RESTLESS LEGS SYNDROME

JOHN H. HARNEY, M.D.

Background: The term restless legs syndrome (RLS) was used initially in the mid-1940s by Swedish neurologist Karl A. Ekbom to describe a disorder characterized by sensory symptoms and motor disturbances of the limbs, mainly during rest. However, early descriptions date back to the 17th century. It is recognized now as a neurologic movement disorder of the limbs, often associated with a sleep complaint. Patients with RLS have a characteristic difficulty in trying to depict their symptoms; they may report sensations such as an almost irresistible urge to move the legs, which are not painful but are distinctly bothersome; this can lead to significant physical and emotional disability. The sensations usually are worse during inactivity and often interfere with sleep, leading to walking discomfort, chronic sleep deprivation, and stress. Once correctly diagnosed, RLS can usually be treated effectively by relieving symptoms; in some secondary cases, it can even be cured.

Pathophysiology: RLS also has been linked to dopaminergic or opiate abnormalities. Centrally acting dopamine receptor antagonists reactivate symptoms when given to patients with the syndrome. Results of single-photon emission computed tomography (SPECT) have suggested deficiency of dopamine D2 receptors. Sympathetic hyperactivity also has been implicated on the basis of observations that sympathetic nerve blockade relieves periodic limb movements of sleep and that alpha-adrenergic blockers improve symptoms of RLS.

Frequency: RLS affects about 10-15% of the general population. A 2004 study by Berger et al showed that RLS affects women more frequently than men. Although the prevalence of RLS increases with age, it has a variable age of onset and can occur in children. In patients with severe RLS, 33-40% had their first symptom before the age of 20 years, although the precise diagnosis of RLS was made much later. It usually progresses slowly to daily, severe disruption of sleep, typically after age 50.

- The criteria for diagnosis of RLS are based on those developed by the International Legs Syndrome Study Group in 1995; 4 basic elements must be present to make the diagnosis. They are as follows:
    - A compelling urge to move the limbs, usually associated with paresthesias/dysesthesias

- Motor restlessness, as seen in activities such as floor pacing, tossing and turning in bed, and rubbing the legs
- Symptoms worse or exclusively present at rest (ie, lying, sitting) with variable and temporary relief on activity
- Circadian variation of symptoms, which are present in the evening and at night. Often, symptoms are relieved after 5:00 am. In more severe cases, symptoms can be present throughout the day without circadian variation.

- Other features commonly associated with RLS but not required for diagnosis include sleep disturbances and daytime fatigue; normal neurologic exam in primary RLS; and involuntary, repetitive, periodic, jerking limb movements, either in sleep or while awake and at rest.
- Approximately 85% of patients with RLS have periodic leg movements of sleep (PLMS), usually involving the legs. PLMS is characterized by involuntary forceful dorsiflexion of the foot lasting 0.5-5 seconds and occurring every 20-40 seconds throughout sleep.
- A large majority of patients (85%) with RLS report difficulty falling asleep at night because of RLS, and they may experience excessive daytime somnolence because of poor sleep quality due to multiple PLMS-induced arousals.

Physical: The physical examination is usually normal in patients with RLS; it is performed to identify secondary causes and to exclude other disorders.

Causes: RLS can be primary or secondary.

- Primary RLS
  - In most cases, RLS is an idiopathic CNS disorder. Such idiopathic disease can be familial in 25-75% of cases. In the familial cases, it appears to follow a pattern of autosomal dominant inheritance
  - Patients with familial RLS tend to have an earlier age at onset (< 45) and slower progression.
  - Psychiatric factors, stress, and fatigue can exacerbate symptoms of RLS.
- Secondary RLS

- RLS can develop as a result of certain conditions or factors, particularly iron deficiency and peripheral neuropathy. These 2 conditions should be excluded before RLS is labeled as primary. Because of the prevalence of these conditions in the general population, their association with RLS needs to be interpreted with caution.

- Other causes are folate or magnesium deficiency, polyneuropathy (either idiopathic or caused by alcohol abuse), amyloidosis, diabetes mellitus, lumbosacral radiculopathy, Lyme disease, monoclonal gammopathy of undetermined significance, rheumatoid arthritis, Sjögren syndrome, uremia, or vitamin B-12 deficiency.

- Women can be affected by RLS during pregnancy, and the syndrome usually subsides within a few weeks after delivery. It affects 25-40% of pregnant women.

- RLS also occurs in as many as 25-50% of patients who have end-stage renal disease and find their symptoms particularly bothersome during hemodialysis. Hyperphosphatemia, anxiety, and a great degree of emotion-oriented coping with stress were independently related to the presence of RLS in uremic patients taking hemodialysis therapy.

Other conditions associated with RLS are anemia; Parkinson disease; gastric surgery; chronic obstructive pulmonary disease (COPD); some tumors; chronic venous insufficiency or varicose veins; medications or certain substances, such as alcohol, caffeine, anticonvulsants (eg, methsuximide, phenytoin), antidepressants (eg, amitriptyline, paroxetine), beta-blockers, histamine-H2 antagonists, lithium, neuroleptics, withdrawal from vasodilators, sedatives, or imipramine; cigarette smoking; myelopathy or myelitis; hypothyroidism or hyperthyroidism; acute intermittent porphyria; fibromyalgia; and cholesterol peripheral microemboli.

Other Problems to be Considered:

Nocturnal leg cramps: These are typically unilateral, painful, palpable, involuntary muscle contractions, often local, with a sudden onset. Like RLS, they may have a circadian pattern and often occur at rest. However, the leg cramps have physical changes including a muscle hardening not seen in RLS.

Akathisia: It is characterized by excessive urge to move the entire body, without a focal sensory complaint in the limbs; often it does not correlate with rest or

show circadian variation, and it usually results from medications such as neuroleptics or other dopamine-blocking agents. It also may be caused by selective serotonin reuptake inhibitors (SSRIs).

Peripheral neuropathy: It can cause leg symptoms that are different from those of RLS; symptoms usually are neither associated with motor restlessness nor helped by movement and do not worsen in evening or nighttime. Typically, sensory complaints are numbness, tingling, or pain. Small-fiber sensory neuropathies, as seen in diabetes, often are confused with RLS; patients with neuropathies may have both neuropathic symptoms and symptoms of RLS.

Vascular disease (eg, deep vein thrombosis)

Painful legs moving toes: Unlike RLS, this condition is not associated with a focal urge to move the limbs, and it does not show a clear circadian pattern.

RLS must be distinguished from sleep-related leg conditions, such as nocturnal leg cramps. These periodic limb movements, also known as PLMS or nocturnal myoclonus, which may be associated with RLS, are stereotyped, repetitive flexion of the limbs (legs alone or legs more than arms), lasting 0.5-5 seconds and usually occurring every 20-40 seconds.

Studies:

- If a secondary cause is suspected on the basis of history, abnormal findings on neurologic examination, or poor response to treatment, a laboratory evaluation should be done. Tests include measurement of levels of BUN, creatinine, fasting blood glucose, ferritin, magnesium, thyroid-stimulating hormone (TSH), vitamin B-12, and folate; Venereal Disease Research Laboratory (VDRL) test; glucose tolerance test; and CBC count.

- Needle electromyography and nerve conduction studies should be considered if polyneuropathy is suspected on clinical grounds, even if results of neurologic examination are apparently normal.

- Polysomnography may be necessary to quantify PLMS or to characterize sleep architecture, especially in patients who continue to have significant sleep disturbances despite relief of RLS symptoms with treatment

Medical Care:

- Nonpharmacologic management

    - Patients with mild RLS who are sensitive to caffeine, alcohol, or nicotine should avoid these substances. Offending medications

also should be discontinued. Mild exercise is helpful in some patients. In general, physical measures are only partially or temporarily helpful. Behavioral treatments with circadian adjustments permit later sleep times.

- Some patients benefit from different physical modalities, such as hot or cold baths, whirlpool baths, limb massage, or vibratory or electrical stimulation of the feet and toes before bedtime.

- Supplementation to correct vitamin deficiencies, electrolytes, or iron may improve symptoms in some patients. In iron deficiency, for example, ferrous sulfate 325 mg may be given with 250 mg of vitamin C. Absorption is increased by taking this on an empty stomach and waiting 60 minutes before eating.

- Patients with prominent varicose veins in the legs may benefit from Ted hose.

- Those with uremia or anemia may find relief after kidney transplantation or correction of anemia, respectively

MEDICATION

Drug Category: *Dopaminergic agents* **see enclosed handout**

Drug Category: *Benzodiazepines* -- These agents may be used as monotherapy in patients with mild or intermittent symptoms or as combination therapy in severe cases. Clonazepam (Klonopin) has been shown to ease sensory symptoms and PLMS in RLS. Other benzodiazepines, such as temazepam (Restoril) and alprazolam (Xanax) also can be effective.

Drug Category: *Opioids* -- Low-potency opioids, such as codeine and propoxyphene (Darvon, Dolene), can benefit patients with mild and intermittent symptoms; higher-potency agents, such as oxycodone hydrochloride (Roxicodone), methadone hydrochloride (Dolophine), and levorphanol tartrate (Levo-Dromoran), may have a role in refractory cases. Because of the risk of addiction, these drugs should be used with caution; their use usually is recommended only in refractory cases.

Drug Category: *Anticonvulsants* -- These agents are used to manage severe muscle spasms. Gabapentin (Neurontin) Tegretol

Drug Category: *Presynaptic alpha2-adrenergic agonists* -- These agents stimulate alpha2-adrenoreceptors in brain stem, activating an inhibitory neuron, which in turn results in reduced sympathetic outflow. Clonidine hydrochloride (Catapres)

DRUG	PRAMIPEXOLE (Mirapex)	ROPINIROLE (Requip)	CARBIDOPA-LEVODOPA CR (Sinemet CR)
Pharmacology	Nonergot dopamine agonist	Nonergot dopamine agonist	Carbidopa-inhibits decarboxylation of peripheral dopamine levodopa-converted to dopamine in brain to dopamine in brain
Pharmaco-kinectics	Tmax: 2hrs ↑ 1hr by food 1/2 life: 8-12 hrs 15% protein bound	Tmax: 1-2hrs; ↑ 2.5 hrs by food 1/2 life: 6hrs 40% protein bound	Tmax: 2 1/2 hrs; ↑ by 30 min by food ↓ absorption with high protein 1/2 life: 4-6 hrs
Renal Impairment	If c.c. <20ml/min ↓ dose by 75%	N.S.	titrate with caution
Hepatic Impairment	N.S.	titrate with caution	titrate with caution
Drug Interations	Cimetidine--↓ P AUC by 50% and 1/2 life by 40% druge eliminated via renal secretion (i.e. rantidine, cimetidine, diltiazem, triamterene, verapamil, quinidine, quinines -- ↓ P by 20%	estrogen --↓ R by 36% cipro -- ↓ R AUC by 84% Cmax by 60% inhibitors of CYPIA2 (ie cimetidine, cipro, dilliazem, enoxacin erthyromycin, fluvoxamine, mexiletine -- ↓ R	↓ L by: antacids MAO inhibitors ↓ L by: anticholnergics benzodiazepines hydantoins ie dilantin papaverine pyridoxine TCA
Contraindications	N/A	N/A	Nonselective MAOI; ie parnate, nardil, history of melanoma, narrow angle glaucoma
Pregnancy Category	C	C	C
Adverse Effects (In early parkinsons vs placebo > 2%)	13% sedation 10% nausea 8% constipation 6% hallucinosis 3% vision abnormality	38% nausea 34% sedation 18% dizziness 11% syncope 8% viral infection 7% fetigue 6% edema 5% dyspepsia vomiting asthenia 4% hallucinosis confusion 3% abdominal pain, anorexia, yawning, dyspnea, abnormal vision, peripheral ischemia	16% dyskinesis 5% nausea 4% hallucinosis confusion 3% dizziness
Laboratory Interactions	N/A	N/A	↓ LFT's, BUN bilirubin + Coombs test false + rxn. for urinary ketones
Dosage and Adminstration	onset: 0.125mg max: 8.0mg	onset: 0.25mg max: 4.0 mg by week 7	onset: 25/100 CR max:800m levodops daytime rebound can occur

Continued from page 1

ARTICLE IN BRIEF:

✔ Two separate research groups have identified three genes that account for 70 percent of all cases of restless legs syndrome.

Two developments made the current studies possible. First were advances in "gene chips," silicon-based DNA arrays, allowing more than half a million unique DNA sequences to be analyzed at once from a single human sample.

Second was the publication of the "HapMap," the catalog of single nucleotide polymorphisms (SNPs) that detail much of the variation in gene sequence among humans. Whole-genome association studies link these two developments by analyzing the SNPs of patients and controls — and finding those SNPs that correlate with the presence or absence of the disease.

"This method allows us to perform an experiment without any hypothesis *a priori*," Dr. Winkelmann said. "This led to the identification of three genes we never thought were involved in RLS. It gives us a new picture."

Dr. Kári Stefánsson said the findings should dispel any doubts that RLS is a bona fide medical condition with a genetic profile.

Profiling the Genes

Dr. Winkelmann's group studied over 1,500 diagnosed RLS patients and almost 3,000 controls. They found the strongest association to a SNP located within the gene *MEIS1*, which is active in limb development and part of a gene network involved in spinal neuron identity pathways makes sense, since sensory symptoms define RLS, and involve the lower limbs. However, she cautioned, it is premature to say that the stage is set for RLS during development. "We don't know what these genes do in the adult."

The third gene, *BTBD9*, has no known function as yet in humans, although in the fly it is active in embryonic development, metamorphosis, and pattern formation in the limbs.

Dr. Winkelmann's data suggest that possessing a single risk allele for MEIS1 increases the risk of developing RLS by 50 percent compared to the alternative allele. Possessing two risk alleles increases the likelihood of RLS even further. The same is true for *BTBD9*, while two copies of the risk allele of the *MAP2K5/LBXCOR1* segment appear necessary to increase the risk for RLS.

Each of the three genes act independently to increase risk. Homozygosity for all three increases the risk by a factor of 20, Dr. Winkelmann said. The "attributive risk" — the proportion of RLS cases that can be explained by these risk alleles — is 70 percent for the combination of the three genes. "The data are very convincing," she said. "Nonetheless, it's very likely there will be other genes discovered that also contribute."

Limb Movements and RLS

The second study, led by David B. Rye, MD, Andrew Hicks, PhD, and Kari Stefansson, MD, PhD, also found the *BTBD9* gene, but linked it specifically to periodic leg movements of sleep (*N Engl J Med* 2007;357:639-647). PLMS is a clinically distinct entity from RLS, which is formally defined based on sensory criteria alone. However, according to Dr. Rye, the field is moving toward recognizing the two as complementary aspects of a single syndrome.

"If you imagine a Venn diagram of the two, periodic limb movements in sleep take up about 90 percent of the RLS circle, and vice versa. RLS is essentially the sensory component of the syndrome, and PLMS is the motor component," said Dr. Rye, professor of neurology at Emory University and director of the Emory Healthcare Program in Sleep Medicine. "This is becoming more and more accepted by RLS specialists."

He noted that patients with PLMS often go on to develop RLS symptoms, and within an RLS family, "asymptomatic" members often have PLMS. In Dr. Rye's study, subjects were not diagnosed in person, but instead with a questionnaire

The next challenge is models that can be used to p basis of the disease.

and PLMS than in those without either condition. Furthermore, the risk allele was specifically linked to PLMS: compared to controls, it was significantly more common in those with PLMS only, but was no more common among those with RLS only. Those with two copies of the risk allele had almost twice as many limb movements per hour of sleep as did those with no copies of the allele.

Dr. Mark W. Mahowald said that the studies should put to rest any arguments that RLS is the result of clever pharmaceutical advertisers.

Iron metabolism is known to be disrupted in RLS. Each copy of the risk allele increased the ferritin index (an inverse measure of body iron stores) in study participants by 5.5 percent, and decreased serum ferritin by 13 percent.

Dr. Rye said he was not surprised that neither the *BTBD9* gene nor the others from the Winkelmann study were specifically involved in known pathways for iron or for dopamine, which is also altered in RLS.

"One of the big themes from the genome-wide association studies is that many identified genes are turning out to be genes that modify other genes," acting upstream from the clinical or biochemical manifestations of the disease, he said. Such genes may be modifying expression levels of intermediary genes, which may themselves impinge on other intermediaries.

Neither was he surprised by the strong effect of a few genes. "I've been staunchly maintaining this for a long time, that it wouldn't surprise me if there were one or two genes responsible." His collaborators, at deCODE Ge-

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son, MD, president and chief executive officer of deCODE Genetics in Iceland, told *Neurology Today* in a telephone interview. The findings should dispel any doubts that RLS is a bona fide medical condition with a genetic profile, he said.

WHAT LIES AHEAD

The next challenge, both Drs. Winkelmann and Rye agreed, is to create animal models that can be used to probe the biologic basis of the disease. "One of the challenging questions we have to address is how these genes lead to involvement of the dopamine and iron systems," Dr. Winkelmann said. "In the long run, this information give us ideas about development of further treatment."

The discovery does not change the therapeutic picture for the moment, which in recent years has been transformed by the introduction of dopamine agonists. But Dr. Rye said the discovery has had an effect on patients, who have felt the backlash of skeptics questioning whether drug companies and the media have engaged in "disease mongering" by exaggerating the prevalence of RLS.

Neurology Professor Mark W. Mahowald, MD, medical director of the Minnesota Regional Sleep Disorders Center at the University of Minnesota Medical School in Minneapolis, noted that there are several medications on the market that seem effective in treating RLS. "Dopaminergic drugs that are widely used to treat Parkinson disease are extraordinarily effective, although we do not yet know why," he said. Dr. Mahowald was not involved in the current study.

John W. Winkelman, MD, PhD, medical director of the Sleep Health Center of Brigham and Women's Hospital in Boston, said the discoveries provide new avenues for research. Dr. Winkelman, who is not related to Dr. Juliane Winkelmann and was not involved in the study, added: "We can look at these genes, and try to determine the gene product, and

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He noted that patients with PLMS often go on to develop RLS symptoms, and within an RLS family, "asymptomatic" members often have PLMS. In Dr. Rye's study, subjects were not diagnosed in person, but instead with a questionnaire that has been used as an effective RLS screening tool. The sensitivity and specificity of the questionnaire was approximately 75 percent, Dr. Rye said. The group performed whole-genome analysis on over 400 subjects meeting the screening criteria for RLS, and over 500 first-degree relatives. Subjects also wore an ankle accelerometer to detect periodic

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Neither was he surprised by the strong effect of a few genes. "I've been staunchly maintaining this for a long time, that it wouldn't surprise me if there were one or two genes responsible." His collaborators, at deCODE Genetics in Iceland, on the other hand, "were a little floored by the results," since attributable risks discovered to date in other disorders have been less than half this size. "They saw this and they couldn't believe it."

"We now have concrete evidence that RLS is an authentic disorder with recognizable features and underlying biologi-

doubts that RLS is a bona fide medical condition with a genetic profile, he said.

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References:

- Winkelmann J, Meitinger T, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. *Nature Genet* 2007;39:1000-1006.
- Stefansson H, DB Rye DB, Stefansson K, et al. A genetic risk factor for periodic limb movements in sleep. *N Engl J Med* 2007;357:639-647.
- Woloshin S, Schwartz LM. Giving legs to restless legs: A case study of