National Sleep Disorders Research Plan

→ Return to Table of Contents

SECTION 5 - SLEEP DISORDERS

Restless Legs Syndrome/Periodic Limb Movement Disorder

Background

Restless Legs Syndrome (RLS) is a sensorimotor disorder characterized by periodic irresistible urges to move the legs, usually associated with unpleasant and uncomfortable sensations in the legs. These symptoms occur during wakefulness, but are exacerbated or engendered by rest/inactivity and partially relieved by movement. The diurnal pattern of symptoms likely reflects modulation by the circadian system. RLS is reported to profoundly disturb sleep, yet the extent of nocturnal sleep disturbance and of daytime sleepiness has not been established. Estimates of RLS in various populations range from 2 to 15%, but incidence and prevalence have not been precisely defined, particularly as a function of gender and ethnicity. Several reports indicate a higher prevalence of RLS among women than men, and in individuals of Northern European ancestry. The etiology and pathogenesis of RLS are thought to involve alterations in efficiency of central dopamine neurotransmission, based largely on the clinical observation that dopaminergic drugs relieve symptoms. The inheritance pattern of RLS suggests an autosomal dominant mode of transmittance, but the genes accounting for this observation are not known. RLS is also associated with iron deficiency, and is quite common in end-stage-renal disease and during pregnancy.

About 85-90% of patients with RLS also exhibit periodic limb movements (PLMs) during sleep. Unlike RLS, which is diagnosed on the basis of history and symptoms, periodic limb movement disorder (PLMD) relies upon quantification of repetitive stereotypic leg movements associated with a brief arousal during sleep monitoring. Patients manifesting PLMD have complaints of daytime fatigue and sleepiness or insomnia. Similar to RLS, PLMD may involve altered central dopamine mechanisms since dopaminergic agents or other drugs that interact with dopamine mechanisms, e.g., opiates, are equally effective treatments for most

Section 5 Content:

patients. The incidence of PLMD, like RLS, is higher in the elderly. Without better understanding of the etiology, pathogenesis, and neurophysiology of these disorders, treatment strategies are limited, and can be unsatisfactory. Both disorders have profound negative impact on quality of life including daytime functioning, work performance, and social and family life.

Controversy exists about the clinical significance of PLMs during sleep in the absence of sensory complaints consistent with RLS. PLMs can occur without associated EEG micro-arousals and in the absence of sleep complaints or of daytime symptoms. If associated with micro-arousals, the frequency of PLMs does not correlate with objective measures of daytime sleepiness or with indices of disrupted sleep. This lack of a correlation may reflect insensitivity in the methods used for scoring EEG micro-arousals and sleep fragmentation. Abnormal limb movements during sleep have been associated with physiological correlates of arousal in autonomic or cortical functioning suggesting that PLMs are part of an underlying arousal disorder. It is possible that abnormal limb movements during sleep may be associated with an unidentified neurophysiological alteration in micro-structure of the EEG sleep pattern.

Progress In The Last 5 Years

- Several potential animal models of RLS and PLMD have been developed based upon interruption of normal dopaminergic responsivity.

- Imaging studies suggest reduced central dopamine receptor binding with age, but only small and inconsistent decreases in dopaminergic transmission have been reported in traditional nigrostriatal dopaminergic pathways in patients with RLS. This finding suggests that alterations might exist in extrastriatal dopaminergic pathways.

- RLS and PLMD are more common in children with attention deficit hyperactivity disorder providing an opportunity to address developmental aspects of these disorders and responsivity to dopaminergic interventions.

- Neurophysiological studies in humans suggest that RLS is associated with inefficiencies of spinal cord inhibition that may be brainstem mediated and state dependent.

- RLS shows high familial aggregation. A recent study of genes involved in central dopaminergic transmission and metabolism showed no evidence of involvement in RLS. However, other recent studies have identified a susceptibility locus for RLS on chromosome 12q in a large French-Canadian family and a polymorphism in a gene involved in catecholamine (monoamine oxidase A) metabolism in women with RLS.

- Central Nervous System (CNS) imaging studies have shown reduced iron concentrations in some brain regions. These reductions correlate with RLS severity and low cerebral spinal fluid (CSF) ferritin combined with high serum and CSF transferrin levels.

- The RLS case definition was updated and revised in 2002. This provides

a basis for the development of specific questionnaires to advance clinical recognition and to clarify RLS prevalence.

- EEG patterns of cortical activation precede PLMs and indices of autonomic arousal, suggesting that PLMD are associated with an underlying arousal disorder.

Research Recommendations

- Determine the role of altered central dopaminergic mechanisms, iron metabolism, and other possible mediators in the pathogenesis of RLS and PLMD through animal and human studies. The development, refinement, and validation of animal models for RLS and PLMD are needed. Modern techniques of neuropathology in the evaluation of brains and spinal cords from patients with RLS and PLMD should be used to identify potential abnormalities underlying these disorders.

- Identify and further characterize genes involved in RLS and PLMD.

- Determine the extent of nocturnal sleep disturbance and daytime sleepiness in children and adults with RLS and PLMs.

- Develop and validate questionnaires based on the new RLS case definition and determine the population-based incidence, prevalence, and morbidity, particularly in children and as a function of gender, race, and ethnic distribution.

- Establish the developmental changes in adults explaining the higher incidence of RLS and PLMD in the elderly.

- Pregnancy and uremia provide reversible models to study the development and remission of RLS and the role of altered iron metabolism. Conduct clinical trials of iron supplementation in RLS patients with low ferritin levels.

- Improve available treatment strategies for RLS and PLMD. Dopamine agonists, opioids, and anticonvulsants are used most frequently and are effective in reducing RLS symptoms and PLMs, but the necessary large multi-center trials and long-term studies have not been conducted. These studies should include assessment of quality of life and assess the sensitivity of existing questionnaires to treatment changes.


National Institutes of Health (NIH)