Restless Leg Syndrome/ Willis-Ekbom Disease Pathophysiology

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KEYWORDS

• Iron • Dopamine • RLS/WED • PLMS • RLS augmentation

KEY POINTS

- Iron management is impaired in restless leg syndrome/Willis-Ekbom disease, leading to brain iron deficiency.
- Brain iron deficiency acting partly through hypoxic pathway activation produces increased presynaptic and synaptic dopamine. This produces postsynaptic down-regulation that overcorrects for the normal evening and nocturnal decrease in dopamine-producing restless leg syndrome/Willis-Ekbom disease symptoms. Increasing dopamine activation in the evening and night corrects this problem reducing restless leg syndrome symptoms.
- Eventual continued increased dopamine stimulation with long-term dopamine treatment leads to further postsynaptic desensitization and gradual worsening of restless leg syndrome/Willis-Ekbom disease, especially at the higher doses and possibly more for shorter-acting medications.
- Brain iron deficiency also reduces myelin, possibly accounting for brain white matter decreases in restless leg syndrome/Willis-Ekbom disease.
- Hypoxia (eg, with chronic obstructive pulmonary disease) activates hypoxic pathways leading to dopamine increases and restless leg syndrome/Willis-Ekbom disease independent of iron status.

INTRODUCTION

Three major clinical features of restless leg syndrome/Willis-Ekbom disease (RLS/WED) unique for common neurologic disorders enabled somewhat surprising pathophysiologic discoveries. RLS/WED has a well-defined phenotype, one accessible and well-defined environmental vector (iron), and dramatic response to increasing activity of one neurotransmitter system (dopamine). Studies based on these 3 pillars of RLS/WED found a complex underlying biology almost the opposite of expectations. The well-defined phenotype enabled important genetic discoveries for RLS. In sleep medicine, only RLS/WED and narcolepsy have well-defined genetic factors, and both have well defined phenotypes missing for the other sleep disorders. Study of the environmental vector of iron deficiency found an underlying iron pathophysiology. The dopamine treatment response drove studies of dopamine pathophysiology.

This article includes sections focused on pathophysiologic findings from each of these 3 areas: genetics, cortical-spinal excitability, and iron and dopamine. There are other less well-developed features of RLS/WED pathophysiology that could be considered, particularly cortical excitability, neuroanatomical considerations, and other neurotransmitter/neuromodulators. The summary in the last section includes a brief note of these.

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GENETICS AND RESTLESS LEG SYNDROME/ WILLIS-EKBOM DISEASE PATHOPHYSIOLOGY

The well-defined RLS/WED phenotype enabled successful genomewide association studies (GWAS) that have now identified RLS/WED risk alleles on 5 specific genomic regions for MEIS1, BTBD9, PTPRD, MAP2k/SKOR1, and TOX3/ BC034767 and on an intergenic region on chromosome 2 (rs6747972).[1–3] Most of these variants also seem to have some relation to the periodic leg movements (PLMS) motor sign of RLS/WED.[4] An RLS/WED risk allele on BTBD9 is also strongly associated with both increased PLMS independent of RLS/WED and with decreased peripheral iron stores (decreased serum ferritin).[5] Another BDBT9 allelic variant relates to RLS/WED diagnosis,[3] increased PLMS,[6] and greater decreases in peripheral iron stores with blood donations.[7] Functional relation of BTBD9 has been further indicated by findings of increased peripheral iron for a BDBT9-mutant mouse[8] and murine ventral midbrain iron content associated with a quantitative trait loci that includes BDBT9.[9] Besides these findings relating in general BDBT9 to iron deficiency in RLS/WED, there has been no significantly substantial discovery of potential genetics pathways to RLS/WED pathophysiology. This commonly occurs for results from GWAS for common diseases, suggesting the need for different approaches.

IRON PATHOPHYSIOLOGY

RLS/WED has one major, well-defined primary environmental factor of iron deficiency. This deficiency was noted in the seminal RLS/WED studies of Ekbom[10] and Nordlander.[11] RLS/WED severity increases with decreased peripheral iron,[12] and its prevalence is about 9 times greater in iron-deficient anemia than general populations.[13] All conditions that compromise iron status have been associated with increased risk of RLS/ WED (eg, pregnancy and end-stage renal disease). Moreover, in these cases, aggressive treatment of the iron deficiency reduces RLS/WED severity. But most RLS/WED patients have normal serum ferritin and little indication for abnormal peripheral iron stores. The pathophysiology appears to be less peripheral and more about central nervous system iron status. Reduced cerebrospinal fluid (CSF) ferritin was reported in 2 separate studies for RLS/WED patients who had normal peripheral iron measures.[14,15]

The single best-documented biological abnormality for RLS/WED is brain iron deficiency. Initial reports showed decreased brain iron based on magnetic resonance imaging (MRI) of the substantia nigra and red nucleus as shown in **Fig. 1**.[16] Brain iron deficiency for RLS/WED has now been confirmed in 6 studies using different methods in different laboratories.[16–21] The brain areas most consistently showing the reduced iron include the substantia nigra and, to a lesser extent, the putamen and caudate. Recent studies with more sensitive measures have documented low iron in the thalamus.[20] The iron deficiency seems to be more regional than global, and the affected regions include not only iron rich areas such as the substantia nigra but also iron-poor areas, particularly the thalamus. Some iron-rich areas have not consistently shown decreased iron for RLS/WED (eg, cerebellar dentate nucleus). Thus, the pathophysiology seems to involve a regional brain iron deficiency present in most RLS/WED patients despite normal iron status.

Changes in iron regulatory proteins from RLS/ WED autopsy studies present a surprisingly complicated interaction. H-ferritin but not L-ferritin is increased in the RLS/WED brains. The H-ferritin

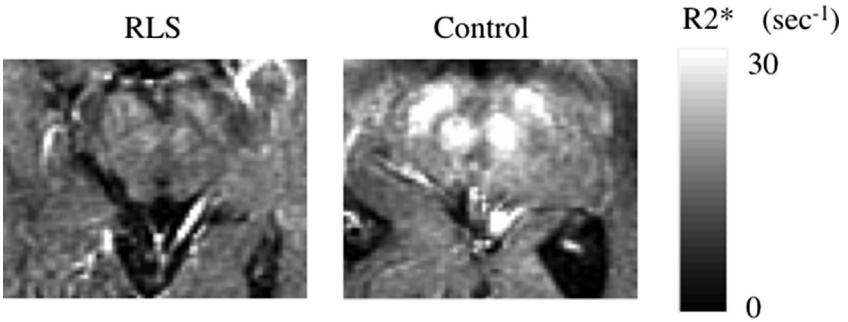

Fig. 1. R2* images in a 70-year-old RLS patient and a 71-year-old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both red nucleus and substantia nigra. (*Adapted from* Allen RP, Barker PB, Wehrl F, et al. MRI measurement of brain iron in patients with restless legs syndrome. Neurology 2001;56(2):263–5; with permission.)