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Sleep disorders: from Neurobiology to Systemic Consequences

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ABSTRACT

Genética, hierro cerebral y circuitos neuronales en el Síndrome de Piernas Inquietas

Genetics, brain iron and neurocircuitry in Restless Legs Syndrome

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The Restless Legs Syndrome (RLS) also known as Willis-Ekbom Disease (WED) although disabling when severe and the second most common sleep disorder affecting about 7% of adult Europeans remains commonly undiagnosed and untreated. RLS disrupts the primary motor-sensory control system essential for sleep, i.e. inhibition of movement and decreased motor response to stimuli. RLS actually engenders sleep-movements with a motor sign of periodic leg movements in sleep (PLMS). RLS is the major disorder disrupting the sensory-motor control system required to enable cortical sleep. Its severity ranges from mild annoying sleep loss to disabling, hurtful suffering most of the day. It affects about 1/3rd of all who have any condition reducing iron status, e.g. pregnancy, renal disease, iron-deficiency anemia. It is twice as common for adult women than men, but nulliparous women have the same risk of RLS as men possibly reflecting pregnancy effects on iron biology.

RLS neurobiology involves both brain iron deficiency despite normal peripheral irons status and also disruption of dopaminergic systems shown by imaging and autopsy to produce increased striatal dopamine that in animal studies relates to lower iron. Other motor-sensory control systems disrupted in RLS include increased sensitivity/excitability of cortical leg motor control and excitability changes in thalamic circuits. The excitability changes involve glutamatergic and adenosinergic neurocircuits.

Genetic studies identified specific RLS risk alleles particularly strong for MEIS1 and BTBD9 genes. Given the central role of iron in RLS it remains possible that epigenetic changes from early-life iron deficiency may have a role in development of RLS in later life.

The neurobiology of RLS translates into developments of promising new treatments including intravenous iron and also dugs affecting glutamate and adenosine pathways. Better use and development of treatments for RLS are needed particularly given the potential long-term effects of RLS on sleep loss and health, particularly cardiovascular health.