

## Restless Leg Syndrome Fighting the Urge

A disorder of the central nervous system, restless leg syndrome (RLS) is characterized by the irresistible urge to move the legs. This urge usually occurs during sleep or periods of inactivity and is frequently accompanied, or caused by, uncomfortable and unpleasant sensations that are partially or completely relieved by movement. Some of the words patients with RLS use to describe the feeling include “creepy-crawly,” “burning,” “tingling,” “twitching,” and “painful.”

The symptoms of the condition tend to occur at exactly the wrong time—when people are trying to relax or sleep. As quality and quantity of sleep become an issue, daytime fatigue and exhaustion follow, affecting work and mental performance (National Institutes of Health 2005).

Although the cause of RLS is unknown, researchers believe that it results from abnormal functioning of the central nervous system. RLS produces excitability in a region of the brain known as the subcortical area. This excitability is caused by a dysfunction in a nerve-signaling chemical called dopamine (Allen RP et al 2001b; Odin P et al 2002). Dopamine is a central neurotransmitter that is particularly important in the regulation of movement.

The exact prevalence of RLS is undetermined. It may be more common than is currently thought because people may not report it to their physicians, and some physicians may wrongly attribute the symptoms to nervousness, insomnia, stress, arthritis, muscle cramps, or aging (National Institutes of Health 2005). RLS is associated with diabetes and smoking. Studies show that it affects between 1 percent and 5 percent of younger adults and up to 20 percent of adults older than 60 years (Kasper DL et al 2005). There is also a clear familial connection; about one third of patients with RLS have multiple family members who are also affected by the condition (Kasper DL et al 2005). The prevalence of RLS closely correlates to race. It is rare among Asians (0.1 percent to 5 percent) (Chaudhuri KR 2003) and most common among people of northern European descent.

Up to 90 percent of patients with RLS experience a more common condition known as periodic limb movement disorder (PLMD), which is especially common in patients who are undergoing dialysis (Rijsman RM et al 2004). PLMD is characterized by involuntary leg twitching or jerking movements during sleep that typically occur every 10 to 60 seconds, sometimes throughout the night. The symptoms cause repeated awakening and severely disrupted sleep. Unlike RLS, the movements caused by PLMD are involuntary. Although many patients with RLS also develop PLMD, most people with PLMD do not experience RLS (National Institutes of Health 2005).

Although the exact cause of RLS is unknown, a number of conditions are associated with it including:

- Iron deficiency
- Low dopamine levels
- Lesions within the spinal cord or peripheral nerves
- Pregnancy-related deficiencies in iron, folate, and magnesium (Lee KA et al 2001; Manconi M et al 2004)
- Kidney disease, particularly end-stage kidney disease
- Medications, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, lithium, and caffeine (National Heart, Lung, and Blood Institute 2000)

RLS is classified into primary and secondary forms. Primary RLS occurs in the absence of other conditions. It tends to onset earlier and is associated with a single genetic defect (Desautels A et al 2001). Secondary RLS is linked to iron deficiency and other conditions such as pregnancy, anemia, kidney disease, and brain dysfunction (Bonati MT et al 2003; Rye DB 2004; Stiasny-Kolster K et al 2004). RLS is also associated with hyperalgesia (increased pain sensation), which is most likely connected to dopamine activity.

### IRON AND DOPAMINE ABNORMALITIES

The brains of patients with RLS exhibit abnormalities in the relationship between iron and dopamine. An enzyme involved in dopamine synthesis—tyrosine hydroxylase—requires iron for proper function. In animal studies, iron insufficiency appears to cause abnormal dopamine function (Allen RP et al 2001a). It is believed that patients with RLS may have impaired iron absorption in the brain (Connor JR et al 2003). The iron deficiencies are pronounced in certain parts of the brain that help control body movement. In autopsies of people with RLS, iron levels have been particularly low in a region of the brain called the substantia nigra (Connor JR et al 2003).

Further evidence of the relationship between iron deficiency and RLS is found in the three major secondary causes of RLS—end-stage renal disease, pregnancy, and iron deficiency, which all involve low levels of iron (Allen RP et al 2001b).

## DIAGNOSIS AND CONVENTIONAL TREATMENT

The diagnosis of RLS begins by excluding other conditions, such as anemia, diabetes, kidney disease, and iron deficiency. Electromyography and nerve conduction studies are sometimes recommended to measure electrical activity in muscles and nerves; Doppler ultrasonography can be used to evaluate muscle activity in the legs.

Such tests can document any damage or disease in nerves and nerve roots (such as peripheral neuropathy and radiculopathy) or other leg-related movement disorders.

In some cases, sleep studies such as polysomnography (a test that records the patient's brain waves, heartbeat, and breathing for an entire night) are undertaken to identify the presence of PLMD (National Institutes of Health 2005). Actigraphy, a sleep test in which a wristwatch-like device is applied to the wrist or ankles to record and measure muscle movements during sleep, may also be recommended.

Once RLS is diagnosed, it can be treated with medications (Rye DB 2004 Dec). Some of the more common conventional medications used to treat RLS include:

- **Levodopa**—Levodopa (L-dopa) is a form of dihydroxyphenylalanine, the immediate precursor to dopamine. However, unlike dopamine, it can be taken orally and cross the blood-brain barrier. Once inside brain cells, the medication converts to dopamine. L-dopa is usually given with other medications that inhibit its effect outside of the central nervous system (Odin P et al 2002). The disadvantages of L-dopa are its short-term effects (1 to 2 hours) and a side effect known as augmentation, whereby RLS symptoms appear earlier in the day and with increasing severity (Odin P et al 2002). L-dopa can also cause nausea.
- **Dopamine agonists**—Alternatives to L-dopa including dopamine agonists such as cabergoline, ropinirole, and pramipexole. In general, dopamine agonists have milder augmentation symptoms compared to L-dopa and are considered the treatment of choice (Kasper DL et al 2005). They have had success in relieving symptoms in more than 70 percent of patients (National Institutes of Health 2005). L-dopa and dopamine agonists can significantly reduce the number of limb movements per hour and improve the subjective quality of sleep.
- **Sleep agents**—Minor tranquilizers such as benzodiazepines (Kasper DL et al 2005).
- **Anticonvulsant medications**—Medications that slow convulsions (Kasper DL et al 2005).

Some medications that induce or worsen RLS include atypical neuroleptic drugs, caffeine, classical neuroleptic drugs (such as D2 receptor antagonists), H2-blocking agents, lithium, metoclopramide, and mianserin (Odin P et al 2002).

## NUTRIENTS TO HELP RESIST THE URGE

Because RLS has been associated with specific nutrient deficiencies, researchers have studied the effects of supplementation in patients who have RLS. The results have been promising.

### **Iron**

A deficiency in iron can trigger RLS. Not only can iron levels be low in people with RLS, but iron storage in the body appears to be abnormal due to a low level of a protein called ferritin and a high level of the transporter protein transferrin. Transferrin transports iron in cerebrospinal fluid and in plasma. Fewer symptoms of RLS are apparent in people with ferritin levels greater than 50 micrograms per liter (mcg/L) (Sun ER et al 1998). A ferritin deficiency can arise from low iron intake, inadequate absorption, or excessive blood loss.

Symptoms of RLS can improve or be resolved completely through oral or intravenous iron supplementation. Studies showed relief from symptoms of RLS after supplementation with 200 milligrams (mg) of intravenous iron administered over a few days (Allen RP et al 2001a,b; Nordlander NB 1953; O'Keefe ST et al 1994).

The absorption of iron from food and supplements can vary based on the form of iron used. Intestinal uptake can vary based on biological need. Heme (deep red, ferrous component of hemoglobin) sources of iron, such as red meat, are utilized the most effectively by the body. Other chelated forms of iron, such as iron protein succinylate or iron bis-glycinate are also excellent. These forms of iron can reverse anemia more quickly and with less constipation than the typical iron salts most doctors prescribe (Hertrampf E et al 2004).

Other nutrients can enhance the activity of iron in the body. Adequate vitamin A is essential, as it helps to mobilize iron from

storage sites. Adding zinc to iron supplements may increase hemoglobin levels more than taking iron supplements alone. In the same way, taking 250 to 500 mg of vitamin C can raise the absorption of iron, although it may also increase its side effects. Iron absorption will increase if it is ingested on an empty stomach (Allen RP et al 2001a).

### ***Folic acid***

Folic acid is the synthetic form of folate, the water-soluble B vitamin that helps produce and maintain new cells in part through the creation of DNA and RNA. Folate can even protect cells from changes to DNA (Mattson MP et al 2003). Also, folate is needed to make red blood cells and prevent anemia (National Kidney and Urologic Diseases Information Clearinghouse 2005).

RLS is related to folate deficiency, particularly in the form of RLS that is associated with familial inheritance and with pregnancy. Patients with this type of RLS have benefited from intake of between 5 and 10 mg of folic acid per day, or from taking folinic acid (Botez MI 1976; Botez MI et al 1977). People taking folic acid should ensure that they receive at least 500 to 1000 mcg of vitamin B12 each day to make sure the folic acid isn't masking a vitamin B12 deficiency.

Some people do not have the enzyme 5-methyltetrahydrofolate reductase, which converts folate into its bioactive form. These individuals often present with high levels of homocysteine and associated health concerns such as heart disease and depression; folinic acid (5-formyltetrahydrofolate) is the only option. It is a metabolically active form of folate, capable of boosting levels of the coenzyme forms of the vitamin in circumstances where folic acid has little to no effect (Kelly GS 1998).

### ***Magnesium***

Magnesium has also been shown to partly relieve RLS. Particularly for people with nighttime RLS, 250 mg of magnesium citrate taken before bed may decrease symptoms and aid sleep. Therapeutic dosages range from 250 to 800 mg of elemental magnesium a day (Rijsman RM et al 1999).

## **LIFE EXTENSION FOUNDATION RECOMMENDATIONS**

Eating a well-balanced diet and getting adequate amounts of iron, folate, magnesium, and vitamin E may help avert or reduce symptoms of RLS. It is also recommended that patients not smoke (Mountifield JA 1985) and reduce their intake of (or avoid entirely) caffeine, sugar, and alcohol (Lutz EG 1978).

To help monitor healthy blood levels of nutrients, patients with RLS might consider having the following blood tests:

- Complete blood cell (CBC) count and chemistry panel
- Serum ferritin
- Red blood cell (RBC) count
- Magnesium
- Vitamin B12

The Life Extension Foundation suggests the following nutrients may be helpful in managing RLS:

- **Folic acid**—400 to 800 mcg daily. Take with 500 to 1000 mcg of vitamin B12 daily in the form of methylcobalamin.
- **Magnesium citrate**—100 to 250 mg before bed, depending on the severity of the symptoms.
- **Iron**—Dosing is based on individual needs. Better forms are iron protein succinylate or iron bis-glycinate. Take with 250 to 500 mg of vitamin C to help the body absorb the iron.

## **RESTLESS LEG SAFETY CAVEATS**

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### **Folic acid**

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

## Iron

- Do not take iron if you have hemochromatosis or hemosiderosis.
- Consult your doctor before taking iron supplements if you have an elevated serum ferritin level, alcoholic cirrhosis, a pancreatic insufficiency, or a history of chronic liver failure, chronic alcoholism, gastritis, peptic ulcer disease, or gastrointestinal bleeding.

## Magnesium

- Do not take magnesium if you have kidney failure or myasthenia gravis.

## Vitamin B12 (cyanocobalamin)

- Do not take cyanocobalamin if you have Leber's optic atrophy.

For more information see the Safety Appendix

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