Restless Legs Syndrome

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KEYWORDS

• Restless legs syndrome • Periodic leg movements of sleep • Iron deficiency
• Dopaminergic agents • Alpha-2-delta calcium channel ligands • Opioid agents

KEY POINTS

- Restless legs syndrome is characterized by an urge to move and associated with an uncomfortable sensation in the legs.
- Restless legs syndrome can lead to sleep-onset or sleep-maintenance insomnia, and excessive daytime sleepiness leading to significant morbidity.
- Brain iron deficiency and dopaminergic neurotransmission abnormalities play a central role in the pathogenesis of this disorder.
- Dopaminergic agents, alpha-2-delta calcium channel ligands, opioids, and benzodiazepines are commonly used agents to treat restless legs syndrome with variable efficacy.

INTRODUCTION

Restless legs syndrome/Willis-Ekbom disease (RLS/WED) is a neurologic sensorimotor disorder that is mainly characterized by an urge to move, which is often associated with paresthesias. The urge to move is usually worse during rest and at night. RLS/WED is commonly associated with periodic leg movements of sleep (PLMS), which are involuntary jerking leg movements. RLS/WED was first described in 1672 by the English physician Thomas Willis.[1] The term "restless legs syndrome" was coined by Professor Karl-Axel Ekbom in 1944.[2,3] RLS/WED is a common disorder, but often underdiagnosed in the general population.

PREVALENCE

There is a wide variation of the age of onset; as such, RLS could present from childhood to older than 80 years of age.[4] Prevalence estimates of RLS/WED vary significantly, depending on the criteria used to define this condition in surveys. Approximately 5% to 10% of adults are estimated to have RLS/WED in North America

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and Europe. The prevalence estimates are lower when the frequency and severity of symptoms are included in the definition.[5] Prevalence of clinically significant RLS is estimated to be around 2% to 3%.[6–9] Increasing prevalence of RLS has been described in women and also with increasing age.[10] Nearly one-third of pregnant women experience RLS in the third trimester and the risk of RLS increases with the number of live births.[11] Prevalence also varies by ethnicity, with lower prevalence in Asian populations.[5] RLS has been described in 2% of school-age children.[12]

ETIOLOGY

The cause of most cases of RLS/WED is unknown, and hence is called primary RLS. A positive family history is present in approximately 40% of patients, with autosomal-dominant inheritance patterns.[13] Familial aggregation of RLS is well described and the proportion of phenotypic variation attributable to genes is 54% to 83%.[14,15] Genetic linkage studies have identified several potential regions of interest. The gene RLS1 on chromosome 12 is common in Icelandic, German, and French-Canadian families, implicating a role for neuronal nitric oxide synthase (NOS1).[16] Multiple single-nucleotide polymorphisms have been identified by genome-wide association studies, suggesting involvement of at least six different gene products: BTBD9, Meis1, PTPRD, MAP2K5, LBXCOR1, and TOX3.[17–21] The implicated genes are widely expressed in the central nervous system and other organs, and at-risk single-nucleotide polymorphisms in each instance are common and present within non-coding, intronic, or intergenic regions. A single single-nucleotide polymorphism (rs3923809) in an intron of BTBD9 is associated with increased risk of RLS and PLMS by 70% to 80%. Nearly one-half of subjects of northern European ancestry were found to carry two copies of this common at-risk variant, which accounts for at least 50% of the population-attributable risk for RLS/PLMS.[22] A dose-dependency between the BTBD9 variant and decrements in iron stores has been observed.[17] The Meis1 variant was found to influence iron homeostasis causing functional decrements.[23] Other genetic factors are also possibly involved, suggesting that RLS expressivity is influenced by a substantial inheritable component.

RLS occurs in association with several disorders (called secondary RLS). The conditions where the frequency of RLS occurs higher than expected than in the general population include iron deficiency; end-stage renal disease; diabetes mellitus; rheumatologic disorders, such as rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus; pulmonary disorders, such as chronic obstructive pulmonary disease and pulmonary hypertension; neurologic conditions, such as Parkinson disease, multiple sclerosis, and migraine; and gastrointestinal conditions, such as gastric surgery, celiac, and Crohn disease.[24–42]

PATHOGENESIS

There is increasing evidence for the role of brain iron insufficiency and dopamine neurotransmission abnormalities in the development of RLS/WED. The remarkable treatment response seen with levodopa and dopaminergic agonists in alleviating RLS symptoms, and the symptomatic worsening observed with dopamine antagonists, has led to the natural hypothesis of a possible role of dopaminergic abnormalities in RLS. The exact mechanisms by which abnormalities in dopaminergic neurotransmission or in dopamine metabolism result in the development of RLS remain unclear.[43–45]

Clinical investigations, neuroimaging modalities, autopsy tissue analysis, cerebrospinal fluid analysis, and experimental models of dietary iron deficiency suggest an