CHAPTER 21

RESTLESS LEGS SYNDROME

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DEFINITION AND CLINICAL FEATURES

The restless legs syndrome (RLS) is characterized by irresistible leg movements, often accompanied by or preceded by dysesthetic or paresthetic sensations in the leg. The dysesthesias may be described as pins and needles, an internal itch, or drawing, creeping, crawling sensations in the calves and legs that occur exclusively during rest and inactive seated or recumbent wakefulness.[1] Movement of the legs or walking often yields prompt relief. Some patients are symptomatic whenever they rest throughout the day, however, a large majority of the patients are worse in the evening and nighttime hours, interfering with and delaying sleep onset, leading to insomnia and chronic mild sleep loss.[2]

The International RLS Study Group formed in 1995, has defined the clinical features of the RLS.[3] The minimal criteria for diagnosis are four features (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.[4]

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.

HISTORY

The RLS probably was described for the first time in 1672 by Thomas Willis in Latin and translated in 1683. He reported that the symptoms of the condition started in the night: "Wherefore, in some, whilst they would indulge sleep, in their beds, immediately follow leapings up of the tendons, in their arms and legs, with cramps, and such unquietness and flying about of their members, that the sick can no more sleep, than those on the rack."[5] A number of authors in the 19th and 20th centuries also mentioned conditions that today would be called RLS, but the first physician to systematically study and produce a comprehensive picture of the disorder was Karl Ekbom,[1] who noted many of its important features. The past ten years have shown a substantially increased interest in RLS researchers.[3] Attempts have been made to understand the pathogenesis and pathophysiology of the condition using a variety of behavior, genetic, neuroimaging, neuropathological, neurophysiological and neuropharmacological approaches. This has led to a better understanding of this condition; however, many questions still remain.

PATHOGENESIS

In most instances, the cause of RLS is unknown. This is generally referred to as idiopathic RLS. However, other testimonials have linked anemia,[6,7] vascular insufficiency,[8] COPD,[9] lumbar spinal stenosis,[9] different peripheral neuropathies,[10] radiculopathies,[3] caffeine abuse,[11] partial gastrectomy,[12] rheumatoid arthritis,[13] Mg deficiency,[14] pregnancy,[15] and Parkinson's disease[16] as causes of secondary RLS.

The neurophysiologic aspects of idiopathic RLS are still in question, however, research seems to suggest that the endogenous, dopaminergic, and opiate systems are involved in the pathogenesis of RLS.[3] Studies reveal that opiates and dopaminergic drugs suppress the signs and symptoms of RLS, while dopamine and mu opiate antagonists (e.g. Pimozide and Naloxone) reactivated the symptoms and reversed the beneficial effect of the agonists. Because dopamine blockade reversed treatment with opioid or dopaminergic agents, whereas opioid antagonism only reversed opioid treatment, it has been suggested that the endogenous opiate system acts by influencing a primary dopaminergic mechanism (Fig. 1).[5]

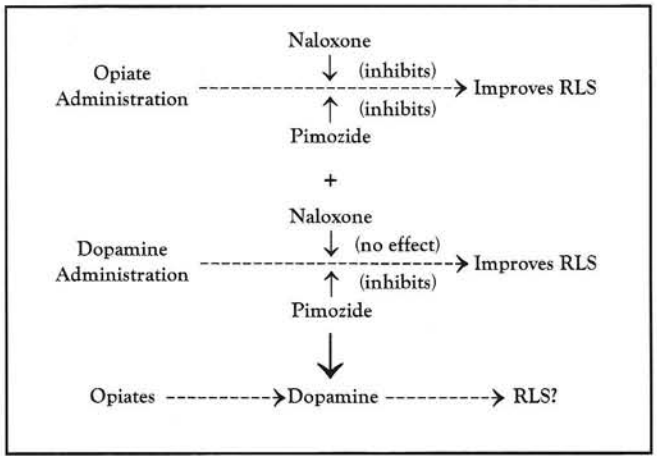

Figure 1. Dopamine vs. Opiate mechanism in RLS.

Further support for the dopaminergic role in RLS can be inferred from three clinical features of RLS. First, the circadian pattern to the RLS symptoms corresponds with the diurnal variation in human dopamine levels.[4] 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.[1,6] Iron supplementation has improved RLS symptoms in those with an iron deficiency.[7] 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.

EPIDEMIOLOGY

In 1960, Ekbom[1] estimated that RLS affected 5% of the population, but further reports consider this figure to be too low. A recent survey of 2019 respondents, all eighteen-years-old or older, reported signs and symptoms consistent with RLS in 10% to 15% of those responding.[17] 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.[3] RLS may be static or progressive and is generally chronic, although remissions may occur. An autosomal dominant mode of inheritance is suggested, and is sometimes present.[18]

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 (Table 2). With sleep disturbances, many patients

Table 2

ADDITIONAL CLINICAL FEATURES OF RLS

1. Sleep disturbances and its consequences.
2. Involuntary movements
   a. Periodic limb movements of sleep (PLMS).
   b. Involuntary limb movements while awake and at rest.
3. Neurological exam normal in the idiopathic (primary) form. May find evidence of peripheral neuropathy or radiculopathy in secondary forms.
4. May begin at any age but usually is most severe in middle to older age groups.
5. Family history is sometimes present (Autosomal dominant).

note a difficulty initiating sleep, maintaining sleep, daytime fatigue or exhaustion, and less commonly, 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).[5] 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).[19] 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.[5]

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.[20]

LABORATORY FINDINGS

Laboratory studies may help document any associated causes of RLS. In most patients, complete blood counts and iron, ferritin, folate and vitamin B_{12} levels are normal.[8] However, the labs are useful to rule out anemia. 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 or radiculopathies. 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.[8]

Single photon emission tomography (SPET) permits the in vivo measurements of regional cerebral radioactivity in the brain following the administration of compounds labeled with photon emitting isotopes. Studies have shown reduced binding of the 123I to a highly selective CNS D2 receptor ligand in patients with RLS not on replacement therapy, and an improved binding in patients on replacement therapy with decreased signs and symptoms of RLS.[21]

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.[5] 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.[22]

Other conditions in the differential diagnosis include peripheral vascular disease (PVD), simple cramps and painful legs/moving toes syndrome. 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

occasionally a metabolic abnormality (e.g. K+) 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.

Finally, painful legs and moving toes may be differentiated from RLS by the following ways: the repetitive, semi-continuous toe movements of painful legs and moving toes are not necessarily influenced by activity, the pain is usually not worse at night, and neurologic imaging or EMG may reveal a lumbosacral radiculopathy.[5]

TREATMENT

Various pharmacologic agents have been proposed for the treatment of RLS and PLMS. Pelletier et al. state successful treatment requires suppression of both the sensory and motor components of RLS due to their independent manifestations.[20] L-dopa, DA agonists, benzodiazepines, opioids, bacolofen, and carbamazepine are agents whose therapeutic efficacy has been shown in double blind studies of either RLS, PLMS or both.[3,23] A questionnaire study among sleep experts indicates that dopaminergic agents and benzodiazepines followed by opioids are the treatment of choice for RLS. In some difficult cases, combination therapies from the three favored classes have been considered necessary as well.[24]

Dopaminergic agents have become the most commonly prescribed medicines for the treatment of RLS. These include precursors (L-dopa), agonists (bromocriptine and pergolide), and facilitating agents (selegiline hydrochloride,[24] which has been mentioned as a possible therapy for RLS). L-dopa itself always is used in conjunction with dopa decarboxylase inhibitor such as carbidopa or benserazide.[5] The efficacy of these dopaminergic agents have been reported in several studies.[25-27] 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, unless the new sustained release form of the drug is used.[26]

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.[28] However, excessive daytime drowsiness has been reported suggesting that a shorter half-life benzodiazepine may be necessary, such as Temazepam or Triazolam.[29]

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.[3,30] Another deterrent to using opiates is their short half lives which leads to 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.[31] Recently, there have been reports about the efficacy of further 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.[5] Baclofen,[32] has been advocated as well.

Initial studies with nonpharmacologic treatment of RLS using transcutaneous nerve stimulation may be of value, particularly in those patients who have demonstrated a tendency toward drug tolerance and in those patients who have prompt but temporary relief during walking.[8]

CONCLUSION

The definition of and minimal criteria for diagnosis of RLS have been presented. The recent increased interest in RLS research has led 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 originally described. 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, if necessary, to a sleep medicine or neurologic physician.

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