

June 1, 2005. An Introduction to Restless Legs Syndrome

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Introduction

Although it was first described in the medical literature over 300 years ago, restless legs syndrome (RLS), a very common and potentially very disabling condition, has been largely overlooked by the medical community until the last decade. After Willis'[1] description in Latin in 1672, it was rediscovered by Karl Ekbom[2] who in 1945 not only documented its common occurrence but also coined the name "restless legs" to describe the condition. Despite this pioneering work, RLS was largely ignored for the next half-century. Several factors have contributed to the recent attention given to RLS. The medical community is recognizing more and more the importance of maintaining optimum health and quality of life; the average life span has dramatically increased; and sleep medicine has come into its own as a subspecialty. Each one of these factors has contributed to the growing recognition of RLS. Although extremely rarely if ever mortal, RLS can cause dramatic distress, greatly disturb quality of life, and profoundly disrupt sleep. The condition is more common in those over the age of 50. Finally, excellent treatments have recently been developed that permit sometimes dramatic relief from the suffering that comes with RLS. Thus, today RLS has become recognized as a common, medically significant disorder that once diagnosed can often be effectively treated.

Diagnosis

Although primarily a sensory abnormality, RLS nearly always produces a motor sign. The diagnosis of RLS depends almost entirely on the clinical history characterizing the sensory abnormality. Diagnosis requires meeting all 4 of the essential criteria established by the International RLS Study Group and the National Institutes of Health (NIH) RLS workshop.[3] The patient must experience an urge to move the legs (an akathisia focused on the legs). This urge is commonly accompanied by an unpleasant sensation (a paresthesia) usually described as a feeling of something active deep within the legs. Many patients will describe only the focal akathisia without any associated paresthesia. Because this is an urge to move the legs, it is a conscious sensory experience and not an unconscious habit, such as repetitive foot tapping, which can occur without the patient's being aware of the movement. The RLS focal akathisia is generally not present continuously throughout the day, but rather occurs episodically. Once present, it persists for several minutes, if not hours, unless the patient takes some effective countermeasure to reduce the symptoms. Although the symptoms are usually relieved by movement, they often return as soon as the movement is stopped. Patients with more severe symptoms will struggle to find an hour or so of rest at night when they can lie or sit down without being driven to move about or get up and walk.

The remaining 3 diagnostic criteria involve the circumstances in which the condition occurs. First, it must occur when the patient is at rest either sitting or lying down. Usually, the longer the duration of rest and the more complete the lack of alerting stimulation, the more likely the symptoms will start. For a diagnosis of RLS, the symptoms must not start while the patient is walking. Second, the symptoms must be at least partly relieved by bodily movement, usually movement of the affected leg. It may also be relieved by other physical activities, such as rubbing or stretching the legs. Also, alerting mental activities, such as an argument or a mentally engaging task, may provide some relief. This condition generally occurs at its worst in the borderland between sleep and waking. Most alerting stimulation will reduce the symptoms, including very hot or cold baths. Movement, particularly walking and emotional social interactions, are, of course, among the most alerting events and the most effective means of reducing symptoms. The specific features of the rest that induce the symptoms or of the alerting activities that reduce the symptoms vary from patient to patient, but generally speaking, quiescence induces and motor activity reduces the RLS symptoms. Third, the diagnostic criteria specify that the RLS symptoms must be worse in the evening and night than at other times of the day. Precisely when symptoms become worse in the evening or night varies considerably depending on the activities of the patient, but the patient should describe being able to stay at rest longer with fewer symptoms in the morning than in the evening. This circadian variation in symptoms often leaves the patient completely symptom-free while at the doctor for an examination, but the patient may dread the evening or night, anticipating the torture of the sleep-depriving sensations. The sidebar provides the 4 basic diagnostic criteria and some common descriptions of the sensory experience, which as noted, may be only the akathisia without any focal paresthesia.

The differential diagnosis of RLS includes leg cramps and positional discomfort. Both can lead to confusion in the diagnosis and need to be specifically ruled out for the diagnosis of RLS to be definitive. Positional discomfort symptoms occur only in one very specific body position and are relieved simply by changing positions without other movement. In contrast, RLS symptoms should occur in any position of rest during the evening or night, and relief should require some alerting activity, such as moving about or walking.

This primarily sensory disorder produces a motor sign characterized by periodic leg movements (PLMs) that occur approximately every 5-90 seconds when the patient is asleep or lying down resting. These PLMs in sleep, although not specific to RLS, occur in at least 80% of RLS patients, and correlate with clinical ratings of RLS severity.[4,5] If the patient does not have PLMs, the differential diagnosis should be reviewed to ensure that that patient does not have another condition producing symptoms like RLS. When present, PLMs support the diagnosis, and the degree of PLMs provides a good objective measure of RLS severity or likely response to treatment.

Risk Factors

Besides being a primary disorder, RLS also occurs secondary to other conditions, particularly iron-deficiency anemia, end-stage renal disease, and pregnancy. In these secondary cases of RLS, when the primary condition resolves, the RLS very often resolves, too. Several other conditions are associated with an increased risk of RLS, including rheumatoid arthritis and gastric surgery. Neuropathy has been associated with increased severity and onset of RLS, but in itself has not clearly been identified with an increased risk factor for developing RLS.

Clinical Profile

Although primary RLS can start at any age, 2 broad phenotypes have been identified according to age of onset. Early-onset RLS, which is defined as RLS that occurs before age 45, is characterized by insidiously advancing symptoms slowly progressing over several years, if not most of the patient's life.[6] First-degree relatives of patients with this type of RLS have a 5-fold higher risk for RLS than the general population.[7] Once RLS starts, it may have periods of remission and in some cases no reoccurrence, but in the large bulk of cases, it is a persisting lifelong disorder.[3]

The prevalence of RLS has recently been evaluated in a few population-based studies with the full diagnostic criteria. A German study based on direct diagnostic interviews reported a population prevalence of 10.6% (7.6% for men and 13.4% for women).[8] Two Swedish population studies using questionnaires similarly showed a higher prevalence for women (13.9%) than men (6.1%).[9,10] A carefully conducted multinational population study in 5 European countries and the United States with a validated questionnaire reported a slightly lower overall prevalence of 7.2%, with again a lower incidence in men (5.4%) than in women (9.0%). That study also identified the prevalence of more severe RLS, which is characterized by the occurrence of at least moderately distressing symptoms 3 or more times a week. The prevalence of this more severe RLS was 2.7% (men 1.7%, women 3.7%).[11] Prevalence seems to be lower in Turkey (3.2%)[12] and even lower in the urban Chinese population in Singapore (.6%).[13]

Etiology

Because all of the secondary causes of RLS noted above involve problems with iron balance, it has been postulated that brain iron insufficiency may be a major cause of RLS. Studies of cerebrospinal fluid have demonstrated abnormally reduced ferritin and increased transferrin for RLS despite normal levels of these iron measures in serum.[14,15] MRI studies of regional brain iron have shown decreased iron content in the substantia nigra, and this decrease correlates with RLS severity.[16] Finally, autopsy studies have found reduced iron, increased transferrin, and reduced H-ferritin, but not L-ferritin, in the neuromelanin cells of the substantia nigra.[17,18] Thus, it seems likely that one primary cause of RLS is brain iron insufficiency.[19]

Treatment

The serendipitous finding by Akpınar[20] that a relatively small dose of levodopa can provide dramatic and nearly complete relief of even very severe RLS symptoms has led to the general assumption that RLS also involves a dopaminergic dysfunction.[21] This notion has been supported by numerous other studies of pharmacologic response. All dopamine agonists evaluated to date have reduced RLS symptoms and conversely the dopamine antagonists tested have exacerbated symptoms. Moreover, dopamine pathology has been found to occur with iron deficiency in animals,[22] and thus it seems likely that the brain iron deficiency seen in some RLS sufferers produces a dopamine abnormality causing the RLS symptoms.[23,24] This putative iron-dopamine pathology for RLS is unlikely to be the only cause of RLS, but at present it is the best documented cause.

RLS has been found to produce a chronic sleep loss more severe than in almost any other condition,[4] and it impairs quality of life as much or more than other chronic diseases, such as depression, congestive heart failure, and hypertension.[25] Fortunately, current treatments with mostly dopamine agonists provide reasonably good improvement in sleep[26] and in quality of life.[27] One dopamine agonist, ropinirole, has recently been approved by the US Food and Drug Administration (FDA) for the treatment of moderate-to-severe RLS. Unfortunately, some patients develop a worsening or augmentation of their underlying RLS conditions while on dopaminergic treatment, which limits the use of these medications for this minority of patients. Other drugs, particularly opiates and some anticonvulsants, such as gabapentin, also provide reasonable treatment for RLS and can be used instead of or in conjunction with a dopamine agonist.

Conclusion

RLS, a distressing sensory motor disorder with some known biological causes, can be diagnosed and usually effectively treated in primary care with referral to a sleep specialist or neurologist when needed for difficult cases. Further understanding of the causes of RLS may eventually lead to even better treatments or even to the prevention of the disorder.

Sidebar

The diagnosis of RLS requires meeting all 4 of the following criteria[2]:

- An urge to move the legs occurs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs;

- The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting;
- 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; and
- 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.

The following are examples of the common subjective reports of the sensations in the legs given by RLS patients:

- "Creepy, crawly";
- "Worms crawling in veins";
- "Pepsi-Cola in the veins";
- "Nervous feet";
- "Itchy bones";
- "Crazy legs or heebie-jeebies";
- "Elvis legs";
- "Toothache feeling - can't leave it alone";
- "Electric-like shocks";
- "Excited nerves"; and
- " Just need to move ."

Patients complain of pain in as many as 35% of clinical cases.

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