Differential Diagnoses of Restless Legs Syndrome/ Willis-Ekbom Disease

Mimics and Comorbidities

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KEYWORDS

• Restless legs syndrome • Differential diagnoses • Willis-Ekbom disease • Mimics • Comorbidities

KEY POINTS

- Restless legs syndrome (RLS) mimics cannot always be differentiated from RLS/Willis-Ekbom disease (WED) based on 4 essential criteria; hence, a fifth criterion has recently been established.
- RLS comorbidities (associated conditions) may provide us important clues for understanding the neurobiology of RLS/WED.
- Iron-dopamine connection, hypoxia pathway activation, and dopamine-opioid interaction are important pathophysiological mechanisms in RLS; this knowledge is derived from our understanding of RLS associations with a variety of medical, neurologic, and other conditions.
- Clinicians must formulate an RLS differential diagnosis based mainly on history and physical examination, but laboratory tests may sometimes be needed to arrive at a correct diagnosis.

Since establishing 4 essential diagnostic criteria for restless legs syndrome/Willis-Ekbom disease (RLS/WED)[1] in 1995 and then slightly modified in 2003,[2] it was realized based on scientific study that some conditions that mimic RLS/WED cannot be differentiated based on these 4 criteria. Hence, the International Restless Legs Syndrome Study Group added a fifth criterion[3] based on expert consensus Diagnostic Criteria of RLS (**Box 1**) to differentiate RLS/WED from these mimics. In addition, several conditions have been suggested to be associated with RLS/WED (symptomatic or secondary). Many of these conditions share an association with depleted iron stores (eg, iron-deficiency anemia, renal failure, pregnancy, rheumatoid arthritis), but others remain unexplored because of a single pathophysiologic diathesis. An intriguing question is whether these comorbid conditions are actually responsible for RLS/WED or the recently reported RLS-specific genetic variants (eg, BTBD9, MEIS1) confer an increased risk of RLS/WED in these comorbid conditions. This article briefly summarizes the conditions mimicking RLS/WED in the first section, pointing out the distinction from true RLS/WED, as well as addressing these comorbid conditions in the second section so that corrective actions can be taken to alleviate or eliminate these associated conditions for optimal management of RLS/WED.

CONDITIONS MIMICKING RESTLESS LEGS SYNDROME/WILLIS-EKBOM DISEASE

Although these mimics do not cause RLS, it is important to be familiar with them to differentiate them from RLS/WED. These mimics can be classified into 4 major cases (**Box 2**):

1. Those that present with abnormal restlessness

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Box 1
Five essential diagnostic criteria for RLS/WED

[a]Criterion 1. An urge to move the legs, usually but not always accompanied by uncomfortable sensations in the legs.

Criterion 2. The urge to move the legs with any accompanying unpleasant sensations begins or worsens during periods of inactivity or quiescence such as lying down or sitting.

Criterion 3. The urge to move the legs with any accompanying unpleasant sensations is partially or totally relieved by movement, such as walking or stretching, as long as the activity continues.

Criterion 4. The urge to move the legs with any accompanying unpleasant sensations during rest or inactivity only occurs or is worse in the evening or night than during the day.

Criterion 5. The above features are not accounted by another medical or behavioral condition (eg, myalgia, arthritis, venous stasis, leg cramps, positional discomfort or habitual foot tapping).

[a] The adult and the pediatric diagnostic criteria are merged together except that the description of these symptoms in criterion 1 should be in the child's own words.

Box 2
Conditions that can be confused with RLS/WED

Presenting with abnormal restlessness

- Akathisia
  - Neuroleptic induced
  - Related to central nervous system degenerative or infectious disease
- Disorders of abnormal muscular activity
  - Myokymia
  - Essential myoclonus
  - Orthostatic tremor
  - Orthostatic myoclonus
- Anxiety/depression
- Attention-deficit/hyperactivity disorder
- Orthostatic hypotensive restlessness while sitting
- Leg stereotypy disorder

Presenting with nocturnal leg discomfort or pain

- Growing pains
- Small fiber neuropathies
- Venous stasis–varicose veins
- Myalgias
- Arthritis
- Radiculopathies
- Delusional parasitosis

Presenting with combined unusual motor activity and leg discomfort or pain

- Painful muscle cramps, including nocturnal leg cramps
- Painful legs and moving toes syndrome
- Muscular pain–fasciculation syndrome
- Cramp-fasciculation syndrome
- Causalgia-dystonia syndrome
- Intermittent claudication

Presenting with nocturnal hypermotor activity

- Rhythmic movement disorder
- Periodic limb movement disorder
- Hypnagogic foot tremor
- Alternative leg muscle activation
- Hypnic jerks
- Propriospinal myoclonus at sleep onset

2. Those presenting with nocturnal leg discomfort or pain
3. Those presenting with combined unusual motor activity and leg discomfort or pain
4. Those presenting with nocturnal hypermotor activity

Akathisia

This condition can be mistaken for RLS/WED, but there are many differentiating features as shown in **Table 1**. The term *akathisia* is derived from the Greek word meaning "inability to sit." The term *akathisia* was first used in 1901 by Ludwig Haskov,[4] the Czech neuropsychiatrist ascribing this to hysteria. However, *akathisia* has emerged as an important side effect of neuroleptics in the second half of the twentieth century; neuroleptic-induced akathisia (NIA) remains the most familiar and acceptable term in contemporary writings.