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The restless legs syndrome

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Abstract

The restless legs syndrome (RLS) is one of the commonest neurological sensorimotor disorders at least in the Western countries and is often associated with periodic limb movements (PLM) during sleep leading to severe insomnia. However, it remains largely underdiagnosed and its underlying pathogenesis is presently unknown. Women are more affected than men and early-onset disease is associated with familial cases. A genetic origin has been suggested but the mode of inheritance is unknown. Secondary causes of RLS may share a common underlying pathophysiology implicating iron deficiency or misuse. The excellent response to dopaminegic drugs points to a central role of dopamine in the pathophysiology of RLS. Iron may also represent a primary factor in the development of RLS, as suggested by recent pathological and brain imaging studies. However, the way dopamine and iron, and probably other compounds, interact to generate the circadian pattern in the occurrence of RLS and PLM symptoms remains unknown. The same is also the case for the level of interaction of the two compounds within the central nervous system (CNS). Recent electrophysiological and animals studies suggest that complex spinal mechanisms are involved in the generation of RLS and PLM symptomatology. Dopamine modulation of spinal reflexes through dopamine D3 receptors was recently highlighted in animal models. The present review suggests that RLS is a complex disorder that may result from a complex dysfunction of interacting neuronal networks at one or several levels of the CNS and involving numerous neurotransmitter systems.

Keywords: Restless legs syndrome; Periodic limb movements; Dopamine; Iron; Opioids; Noradrenaline; Spinal cord

Contents

Abbreviations: CNS, central nervous system; CPG, central pattern generator; CSF, cerebrospinal fluid; CSP, cortical silent period; D3KO, D3 knock-out; DAT, dopamine transporter; EMG, electromyography; GH, growth hormone; ICF, intracortical facilitation; ICI, intracortical inhibition; IRLSSG, international restless legs syndrome study group; IRPs, iron regulatory proteins; MEP, motor evoked potentials; MRI, magnetic resonance imaging; PAM, periodic arm movements; PET, positron emission tomography; PLM, periodic limb movements; PD, Parkinson's disease; PRL, prolactin; PSG, polysomnography; RLS, restless legs syndrome; SN, substantia nigra; BH4, tetrahydrobiopterin; TfR, transferrin receptor; TH, tyrosine hydroxylase; SSRIs, selective serotonin re-uptake inhibitors; SPECT, single-photon emission computed tomography; TMS, transcranial magnetic stimulation; VTA, ventral tegmental area

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1. Introduction

The restless legs syndrome (RLS) remains one of the most intriguing and commonest chronic sensorimotor disorders, yet it is still a poorly recognized condition in primary care settings as physicians are frequently unaware of the condition and misdiagnosis is common (Allen et al., 2005; Hening, 2004; Tison et al., 2005; Van De Vijver et al., 2004; Walters et al., 1996). Even though RLS was first identified and characterized in the forties (Ekbom, 1945), it is only recently that the International Restless Legs Syndrome Study Group (IRLSSG) outlined its clinical features (Allen et al., 2003). The underlying neurophysiological and biochemical mechanisms are currently being investigated and recent animal and molecular studies have also begun to elucidate the still uncertain nature of the basic pathophysiology of RLS.

In the present review, we have attempted to summarize the most relevant and recent clinical, epidemiological and genetic aspects of RLS. Much of the manuscript also concerns the secondary forms of RLS as we believe that some may share a similar pathophysiology. The latter has been discussed in separate sections devoted to major biochemical and neurotransmitter systems, brain structures and particularly to spinal mechanisms thought to be involved in the pathophysiology of RLS. Finally, the article concludes with a summary of certain major animal models with pathophysiological significance which have emerged over recent years and which are likely to influence future research in this field.

Despite extensive literature on the topic, RLS appears increasingly to be a complex disorder whose underlying pathophysiology is still unraveled. However, this should not impede clinical and fundamental research efforts for better recognition of the disease.

2. Clinical presentation

RLS is a common and treatable chronic sensorimotor disorder clinically characterized by a compelling urge to move the limbs, accompanied by uncomfortable and unpleasant sensations in the extremities. Typically, the legs are mostly affected but arm involvement has also been reported (Ekbom, 1960; Michaud et al., 2000; Montplaisir et al., 1997; Ondo and Jankovic, 1996). The diagnosis of RLS is clinical and is based on the patient's description. Subjective symptoms, which are the hallmark of the condition, were first extensively described by Ekbom in the 1940s (Ekbom, 1945), but consensual diagnostic criteria were recently outlined allowing a more uniform diagnosis worldwide (Walters, 1995), and were then updated by the IRLSSG (Allen et al., 2003). Accordingly, four mandatory clinical features are required to establish the diagnosis of RLS, namely (i) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (ii) an urge to move or unpleasant sensations that begin or worsen during periods of rest or inactivity such as lying or sitting; (iii) an urge to move or unpleasant sensations that are partially or totally relieved by movement, such as walking or stretching, at least as long as the