe this therapy for long-term use.[5,45] Another deterrent to using opiates is their short half lives, which leads to rebound and a second night-time dosing unless a longer acting opioid is used.

Carbamezapine, an anticonvulsant, proved to be an effective treatment in double-blind studies with reduction of the RLS symptoms.[46] Also, there have been reports about the efficacy of other anticonvulsant agents, such as valproate sodium and gabapentin in patients with PLMS and RLS respectively. These agents generally are tried once the initial therapy fails.[10]

Pelletier et al state successful treatment requires suppression of both the sensory and motor components of RLS due to their independent manifestations.[33] In some difficult cases, combination therapies from the 3 favored classes have been considered necessary as well.[47]

CONCLUSION

The definition of and minimal criteria for diagnosis of RLS have been presented. A review of the last several years of research continues to lead to a better understanding of the pathophysiology and dopaminergic role in idiopathic RLS. Possible secondary causes of RLS were also mentioned. The current literature suggests idiopathic RLS may be familial, with an autosomal dominant mode of inheritance, and it is much more prevalent than recognized. It is still an under-diagnosed and under-treated condition. The information presented will enable the podiatric physician to be more conscious of RLS and PLMS, make a proper diagnosis, initiate treatment, or make an appropriate referral.

REFERENCES

1. Ekbom KA. Restless legs syndrome. *Neurology* 1960;10:868-73.
2. Gorman CA, Dyck PJ, Pearson JS. Symptom of restless legs. *Arch Intern Med* 1965;115:155-60.
3. Walters AS, et al, for the The International Restless Legs Study Group. Toward a better definition of the restless legs syndrome. *Movement Disorders* 1995;10:634-42.
4. Henning W. The clinical neurophysiology of the restless legs syndrome and periodic limb movements. Part 1: diagnosis, assessment and characterization. *Clin Neurophysiol* 2004;115:1965-74.
5. Trenkwalder C, Paulus W, Walters AS. The restless legs syndrome. *Lancet Neurol* 2005;4:465-75.
6. Trenkwalder C, Walters AS, Hening W, Campbell S, Rahman K, Chokroverty S: Circadian rhythm of patients with the idiopathic restless legs syndrome. *Sleep Research* 1995;24:360
7. Trenkwalder C, Paulus W. Why do restless legs occur at rest? Pathophysiology of neuronal structures in RLS. Part 2: neurophysiology of RLS. *Clin Neurophysiol* 2004;115:1975-88.
8. Ferini-Strambi L, Bonati MT, Oldani A, Aridon P, Zucconi M, Casari G. Genetics in restless legs syndrome. *Sleep Med* 2004;5:301-4.
9. Walters AS, Picchietti D, Hening W, Lazzarini A. Variable expressivity in familial restless legs syndrome. *Arch Neurol* 1990;47:1219-220.
10. Trenkwalder C, Walters AS, Hening W. Periodic limb movements and restless legs syndrome. *Neurol Clin* 1996;10:629-50.
11. Fry JM: Restless legs syndrome and periodic leg movements in sleep exacerbated or caused by minimal iron deficiency. *Neurology* 1986;36 Suppl 1:276.
12. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age Ageing* 1994;23:200-3.
13. O'Keefe ST. Secondary causes of restless legs syndrome in older people. *Age Ageing* 2005;34:349-52.
14. Earley CJ, Heckler D, Allen RP. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. *Sleep Med* 2005;6:301-5.
15. McParland P, Pearce JM. Restless legs syndrome in pregnancy: case Reports. *Clin Exp Obstet Gynecol* 1990;17:5-6.
16. Pien GW, Schwab RJ. Sleep disorders during pregnancy. Sleep 2004;27:1405-17.
17. Manconi M, Govoni V, DeVito A, Economou NT, Cesnik E, Mollica G, Granieri E. Pregnancy as a risk factor for restless legs syndrome. *Sleep Med* 2004;5:305-8.
18. Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S, et al. Restless Legs syndrome in end stage renal disease. *Sleep Med* 2004;5:309-15.
19. Callaghan N. Restless legs in uraemic neuropathy. *Neurology* 1966;16:359-61.
20. Leban MM, Viola SL, Femminineo AF, Taylor RS. Restless legs syndrome associated with diminished cardiopulmonary compliance and lumbar spinal stenosis-a motor concomitant of "Vespers curse." *Arch Phys Med Rehabil* 1990;71:384-88.
21. Lopes LA, Linsode M, Adeodato VG, Quental DP, de Bruin PF, Montenegro RM, et al. Restless legs syndrome and quality of sleep in type 2 diabetes. *Diabetes Care* 2005;289:2633-6.
22. Krueger BR.Restless legs syndrome and periodic movements of sleep. *Mayo Clin Proc* 1990;65:999-1006.
23. Lutz EG. Restless legs, anxiety, and caffeinism. *J Clin Psychiatry* 1978;39:693-8.
24. Banerji NK, Hurwitz LJ. Restless legs syndrome with particular reference to its occurrence after gastric surgery. *Brit Med J* 1970;4:774-5.
25. Salih AM, Gray RE, Mills KR, Webley M. A clinical, serological and neurophysiological study of restless legs syndrome in rheumatoid arthritis. *Br J Rheumatol* 1994;33:60-3.
26. Popoviciu L, Asgian B, Delast-Popoviciu D, Alexandrescu A, Petrutiu S, Bagathal I. Clinical, EEG, electromyographic and polysomographic studies in restless legs syndrome caused by magnesium deficiency. *J Neurol Psychiatry* 1993;31:55-61.
27. Lang AE. Restless leg syndrome and Parkinson's disease: insights into pathophysiology. *Clin Neuropharmacol* 1987;10:476.
28. Zucconi M, Ferini-Strambi L. Epidemiology and clinical findings of restless legs syndrome. *Sleep Med* 2004;5:293-9.
29. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med* 2004;5:237-46.
30. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005 165: 1286-92.
31. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med* 2004;164:196-202.
32. Smith RC. Relationship of periodic movements in sleep (nocturnal myoclonus)and the Babinski sign. *Sleep* 1985;8:239-43.
33. Pelletier G, Lorrain D, Montplaisir J. Sensory and motor components of the restless legs syndrome. *Neurology* 1992;42:1663-6.
34. Walters AS, Hening W, Rubinstein M, Chokroverty S. A clinical and polysomnographic comparison of neuroleptic-induced akathisia and the idiopathic restless legs syndrome. *Sleep* 1991;14:339-45.
35. Akpinar S. Restless leg syndrome treatment with dopaminergic drugs. *Clin Neuropharmacol* 1993;16:120-6.
36. Allen RP, Kaplan PW, Bochholtz DW, Walters JK. A double-blind, placebo controlled study of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep* 1993;16:717-23.
37. Brodeur C, Montplaisir J, Godbout R, Marinier R. Treatment of restless legs syndrome and periodic movements during sleep with L-Dopa: a double-blind controlled study. *Neurology* 1988;38:1845-8.
38. Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi K. TREAT RLS 2 (Therapy with Ropinirole: Efficiacy and Tolerability in RLS 2) *Study Group. Mov Disord* 2004;19:1414-23
39. Boggan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SY. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo controlled clinical trail. *Mayo Clin Proc* 2006;81:17-27.
40. Allen R, Becker PM, Bogan R, Schmidt M, Kushida CA, Fry JM, et al. Ropinirole decreases periodic limb movements and improves sleep parameters in patients with restless legs syndrome. *Sleep* 2004;27:907-14.
41. Comella CL. Restless legs syndrome: treatment with dopaminergic agents. *Neurology* 2002; 58 Suppl 1:S87-92.
42. Friedlander AH, Mahler ME, Yagiela JA. Restless Legs Syndrome: manifestations, treatment and dental implications. *J Am Dent Assoc* 2006;137:755-61.
43. Boghen D. Successful treatment of restless legs with clonazepam. *Ann Neurol* 1980;8:341.
44. Doghramji K, Brownman CP, Gaddy JR, Walsh JK. Triazolam diminishes daytime sleepiness and sleep fragmentation in patients with periodic leg movements in sleep. *J Clin Psychopharmacol* 1991;11:284-90.
45. Walters AS, Wagner ML, Hening WA, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double blind trial of oxycodone versus placebo. *Sleep* 1993;16:327-32.
46. Telstad W, Sorenson O, Larsen S, Lillevold PE, Stensrud P, Nyberg-Hansen R. Treatment of the restless legs syndrome with carbamazepine: a double blind study. *Brit Med J* 1984;288:444-6.
47. Hening WA. Treatment of the restless legs syndrome: current practice of sleep experts. *Neurology* 1995;45 suppl 4:445.