Restless Leg Syndrome in Neurologic and Medical Disorders

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KEYWORDS

• Restless leg syndrome • Leg quietness homeostasis • Neurotransmitters • Motor unit potentials • Flip-flop switch

KEY POINTS

- RLS is caused by imbalanced activity of neurotransmitters associated with a variety of physiologic and pathologic conditions.
- Leg quiescence homeostasis (LQH) reflects variable conditions of sustained muscle inactivity during sleep and wakefulness.
- Perturbed neurotransmitter activity occurs under variable LQH steady states.
- Flip-flop switch model of the sleep-wake cycle may be applied to rest and restless situations.

INTRODUCTION

Thomas Willis originally described in the seventeenth century "the diseased are no more able to sleep, than if they were in a place of the greatest torture." This description was rediscovered and termed restless leg syndrome (RLS) in the mid-twentieth century by Ekbom.[1] Diagnostic criteria for this prevalent syndrome elaborated in a consensus meeting in 2002[2] are being continuously revised considering that RLS is persistently underdiagnosed.[3,4] RLS is associated with general risk factors including female gender, pregnancy, lower socioeconomic status, poor health, elderly age, and positive family history of RLS.[5–9]

Primary RLS includes idiopathic disease of unknown cause and familial disease with genetic predisposition often associated with mutations in chromosomes 2p, 9p, 12q, 14q, 16p, and 20p.[10,11] The association of RLS with a variety of diseases and disorders is evidence of involvement of multiple factors in the pathophysiology of this syndrome. Outstanding is the interesting incidence of RLS in the last trimester of pregnancy persisting for several months after delivery, which is not a pathologic condition.[4]

ASSOCIATED DISORDERS

RLS is associated with a variety of neurologic disorders of various etiologies,[12,13] including peripheral neuropathy[14,15]; cerebrovascular disorders, headaches and particularly migraine[16]; persistent anxiety[17]; autoimmune disorders affecting the nervous system; radiculopathies[18]; movement disorders; and psychiatric disorders.[7–9] Despite the association between RLS and Parkinson disease,[8,19–21] a clear causal association has not yet been determined,[21] as with other neurodegenerative disorders.[22] Although a summary of 32 epidemiologic studies found that idiopathic RLS is often associated with comorbid factors, such as mood disorders and insomnia,[23] there is no apparent relationship between the incidence and severity of RLS and comorbid factors, such as anxiety, depression, and pain in Parkinson disease.[24]

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Obstructive sleep apnea is often associated with increased incidence of periodic limb movements (PLM)[25] and RLS; however, the latter does not correlate with hypersomnia characteristic of sleep-related breathing disorders.[26] RLS is variably responsive to obstructive sleep apnea treatment by continuous positive air pressure.[27] Other sleep disorders including hypersomnia, narcolepsy, and disrupted sleep are associated with increased RLS incidence, and are usually accompanied by elevated markers of inflammation.[9] The association of RLS with sleep deprivation and/or fragmentation may be caused by reduction in pain thresholds, modulated by a variety of neurotransmitters, particularly dysfunction of monoaminergic circuits.[28]

The association of RLS with autoimmune disorders has been long recognized[29] with significant comorbidity of inflammation, intestinal bacterial overgrowth, iron deficiency, and peripheral neuropathy, suggesting an immunologic basis of secondary RLS.[30] Some studies found elevated inflammatory cytokines, most prominent interleukin-6 and tumor necrosis factor-α,[30] although other studies failed to observe such a correlation.[31] Autoimmune and inflammatory disorders include celiac[32]; Sjögren syndrome; rheumatoid arthritis[33,34]; systemic lupus erythematosus[30]; inflammatory bowel disease[35]; fibromyalgia[36]; and several less defined disorders often classified as musculoskeletal system and connective tissue disorders, such as osteoarthritis, polyarthropathies, disorders of muscle, ligament and fasciae, disorders of joints, and disorders of synovium, tendons, and bursa.[31,37,38] Noteworthy is the four-fold higher incidence of RLS in patients with multiple sclerosis than in the general population,[31,39] which is often associated with higher scores of disability,[40] primary progressive disease, and cervical spine lesions.[41]

The initial disorder associated with RLS has been anemia, particularly iron deficiency anemia,[1] although it is frequently encountered in other element deficiencies, such as folic acid.[42] It is possible that anemia *per se* is a predisposing factor, because RLS appears at increased incidence in patients with hereditary hemolytic anemias.[8,43] Likewise, anemia as a common symptom of iron and folate deficiencies may underlie the higher incidence of RLS in pregnancy.[44] However, the proposed mechanism predisposing to RLS is a decrease in cerebral iron concentrations,[45] which serves as a cofactor of tyrosine hydroxylase required for dopamine synthesis.[46] Relative iron deficiency in the brain may be caused by excessive hepatic synthesis of hepcidin under conditions of systemic inflammation.[31]

RLS is associated with several disorders causing decreased cerebral, spinal (cervical and lumbar), and peripheral blood flow.[47] These conditions are caused by several respiratory, cardiac, and vascular pathologies responsible for inadequate oxygenation or compromised peripheral circulation. Indeed, peripheral hypoxia and low oxygen pressure in resting and immobilized subjects is associated with the appearance of RLS symptoms.[48] First, RLS is prevalent in various respiratory conditions including asthma, emphysema, bronchiolitis,[38] and recipients of lung transplants,[49] and the incidence is as high as 50% during acute exacerbations of chronic obstructive lung disease.[50,51] Second, patients suffering from coronary artery disease and heart failure often experience RLS,[52] with questionable participation of sympathetic hyperactivity in PLM.[53] Third, peripheral vascular disease precipitates RLS. Afferent vascular insufficiency has been treated with external counterpulsation, achieving sustained amelioration of symptoms.[54] Peripheral vascular insufficiency may also be caused by impaired venous return, and RLS has been successfully treated in some cases by endovenous laser ablation.[55]

Acute and chronic renal failure[56] and various causes of uremia[13] are conditions associated with high incidence of neuromuscular disorders. Patients with uremia often experience RLS in association with sleep disorders, excessive daytime sleepiness, anxiety, and depression, although it is difficult to determine which are the primary causes and which are the secondary consequences.[57] Although persisting throughout extended periods of dialysis, RLS disappearance within several months after successful renal transplantation establishes a causal relationship to renal disorders and uremia.[58,59] Notably, uremia-associated RLS is rather refractory to treatment with dopamine agonists.[60]

Additional metabolic disorders associated with increased RLS incidence include diabetes,[7] obesity,[5] and variations in thyroid function (thyrotoxicosis and hypothyroidism) possibly by modulation of dopamine levels.[61]

Antidepressants provoke PLM[62] and case reposts disclose exacerbation or induction of RLS including tricyclic antidepressants, selective serotonin reuptake inhibitors, antihistamines, and lithium, along antipsychotic and antiepileptic agents.[63]

A HYPOTHESIS ON THE MECHANISM OF RESTLESS LEG SYNDROME

Interpretation of the multiple disorders associated with RLS points to iron deficiency and chronic