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Comprehending and Managing Restless Leg Syndrome

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Abstract

A need to move that arises during rest or is made worse by rest, that happens in the evening or at night, and that goes away or gets better with movement is the hallmark of restless legs syndrome (RLS), a frequent sensorimotor disease. The degree, frequency, and age of the start of symptoms vary greatly; severe types can impair mood, quality of life, and sleep. Periodic leg movements are common in RLS patients while they sleep or are at rest. RLS is seen as a complicated disorder, with comorbidities, environmental variables, and predisposing genetic factors all contributing to the disorder's manifestation. RLS can occur on its own or in conjunction with comorbid conditions, such as renal disease and iron deficiency, as well as cardiovascular illness, diabetes mellitus, neurological, rheumatological, and respiratory conditions. Although the etiology is yet unknown, theories include altered adenosine and glutamatergic pathways, brain iron insufficiency, and failure in the dopaminergic and nociceptive systems. Because doctors don't detect RLS well, it's frequently misdiagnosed and treated. In severe forms, treatment recommendations advise starting medication with low dosages of α2δ ligands or dopamine agonists. Even while dopaminergic therapy is very successful at first, prolonged use of it might cause augmentation, a severe worsening of symptoms. Iron preparations and painkillers are further therapy.

Keywords: RLS (restless leg syndrome), CNS (central nervous system), SSRI's (selective serotonin reuptake inhibitors, TCA's (tricyclic antidepressants), TSH (thyroid-stimulating hormone) ICD (impulse control disorder), BUN (Blood urea nitrogen)

INTRODUCTION

Restless legs syndrome (RLS), also called Willis-Ekbom disease, is a common and chronic condition that causes an uncontrollable urge to move the legs. It is a multifaceted movement disorder affecting the limbs. This is frequently linked to strange, painless feelings that worsen with movement after beginning at rest. There is a daily trend of symptoms getting worse at night. Periodic leg movements during sleep, characterized by involuntary leg jerks, are associated with disrupted sleep patterns. In the United States alone, these episodes affect over three million people each year [1].

AETIOLOGY

Primary and secondary restless legs syndrome are the two categories of the condition based on their causes [2].

RLS is frequently classified as a main CNS disease. In 25–75% of cases, this idiopathic illness may run in the family. RLS is known to exhibit either autosomal dominant or recessive patterns in familial situations.

Individuals with familial RLS typically exhibit slower disease progression and an earlier onset (less than 45 years of age). Genetic anticipation is the term used to indicate a gradually declining age of onset in subsequent generations in certain familial instances. RLS symptoms may also be made worse by psychological variables, stress, and exhaustion.

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Secondary restless legs syndrome can occur secondary to some disorders including [3, 4]:

- Iron deficiency.
- End-stage renal disease.
- Diabetes mellitus.
- Rheumatic disease.
- Venous insufficiency.
- Peripheral neuropathy.
- Folate or magnesium deficiency.
- Amyloidosis.
- Lumbosacral radiculopathy.
- Fibromyalgia.
- Celiac disease.

The symptoms of restless legs syndrome have been documented to be brought on by or made worse by medications. These include beta-blockers, alcohol, caffeine, lithium, selective serotonin reuptake inhibitors (SSRIs), diphenhydramine, tricyclic antidepressants (TCAs), antidopaminergic drugs (such as neuroleptics), and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Nearly one-third of pregnant women experience restless legs syndrome, although fortunately, the symptoms go away a few weeks after delivery. In contrast to women who did not experience RLS during pregnancy, patients who experienced RLS during pregnancy showed a 4-fold higher chance of developing chronic RLS in a long-term follow-up study [5].

Between 25 and 50 percent of individuals with end-stage renal illness have RLS; hemodialysis usually makes these patients' symptoms worse. In uremic patients receiving hemodialysis, one study found that RLS was independently associated with anxiety, hyperphosphatemia, and stress-reduction techniques. Following a kidney transplant, RLS may go away [6].

Signs and Symptoms

- Symptoms like crawling, creeping, pulling, scratching, drawing, or stretching are described by patients.
- In less severe situations, people will shift about in bed, kick, or massage their legs to feel better. On rare occasions, the arms could be impacted. Patients with more severe symptoms often feel driven to get out of bed and walk around to find relief.
- Periodic leg movements are marked by involuntary, forceful dorsiflexion of the foot lasting 0.5 to 5 seconds, typically occurring every 20 to 40 seconds during sleep. These movements often cause limb twitching during sleep and affect about 80% of individuals with restless legs syndrome.
- People with restless legs syndrome often experience unpleasant sensations along with a strong urge to move their lower limbs. This urge is usually milder during the day but becomes more intense in the evening and at night. Symptoms tend to occur during rest, sleep, or periods of inactivity.
- Walking or stretching the legs can help reduce the need to move the lower extremities, either fully or partially. The symptoms tend to disappear or remain minimal as long as the person stays active.
- At night, the urge to move the lower limbs becomes more intense, often making it difficult to fall asleep. This can leave the patient feeling tired and drained during the day. It's important to note that these symptoms should not be mistaken for other conditions like tardive dyskinesia, leg cramps, muscle spasms, or discomfort due to positioning.
- During sleep, the leg movements, which are often involuntary, may include abrupt dorsiflexion motions that last 1–5 seconds and repeat every 30–40 seconds. Children typically have positive family histories [7].

PATHOPHYSIOLOGY

It's unclear exactly what causes restless legs syndrome [5–8]. Iron reserves in particular brain regions decrease and the dopaminergic system malfunctions in idiopathic restless legs syndrome. Numerous

big kindreds with distinct susceptibility loci for restless legs syndrome have been reported, suggesting that there may be an autosomal dominant inheritance. This implies that the illness has a genetic foundation [9, 10].

Pathophysiology of uremic restless legs syndrome may entail subclinical peripheral nerve disorders, anemia, functional iron deficiency, and calcium/phosphate imbalance.

Pregnancy may also be impacted by low blood iron, and ferritin levels, pre-eclampsia, vitamin D deficiency, calcium metabolism, and high estrogen levels. Genetic polymorphisms in genes, such as BTBD9 and MEIS1 have been linked to restless legs syndrome.

Research involving human neuropathology and imaging has shown decreased iron levels in the substantia nigra, thalamus, and other brain regions. At the same time, these areas exhibit a relative excess of dopamine [11, 12].

During pregnancy, particularly in the third trimester, restless legs syndrome is very common.

Types

1. Intermittent RLS.
2. Chronic persistent RLS.
3. Refractory RLS.

Intermittent RLS

Restless leg symptoms that are severe enough to need medical attention but often occur less than twice a week are known as intermittent RLS. Chronic persistent RLS.

Restless leg symptoms that are frequent and bothersome enough to need daily treatment—typically occurring at least twice a week and causing moderate to severe distress—are referred to as chronic persistent RLS.

Refractory RLS

Restless legs that are not responding to monotherapy with acceptable dosages of first-line medications because of a decrease in efficacy, augmentation, or side effects are known as refractory RLS. (It is important to question the diagnosis's correctness if apparent RLS has never responded to acceptable dopamine agonist dosages given at the right periods.)

SPECIAL CONSIDERATION

Pregnancy and Lactation

Pregnancy can cause RLS to begin or worsen, with the third trimester seeing the highest prevalence and severity. Although symptoms usually go away or improve around delivery, women who experience pregnancy-related RLS are more likely to get it again in the future or later in life.

Diagnostic Evaluation

- During pregnancy, RLS may begin or develop, peaking in incidence and severity during the third trimester.
- Women with pregnancy-related RLS are more likely to develop RLS in subsequent pregnancies or later in life, but symptoms usually get better or go away around delivery.
- It is advised that all patients with RLS symptoms undergo iron testing. A thorough evaluation should include serum iron, ferritin, transferrin saturation, and total iron-binding capacity. If a full iron panel is not available, checking ferritin levels is essential. If a secondary cause is suspected, additional tests like a complete blood count (CBC) and assessments of specific levels should be conducted:

- Blood urea nitrogen (BUN).
- Fasting blood glucose.
- Creatinine.
- Magnesium.
- Vitamin B-12.
- Thyroid-stimulating hormone (TSH).
- Folate.

Treatment

A sleep aid was authorized for commercial use by the US Food and Drug Administration (FDA) in 2014 for individuals suffering from RLS. Vibrations from the device counter are used to stimulate the patient's legs. After two randomized studies demonstrated that the gadget improved sleep compared to a placebo pad, it was approved [13].

Patients should avoid caffeine, antidepressants, antipsychotics, dopamine-blocking antiemetics, and centrally acting antihistamines. The symptoms can be reduced by iron replenishment, exercise, massage, heat, and short daily dialysis for patients with renal failure.

Pramipexole, ropinirole, rotigotine, and cabergoline are examples of dopamine agonists that have been shown to lessen symptoms and enhance quality of life and sleep. Extreme weight gain and gambling addiction are among the side effects of pramipexole and ropinirole.

Another option is to utilize the rotigotine transdermal patch. It has a modest risk of clinically significant amplification of restless-legged syndrome and is well tolerated [14].

A large meta-analysis involving 3,286 participants found that pramipexole may be more effective than ropinirole in relieving symptoms for individuals with primary moderate-to-severe restless legs syndrome. In limited research, rotigotine helped patients with end-stage renal disease (ESRD) with their periodic limb movements and symptoms of restless legs syndrome in the short term.

For the initial therapy of individuals with severe sleep disturbance, concomitant insomnia, anxiety, pain, or a history of an impulse control disorder (ICD), alpha2-delta calcium-channel ligands (gabapentin or pregabalin) should be investigated [15–17].

The medications work for one to five years, but they also have side effects that make people less likely to take them as prescribed. These days, a dopamine receptor agonist or an alpha2 delta calcium channel ligand are the first-line treatments. Patients with low blood ferritin levels are recommended to take extra iron. Pregnancy-related restless legs syndrome typically goes away after birth.

While exercise can be helpful for many people, it is often not practical during the night.

- A guidance was created by the International Restless Legs Syndrome Study Group (IRLSSG) for the long-term pharmacologic treatment of RLS [18]. Based on the findings of 61 studies, the Task Force made the following recommendations:
  - Pregabalin – Effective for up to a year in treating RLS
  - Ropinirole, pramipexole, and rotigotine – Effective for up to six months
  - Gabapentin enacarbil for 1 year, levodopa for 2 years, and rotigotine for 5 years - probably effective for durations ranging between 1 and 5 years
  - Pergolide and cabergoline – Due to safety concerns, they are not being used in treating RLS

Patients with ferritin levels below 50 ng/mL should be given iron replacement. In cases of iron deficiency, ferrous sulfate 325 mg combined with 250 mg of vitamin C can be prescribed. To enhance absorption, it should be taken on an empty stomach, with no food for at least 60 minutes. Parenteral iron may also be necessary for treating RLS due to iron deficiency. For nonpharmacological treatments, the following recommendations should be made to patients [19].

- Sleep hygiene.
- Exercise.
- Hot or cold bath.
- Limb massage.
- Vibratory or electrical stimulation of the feet.
- The elimination of caffeine before bedtime.

Complications

The symptoms of restless legs syndrome can range from minor to significant affecting a person's life. Many RLS sufferers have trouble falling or staying asleep.

Severe RLS symptoms can lead to sadness and impair quality of life. RLS may make it difficult to nap, but insomnia may cause excessive daytime drowsiness.

CONCLUSIONS

The management of restless leg syndrome has steadily advanced during the past decades, resulting in increased relief for patients with this distressing disorder. The complex factors involved in the development of RLS, including both primary and secondary forms, as well as its association with comorbid conditions like ADHD, have highlighted the clinical significance of this sensorimotor neurological disorder.

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