RESTLESS LEGS SYNDROME
Donna Windish, MD, MPH
Week 9

Educational Objectives:

1. Recognize the five clinical criteria needed to diagnose restless legs syndrome (RLS)
2. Describe the epidemiology and causes of RLS
3. Understand the treatment options for RLS and their limitations

CASE ONE:

Ms. Genou is a 41-year-old woman who comes to the office with complaints of leg problems. She notes during her pregnancy three years ago that she had an uncomfortable sensation in her legs while trying to fall asleep at night. She describes the sensation as if something were creeping or crawling inside of her which made her have a sudden urge to move her legs. At times, she needed to rub her legs or get out of bed and walk around which would usually resolve the symptoms. However, once she returned to bed, the symptoms would occur again. She did not seek treatment at the time and her symptoms completely resolved until she started having similar symptoms six months ago. She comes in today feeling tired because of recurrent symptoms in her legs at night. She tells you that her mother said she has problems with “jumpy legs” at night and is worried that something is wrong and would like a prescription to help her go to sleep restfully.

Questions:

1. You think the patient may have restless legs syndrome (RLS). What are the diagnostic criteria for this disorder?

The diagnosis of restless legs syndrome is a clinical one. The original diagnostic criteria for RLS were first proposed by the International Restless Legs Study Group in 2003 and modified in 2012. There are five diagnostic criteria that all must be present to make the diagnosis:

- An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the urge to move is present without the uncomfortable sensations, and sometimes the arms or other body parts are involved in addition to the legs.
- The urge to move or unpleasant sensations that begin or worsen during periods of rest or inactivity such as lying or sitting
- The urge to move or unpleasant sensations that are partially or totally relieved by movement such as walking or stretching; at least as long as the activity continues
• The urge to move or unpleasant sensations that are worse, or only occur, in the evening or night. When symptoms are severe, the worsening at night may not be noticeable, but must have been previously present.
• The symptoms are not solely accounted for by another medical or behavioral condition, such as leg cramps or habitual foot tapping.

Supportive criteria for the diagnosis of RLS include:

• A family history of RLS
• A positive response to dopaminergic drugs
• Periodic limb movements during wakefulness or sleep as assessed with polysomnography or leg activity devices

Up to 80% of patients with RLS experience periodic limb movements of sleep (PLMS). These are brief repetitive movements of the legs (jerking) of which the sleeper is unaware.

2. **Does the patient have any factors that may put her at risk for this syndrome?**
The prevalence of RLS ranges from five to 10% in North American and European adults, with women having a two-fold higher incidence than men. The onset of RLS can be at any age, but most commonly presents in middle age or older patients. This patient is in her early 40s. RLS is the most common movement disorder in pregnancy with 15-30% of women being affected, usually in their third trimester. This patient described symptoms during her recent pregnancy. There is also a strong genetic component associated with RLS, with a range of 18-60% of patients having a family history of the syndrome. This patient’s mother may also have RLS given the description of “jumpy legs” at night.

3. **What is the cause of RLS?**
There are two types of RLS, primary (or idiopathic) and secondary.

The cause of **primary RLS** is not known. However, many studies have suggested that there is a genetic component with an autosomal dominant inheritance pattern. Clinically, patients treated with dopaminergic medications have shown an excellent response in symptoms, suggesting that dopamine deficiency may be a key factor in the disorder. RLS has been associated with a down regulation of dopamine D2 receptors in the putamen, and the degree of loss of the receptors correlates with the severity of the disorder. Dopamine levels are lowest at night and become insufficient to overcome post-synaptic resistance, therefore, symptoms are usually present at bedtime. Although administration of dopaminergic agents can easily overcome the postsynaptic resistance, over time dopaminergic agents can lead to increased receptor desensitization and subsequent lack of dopaminergic treatment efficacy, known as “RLS augmentation.”
In addition, low intercerebral iron stores, particularly in the basal ganglia, may also play a role in the disorder. Iron deficiency affects dopaminergic function by increasing tyrosine hydroxylase, which increases extracellular dopamine. These higher levels of extracellular dopamine will decrease the number and sensitivity of postsynaptic dopamine receptors in the brain.

**Secondary RLS** occurs in several states or disorders including:

- Acquired iron deficiency with up to 30% experiencing RLS symptoms
- Chronic renal failure
- Peripheral neuropathy
- Pregnancy
- The use of several medications including most antidepressants (except bupropion), dopamine antagonists (as seen in antiemetics and neuroleptic agents used to treat psychoses), and possibly antihistamines

CASE ONE CONTINUED:

On further history, you note that the patient does not take any medications or illicit drugs, and does not have any chronic medical conditions. Your physical exam reveals a person who looks well with normal weight, normal vital signs, and normal complete physical exam. Specifically, she has completely normal neurologic, musculoskeletal, and peripheral vascular exams.

### 4. What additional testing might you wish to pursue to help with your diagnosis of this patient?

Although RLS is a clinical diagnosis, laboratory testing to exclude secondary causes of the disorder should be considered. These include iron studies with a ferritin level, complete blood count to look for anemia ($45), and assessment of renal function. Even if iron deficiency is diagnosed with low serum ferritin levels ($45), the diagnosis of RLS is supported, but this is not sufficient for the diagnosis (Cost information accessed from healthcarebluebook.com).

Polysomnography ($935) in a sleep laboratory is not necessary to make the diagnosis but may be helpful to exclude other causes of poor sleep such as obstructive sleep apnea or in cases when RLS is resistant to treatment.
5. **What other conditions should you consider in your differential diagnosis for RLS?**

   In your consideration of RLS, you should attempt to rule out other conditions associated with leg disorders, including:
   
   - **Peripheral neuropathy**—this pain is usually neuropathic and associated with sensory paresthesias; pain can be worsened when the area is touched, but not necessarily changed by movement.
   - **Lumbosacral radiculopathy**—this is often asymmetric neuropathic pain associated with low back pain and can be made worse with movement.
   - **Nocturnal leg cramps**—this pain is described as sudden muscle tightness relieved by aggressive muscle stretching or massage and not by simple leg movements.
   - **Akathisia**—this is an inability to sit still with a feeling of motor restlessness; these symptoms are more constant and do not localize to the legs and are often a side effect of phenothiazine antipsychotic drugs and SSRI antidepressants. In contrast to akathisia, RLS has a more circadian rhythm which is worse at night when sitting or laying in bed.

6. **What treatment options are available for restless legs syndrome?**

   **Nonpharmacologic therapy:** If symptoms are mild or intermittent, one can try behavioral therapy [moderate regular exercise, mental stimuli (such as games or puzzles) at times of rest], sleep hygiene, leg massage, and lifestyle modifications (including avoiding caffeine and alcohol intake, heavy meals). Regular exercise and leg massage may have the most evidence to support their use.

   **Iron replacement:** If iron deficiency is found to be a factor, use iron supplementation to achieve a goal ferritin level >50 ng/mL (>50 mcg/L) and iron saturation >20 percent.

   **Dopamine agonists:** These agents are associated with moderate improvements in symptom severity, self-reported sleep quality, and disease-specific quality of life. Non-ergotamine agonists (pramipexole, ropinirole, and rotigotine patch) are the preferred agents over levodopa given their long half-lives. They should be administered two hours before onset of symptoms (i.e., sleep). Side effects include mild transient nausea, lightheadedness, and fatigue, which typically all resolve within 10-14 days. Other side effects such as nasal stuffiness, constipation, insomnia, and leg edema can occur and are reversible with medication cessation. Rarely, these medications can be associated with impulse control disorders such as gambling and inappropriate hypersexuality. Thus, in patients with known psychotic disorders, dopamine agonist therapy should be avoided if possible.

   All of these agents can be associated with **RLS augmentation**. Augmentation means the onset of symptoms occurs earlier in the day, has increased severity and spreads to other parts of the body such as the arms, trunk, or face. Augmentation symptoms are more common with the use of levodopa (up to 80% of users) and in chronic use of any of the dopamine agonist medications. Dose increases can help overcome augmentation; however, the recommendation is to keep doses low because continued increase in the...
medications will continue to worsen symptoms. In this case, stopping the medication completely and using alternative therapy will need to occur.

**Gabapentin and Pregabalin:** Both may be effective in improving RLS symptoms and sleep, especially in those patients with neuropathic pain symptoms.

**Opioids:** For intermittent RLS, low to intermediate potency opioids, such as codeine, may be helpful. When RLS is refractory to other medications, oxycodone, hydrocodone, and methadone can be used.

**Benzodiazepines:** Clonazepam is the only reported drug in this class to improve RLS symptoms. Other medications in this class have not been shown to work on RLS symptoms specifically, but can induce sleep.

### 7. What is periodic limb movement disorder, and how is it different from RLS?

Periodic limb movement disorder (PLMD) has the following diagnostic criteria:

- Clinical evidence of disturbed sleep or daytime fatigue (can use Epworth Sleepiness Scale)
- Polysomnography demonstrates repetitive movements that are 0.5 to 10 seconds in duration, typically separated by an interval of 20 to 40 seconds (range 5 to 90 seconds)
- On polysomnography, there are more than 15 periodic limb movements per hour of sleep time in adults and more than five per hour of sleep in children
- The periodic limb movements are not better explained by another disorder

PLMD must be differentiated from a related condition, known as periodic limb movements in sleep (PLMS), which is not associated with the presence of clinical sleep disturbance or daytime fatigue. RLS can be associated with PLMS, BUT it is important to note that RLS with PLMS is not PLMD. Given this definition and restrictions, PLMD is a rare disorder.
Primary References:


Donna Windish completed her residency at the University of Rochester, Strong Memorial Hospital, and general internal medicine fellowship at Johns Hopkins University School of Medicine. Her scholarly interests include medical education, the important use and interpretation of biostatistics in reading and interpreting the medical literature, and quality improvement.
CME Questions:

1. **Which of the following is a diagnostic feature of RLS?**
   a. The urge to move or unpleasant sensations that are not relieved by movement such as walking or stretching
   b. The urge to move or unpleasant sensations that begin or worsen during periods of rest or inactivity such as lying or sitting
   c. The urge to move or unpleasant sensations that are worse in the morning or afternoon than during the evening or night

2. **What is RLS augmentation?**
   a. The use of two medications greatly improves the symptoms of RLS
   b. The symptoms have onset earlier in the day, have increased severity, and spread to other parts of the body such as the arms, trunk, or face
   c. Using nonpharmacologic and pharmacologic therapy improves RLS symptoms

3. **Which therapy is considered a first line treatment for primary RLS that is mild or intermittent?**
   a. Leg massage
   b. Increased caffeine intake
   c. Alcohol
   d. Oxycodone

Answers:

1. **b**  *RLS symptoms usually improve with movement and are worse in the evening hours not during the day.*
2. **b**  *Augmentation means the symptoms have onset earlier in the day, have increased severity and spread to other parts of the body such as the arms, trunk or face.*
3. **a**  *Leg message can be helpful for mild or intermittent RLS. Caffeine and alcohol use can make RLS symptoms worse. Oxycodone should be used for refractory or severe RLS and not for minimal symptoms.*