TAKING A STAND

Decried by critics as an example of "medicalizing" a minor problem, RLS has faced scrutiny tougher than most neurological disorders. Here's a look at how, when and most importantly, why you should treat it.

By Zac Haughn, Associate Editor

Before their ads hit the airways and splashed into the printing press ink, most American's familiarity with restless leg syndrome likely came from *Seinfeld*. In one episode, Kramer complains about a new partner's restless legs and tells Elaine, "She's throwing off my sleep. She's got the jimmy legs." And with that—and an emphatic judder of his leg for Elaine's demonstration—"jimmy legs," also known as RLS, were effectively introduced on a mass level. A wild-eyed, leg-shaking Kramer was probably not the best spokesmen to make such an introduction, but it might have been telling given the criticism, and often ridicule, that is dished out against it.

RLS often finds itself on the short end of the stick with a significant amount of mainstream press dedicated to examining how serious its pain is, and it has been derided as a media or big pharma-induced sickness. This is a notion that's rejected by some neurologists as harshly as those in the mainstream who reject RLS as an illness. "I recall one 80-year-old grandmother who came to my clinic surrounded by her four grown daughters [and] said she would 'kill herself' if one more doctor couldn't help her," remembers Nancy S. Collins MD, Associate Professor of Neurology and Director of Neurology Curriculum at the Rosalind Franklin University of Medicine and Science/The Chicago Medical School. "She was crying and begged for help. Her daughters were desperate and angry that their mother was so miserable [so] I started her on low dose pramipexole. Next visit, the patient and all the daughters hugged me."

This disposition is shared throughout much of the neurological field. RLS "is hardly an example of 'medicalizing' minor problems. It is not a 'minor' condition, and it severely compromises quality of life," says Mark W. Mahowald, MD and Director of the Minnesota Regional Sleep Disorders Center and Chief of the Dept. of Neurology, Hennepin County Medical Center.

The stigma around RLS may be a result of where the focus is placed. "RLS is loaded with subjective complaints that don't attract the same level of attention as other disorders with obvious physical limitations. The media would become more understanding if they were to interview patients with severe RLS," says Antonio Culebras, MD and Professor of Neurology at SUNY Upstate Medical University.

Or at least patients with clinically significant RLS. "The critical issue is to define clinically significant. RLS researchers have defined the threshold as having RLS symptoms at least

AGAINST RLS

two days of the week," Dr. Culebras says. Clinically significant RLS decreases the quality of life as severely as other chronic conditions such as type 2 diabetes, arthritis and depression. This can cause daytime fatigue and sleepiness and contribute to depression.

To quantify the total and unique burden of RLS on patient-reported health-related quality of life, the Stanford Center of Excellence for Sleep Disorders sought to estimate the disease burden by comparing Short-Form (SF-36) scores between individuals with RLS and numerous patient and general populations in the US. In the May issue of *Quality of Life Research* they reported all SF-36 measures were considerably below adjusted US general population norms. Five of the eight scales—physical functioning, role physical, bodily pain, general health, vitality—were below US norms by 0.8 or more standard deviations (SD), and the remaining three—social functioning, role emotional, mental health—were 0.5 SD below norm. They concluded, "After controlling for the impact of age, gender, and disease comorbidity, RLS was associated with unique burden on both physical and mental aspects of HRQoL."

Of course, this study and others will likely do little to relieve RLS from comedic circles or educate the public on how debilitating the disease can be, but hopefully, among many other forces, it can push any physicians on the fence to address RLS. Failing that, neurologists might heed the name change advice of a letter to the editor to *The New York Times*: "Perhaps substituting "nocturnal neuromuscular spasmodic agitation" would help to emphasize that this affliction is a chronic, debilitating sleep disorder and that like Parkinson's disease it has no relation to activity level."

Making the Right Call

The pathophysiology of RLS remains complex and is yet to be fully expounded. It is largely a disorder of the central rather than peripheral nervous system, and dopaminergic dysfunction in subcortical systems seems to play a significant part. Determining the right diagnosis is especially important before starting a patient on a prescription, because "many patients do not require medication, and symptoms often can be relieved with good sleep hygiene and avoidance of medications and factors that provoke symptoms," says Dr. WA Hening, of the Robert Wood Johnson Medical School in the January 2007 issue of *The American Journal of Medicine*. "Recent large-scale clinical trials have proved the efficacy of therapy for RLS when it is required."

Underdiagnosis remains an issue in RLS, which "affects up to 10 percent of the adult population, increasing with increasing age," according to Dr. Mahowald. "It is underdiagnosed because most physicians were never taught about it, and if you haven't heard of it, there is no way one could 'figure it out.'" RLS might also be underdiagnosed due to a poorly functioning physician-patient relationship. "It is definitely underdiagnosed because of poor recognition of symptoms by patients and lack of key questions by physicians," says Dr. Culebras. Severe RLS, with disabling consequences has a prevalence of two to four percent, adds Emmanuel Mignot, MD, PhD, a Howard Hughes Medical Institute investigator as well as Professor of Psychiatry and Behavioral Sciences at the Stanford University Center For Narcolepsy.

RLS is diagnosed clinically by the four criteria by the

International Restless Legs Syndrome Study Group. The criteria states a person is to have RLS if:

1. Desire to move the extremities usually associated with discomfort or disagreeable sensations in the extremities.

2. Motor Restlessness-patients move to relieve the discomfort, for example walking, or to provide a counter-stimulus to relieve the discomfort, for example, rubbing the legs.

3. Symptoms are worse at rest with at least temporary relief by activity.

4. Symptoms are worse later in the day or at night.

But diagnosing may not always go as smoothly as it should. Patients may not be articulate in describing their symptoms, or may focus on daytime fatigue as their problem, triggering an investigation by unsuspecting clinicians of thyroid disease, anemia, and other related ailments, says Dr. Culebras. "Key questions such as 'do you have discomfort in your legs in the evening?' or ''do your legs keep you from sleeping?' may trigger a line of responses that lead to the diagnosis," he says. It may also be helpful to ask the patient's partner if the patient kicks during sleep.

The differential diagnosis is generally with other conditions that are associated with daytime fatigue and sleep-related disorders. "I suspect that a substantial number of patients with RLS have been diagnosed as having fibromyalgia or depression," says Dr. Culebras. When the differential diagnosis focuses on leg discomfort in the evening, conditions that should be considered are peripheral neuropathies and leg cramps, both of which can be easily differentiated from RLS. Akathisia or constant shifting of the legs occurs in those treated with antipsychotic medication and some Parkinson's disease patients, adds Dr. Culebras.

Treatment

Before sending a patient to the pharmacist, consider the non-pharmacological options. First, during the clinical interview, check for anything that would cause decreased iron stores, including frequent blood donation. If serum ferritin levels are found to be <45ng/dl, you may want to treat the iron deficiency with oral supplements of 325mg of ferrous sulfate three times daily and 100-200mg vitamin C to enhance absorption. Serum ferritin levels should be followed at three- to six-month intervals until iron therapy is discontinued.

It's also important to evaluate the patient's current medication regimen for anything that may cause or worsen symptoms of RLS. Be sure to find out the patient's recent history of coffee, alcohol and nicotine use; all have been linked to RLS symptoms. "It is the role of the doctor and the patient to decide what is the best course of action and this may involve doing nothing, or trying but with the intent of stopping if it is not giving a good cost-benefit ratio. We have exactly the same problem with insomnia," says Dr. Mignot.

When pharmacotherapy is necessary, there are several issues physicians should mind. Patients will likely need a regimen for the rest of their lives and treating the comorbid conditions may alter the treatments you prescribe for RLS. To keep control over any adverse affects and monitor efficacy, it may be best to initiate the drugs at the lowest possible dosage and gradually titrate them upwards. Off-label drugs are often given at lower doses for RLS than their indicated use. However, intractable cases may need more than one drug, and an effective long-term therapy may prove difficult.

Dopamine agonists are the optimal pharmacological treatment when treating RLS. Pramipexole and ropinirole have FDA approval while levodopa has been shown to be effective, but it carries the risk of augmentation. Physicians should caution patients who experience symptom augmentation while taking a dopaminergic medication not to increase the medication dose. Rather, the patient should return to the prescribing physician for follow-up consultation. The treatment of augmentation may involve adjusting the timing or the dose of the medication or switching to another agent.

To determine whether or not augmentation is present, the patient should be asked if there is a relationship between the time of medication intake and symptom intensity. Another key feature of augmentation is the spreading of sensation to previously uninvolved body parts. Those showing signs of augmentation may experience less effect from treatment than the initial response, have symptoms occur at least two hours earlier than what was typical before initiating the therapy, experience less time between the onset of quiescence to symptom onset, and may begin to experience periodic limb movements even while awake.

Patients should also be advised to make lifestyle changes and to be prepared to make sacrifices. "Patients should quit smoking, refrain from caffeine-containing beverages and improve their exercise regimen. If iron is low they should take iron supplements," he says. Opiates and benzodiazepines can also be prescribed. "These medications are often dramatically effective," Dr. Mahowald says of the three drug classes. If the RLS is a serious impediment to restful sleep, Dr. Mahowald says he doesn't recommend the patient be put on a sleep-promoting drug in addition to a medication for the RLS itself. "The conventional medications prescribed for insomnia are not at all effective."

Benzodiazepines may also improve sleep and reduce arousals due to periodic limb movements of sleep, although they would be less effective in eliminating motor and sensory abnormalities. These are used most often for mild or intermittent RLS and may be combined with dopaminergic agents in the management of severe RLS symptoms.

Opioids may also be an option. In clinical studies with small sample sizes, opioid use has been shown to alleviate paresthesias or dysesthesias, motor restlessness and associated sleep disturbances. Due to its adverse effect profile, this class of medication is typically reserved for patients with severe unrelenting symptoms of RLS.

Although origins of the problem may be unclear, noting when the symptoms occur is crucial, as this will allow physicians to differentiate between primary and secondary RLS. The onset of symptoms in primary RLS is more insidious and occurs at an earlier age, typically before the patient reaches age 40. Patients with primary RLS are also more likely to have affected family members than either the general population or even those patients with the secondary forms of the condition.

Of the two types, RLS is normally primary—often familial, according to Dr. Mahowald, and is idiopathic. A 2001 study by a French-Canadian group reported on 25 family members, 14 of whom had RLS. The researchers suggested "an autosomal recessive mode of inheritance in this family, with several candidate locations on chromosome 12," according to the movement disorder advocacy group, WE MOVE. "I suspect that multiple genes predispose strongly to RLS and that those will be discovered soon," says Dr. Mignot.

Secondary forms of RLS are seen in pregnancy, iron deficiency, diabetes, and renal insufficiency. "Iron deficiency in the brain plays a significant role and idiopathic RLS patients may not respond well to dopaminergic therapy if the iron stores, as measured by serum ferritin, are low," Dr. Culebras says. In a study published in the May 21st issue of *Movement Disorders*, researchers concluded, "iron substitution is justified in people with iron deficiency related RLS (ferritin concentration lower than 50mug/L)."

Individuals with secondary RLS from iron deficiency will respond optimally to iron supplementation. That aside, the approach to treatment is correction of the precipitating factor but the pharmacologic approach is similar between the two types. Women who experience RLS before pregnancy may have worsened symptoms if they become pregnant. Once delivery is complete, the severity of RLS symptoms may return to prior degree and those women who began to experience RLS during pregnancy will typically have their symptoms subside after delivery.

However, some clinicians believe that even the distinction between idiopathic and secondary is artificial. "Their argument is that identifiable causes of secondary RLS are in essence precipitating, contributing or aggravating factors of idiopathic RLS," says Dr. Culebras. "Otherwise why would some patients with diabetic peripheral neuropathy or some pregnant women develop RLS and others not?"

RLS is often associated with periodic leg movements that occur during sleep and decrease the quality of nocturnal sleep. Characterized by repeated stereotypic movements of the legs, these movements generally comprise upward extensions of the great toe and foot as well as bending of the ankle, knee, or hip. They have an occurrence of every 15 to 40 seconds and are experienced for half a second up to six seconds, normally during non-REM sleep. There also seems to be a correlation between severity of RLS and how many periodic limb movements.

PLMS triggers arousals that may drive the blood pressure up. "There is credible evidence that patients with RLS and PLMS may develop high blood pressure and are at risk of vascular disease," Dr. Culebras says. Most patients with RLS also have PLMS, but a specialized sleep study is usually necessary for confirmation. Like Dr. Mahowald, Dr. Culebras doesn't generally recommend sleep aides in RLS patients. "Some patients with severe forms of RLS and PLMS require polypharmacy including clonazepam, which aids sleep initiation and maintenance," he says.

Side effects associated with RLS drugs are generally mild. A study in the January issue of *Neurological Sciences* followed patients with primary RLS treated with levodopa, pramipexole, ropinirole, transdermal rotigotine, pergolide and cabergoline. "Adverse events with these drugs are those usual for dopaminergic agents, and are usually mild and reversible, probably because of the relatively low doses needed," the study concluded. However, it added, "Augmentation, *i.e.*, worsening of RLS symptoms not due to progression of the disease […] represents a worrisome side effect of dopaminergic drugs, especially levodopa." Certain medications may worsen RLS. Anti-nausesa drugs, certain antihistamines, antidepressants (both tricyclics and SSRIs) and antipsychotic drugs have been known to exacerbate RLS symptoms.

As with most movement disorders, what effect Botox might have is being debated and studied in the RLS community. Published in the March 13th issue of *Medical Hypotheses*, a study reported the drug has been shown to ameliorate pain syndromes, perhaps reducing peripheral and central sensitization to pain. "We postulate that BTX can be injected subcutaneously to the lower limbs to effect amelioration of the symptoms of RLS," the authors concluded. Drs. Mahowald and Culebras both remain skeptical at best of Botox's place in RLS treatment. "Botox has no place in the treatment of RLS because dopamine agonists are so effective at low doses," Dr. Culebras says. On the heels of such studies that have reported its effectiveness, Dr. Mahowald says, "our center has no experience. It is very expensive, and should only be used when more conventional and less expensive medications have failed." **PN**