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Interrogating the Prevalence of Restless Leg Syndrome in Spinal Cord Injury Patients

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Abstract

Restless Leg Syndrome (RLS)/Willis-Ekbom Disease (WED) is a common sensimotor disorder, characterized by uncontrolled urge to move the extremities along with uncomfortable sensations, especially at night and in periods of inactivity, leading to deprivation of sleep. A growing number of case-reports and recent studies have reported a high prevalence of RLS/WED in Spinal Cord Injury (SCI) patients. The underlying mechanism is not fully known. The main proposed mechanisms include the stimulation of a Central Pattern Generator (CPG), disruption of the dopaminergic tract and neuroplasticity changes. The purpose of the present review is to elucidate the current knowledge concerning the prevalence of RLS/WED in SCI patients and the pathophysiology with up to date information.

Keywords: Restless leg syndrome; Periodic limb movements; Sleep disorder; Hyperexcitability

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Restless Leg Syndrome: Diagnosis and Pathophysiology

Restless Leg Syndrome (RLS), also referred to as Willis-Ekbom disease (WED), is a common sensimotor disorder, characterized by a persistent urge to move mainly the legs, together with paresthesia-like sensations in the lower limbs, especially during periods of inactivity [1,2]. RLS/WED is currently considered as a common disease with a prevalence of 1% to 5% [3,4]. Women are affected twice as often as men and the occurrence increases with age. The clinical manifestations of RLS/WED vary in frequency and severity, and are influenced by both environmental and genetic factors. The diagnosis of RLS/WED is primarily based on the neurological examination and the patient's medical history, and can be made when all of the following diagnostic criteria, established and revised by the International RLS Study Group in 2012 (IRLSSG) [2], assemble:

- A persistent urge to move the legs, usually followed by unpleasant and uncomfortable sensations in the lower limbs, giving the impression that it is caused by them. Sometimes other parts of the body, such as the arms are also involved.
- The symptoms begin or deteriorate during periods of inactivity or rest.
- Total or partial relief with movement, at least as long as it lasts.
- The symptoms worsen or occur only in the evening or at night.
- The aforementioned criteria must not solely serve as symptoms, primary, to other behavioral or medical conditions.

Periodic Limb Movements during Sleep (PLMS) are recorded in over 80% to 90% of RLS/WED patients. They consist of periodic, stereotypical and often bilateral jerking of the big toe, usually accompanied by flexion of the knees, hips, ankle and/or upper extremities [5]. When present, they support the diagnosis of RLS/WED but they are also frequent in other sleep disorders, as well, including Obstructive Sleep Apnea Syndrome (OSAS), REM sleep behavior disorder and narcolepsy [6]. RLS/WED was a neglected disorder until recently and only a couple of decades ago did research set the standards for this common condition that affects the patients' health and quality of life. The pathophysiology of the disease has not yet been fully elucidated [1,7-9]. Generally, RLS/WED can be classified into primary or idiopathic and secondary. Idiopathic RLS/

WED, with no known cause, accounts for the majority of cases. It has an early onset, affecting individuals under the age of 30 years, and a progressive clinical course [1,10]. Genome Wide Association Studies (GWAS) have come upon six different genes: MEIS1, BTBD9, MAP2K5, PTPRD, TOX3 and SKOR1; their allelic variants altogether have been found to account for about 50% to 80% of the risk for RLS/WED [11,12]. Brain iron and dopaminergic dysregulation also seem to play an important role in the pathogenesis of the disease [13]. The chief underlying mechanism of the low brain iron detected in the brain of RLS/WED patients is thought to be the dysregulation of iron transport across the endothelial cells of the Blood-Brain Barrier (BBB) [5]. Circadian changes in the status of the brain iron may also be involved in the pathophysiology of the disease, as significantly lower ferritin levels have been found in the CSF of RLS/WED patients in comparison with healthy controls, during the nighttime [13]. Moreover, as iron acts as a co-factor in the biosynthesis of dopamine, its insufficiency is thought to affect the dopamine metabolism into the brain [14]. Secondary RLS/WED, clinically similar to the idiopathic form, occurs under certain conditions, with end-stage renal disease, iron deficiency anemia and pregnancy being the most prevalent [15-19]. Other frequent medical conditions accompanied by RLS/WED include cardiovascular diseases, diabetes mellitus, peripheral neuropathy, rheumatoid arthritis and radiculopathy [20]. Isolated cases of RLS/WED in patients with Spinal Cord Injury (SCI) have also been reported and a few recent studies have documented an increased incidence of RLS/WED among SCI patients but its prevalence is still not well established [21-26]. The purpose of the present review is to evaluate the occurrence of RLS/WED in SCI patients, based on published data up to date, and examine the possible underlying pathophysiological mechanisms.

RLS/WED in SCI Patients: Frequency and Diagnostic Pitfalls

Kumuru et al. [25] conducted a cohort study in 154 cervicothoracic and 41 lumbosscral SCI patients to determine the severity and frequency of RLS/WED. They reported a higher prevalence of RLS/WED among SCI patients (17.9%) than it has been documented in the general population. In most patients, RLS/WED symptoms began during the first year of the SCI, appeared in higher frequency in lumbosacral patients and were mainly severe. Earlier, Telles et al. [24] had reported a high prevalence of RLS/WED and PLMS in a small group of cervical and thoracic SCI patients (100%), emphasizing on those evaluated as ASIA A, in comparison with healthy controls (18,30%).

Several studies and case-reports have also reported the occurrence of PLMS in SCI patients [27-32]. However, the diagnosis of RLS/WED in SCI patients seems to have been a challenge, due to the concomitant symptoms and their resemblance to other disorders, following SCI. Nilsson et al. [23] recorded 4 cases of SCI with RLS/WED, initially misdiagnosed and treated as Neuropathic Pain (NP) or post-traumatic spasticity, with poor responses to analgesic or antispastic treatment. The patients responded well enough to the dopamine agonist, pramipexole. Moreover, Kumuru et al. [26] reported 7 patients with RLS/WED after SCI, primarily diagnosed and treated as NP, due to the motor impairment and the coexistent NP, also with poor clinical outcome. RLS/WED was suspected since the sensory irritations worsened at rest, especially in the evening or during the night and was relieved by motion. The polysomnography revealed rhythmic limb movements, just before or during sleep, and the satisfactorious response to dopamine agonist supported the diagnosis of RLS/WED.

Challenges in Pathophysiology

Apart from the current knowledge concerning the pathogenetic mechanisms in RLS/WED, the high prevalence of the Syndrome, following SCI arises the interest in the pathophysiology correlating these two entities. The exact mechanism is not well known, while a lot of potential mechanisms have been proposed and gained popularity. The main of them will be described in the present mini-review. Spinal cord injury may release the RLS/WED symptoms by intermitting the inhibitory descending spinal pathways and thus, activating a Central Pattern Generator (CPG). A CPG has been suggested to have a major role to the clinical manifestations of RLS/WED, leading to spinal motor neuron Hyperexcitability [25,26]. The Flexor Reflex Afferent (FRA) has been found to facilitate the action of the CPG and has been proposed to be the implement through which CPG acts, and also responsible for the alleviation of RLS/WED symptoms by movement [33]. Damage to A11 nuclei, the only source of dopamine in the spinal cord, could lead to spinal cord Hyperexcitability and, subsequently, to PLMS and RLS/WED, as it has been demonstrated in animal models. Since the axons of A11 nuclei extend along the whole spinal cord, SCI could interrupt the dopaminergic tract and release RLS/WED symptoms [34-36]. Iron deficiency and comorbidities associated primary with the SCI could also exacerbate or lead to RLS/WED at the first place, and should not be ignored. Such circumstances include: possible bleeding, surgery, infection, antidepressants or neuroleptic medication [2]. On the other hand, certain medications, such as gabapentin, pregabalin or opioids that could improve RLS/WED, might be misleading and hide the severity of RLS/WED [26,37]. Neuronal plasticity in supraspinal regions has also been hypothesized to contribute to the pathophysiology of RLS/WED and PLMS after SCI [24]. Dysfunctional neuroplastic changes in the thalamocortical circuit have been observed in RLS/WED patients and might be related to the severity and the sensations disruption of RLS/WED [24,38]. Moreover, changes related to thalamic Hyperexcitability and the pain pathway have been described, possibly leading to sleep-arousals, disruptions of the limbic system and the perception of pain in RLS/WED patients [24,26,38]. Furthermore, neuroplastic responses in cortical and subcortical regions, related to hyperactivity and insomnia, might be involved in PLMS after SCI [39]. However, RLS/WED prevalence even in patients with complete interruption of the sensory and motor tract is a matter of further investigation.

Treatment of SCI Patients with RLS/WED

RLS/WED should be treated according to published guidelines [40,41]. These guidelines mainly refer to idiopathic RLS, as there is a lack of randomized controlled clinical trials for most secondary RLS except in patients on Hemodialysis. When addressing SCI patients as first step clinicians must be able to diagnose RLS/WED and then to determine whether symptoms require treatment. Treatment should be considered if RLS symptoms interfere with sleep or daytime function to an important degree [41]. Dopaminergic agonists have been approved for RLS/WED treatment. Iron deficiency may cause secondary RLS and respond to iron supplementation and is of high importance to check iron status and treat the iron deficiency first if indicated. In many cases correction of serum ferritin level (serum ferritin >75 mg/L) result in relief of symptoms. The beneficial results in SCI patients with RLS/WED after physical activity have been reported and concern the relief of limb movements, decrease

of depressive symptoms, improvement of sleep quality and their quality of life, in general [21,27,28]. The relief by physical activity can be attributed to the secretion of β-endorphins and dopamine during and after exercise, resulting in stimulation of the opiate and the dopaminergic system and, subsequently, in muscle relaxation, mediation of pain, neurochemical balance and reduction of RLS/WED symptoms [27,42]. Thus, physical exercise should be recommended as a therapeutic approach, to RLS/WED and PLMD patients.

Conclusions

RLS/WED occurs in high prevalence among SCI patients. The exact mechanisms are unclear, including activation of the CPG, damage of the dopaminergic tract and neuroplasticity. Since RLS/WED diagnosis might be challenging in SCI patients, due to comorbidity, clinicians should be aware and stick to the diagnostic criteria to avoid needless suffering in these patients. More studies need to be conducted, with larger cohorts, to further determine the incidence of RLS/WED in SCI patients. Future research should focus on elucidating the underlying pathogenetic mechanism that leads to the release of RLS/WED symptoms after SCI to assist the clinical practice and the development of new therapeutic approaches that could further improve the patients' quality of life.

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