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Editorial

A Glance into the Restless Legs Syndrome

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Restless legs syndrome (RLS) is a chronic, progressive, sensorimotor movement disorder of the limbs with abnormal sensations that often lead to an urge to move the legs that the patients cannot resist [1]. Since Sir Thomas Willis was the first to describe the syndrome in the 17th century, and the term "Restless Legs Syndrome" was used by Karl A. Ekbom in the 20th century, the synonym for RLS is "Willis-Ekbom Disease". The average years of onset is reported as the 3rd - 4th decades with a prevalence of 5-15 % which increases with age [2]. There is a well-known female gender and white race tendency for RLS. It can be primary with positive family history or secondary to the risk factors including low serum iron levels, iron deficiency anemia, pregnancy, end-stage renal disease undergoing hemodialysis, in particular, drugs (antipsychotics, antiemetics, lithium, tricyclic antidepressants), RLS can show a comorbidity with several conditions as Parkinson' s disease, diabetes mellitus, etc [2,3].

Since the patients have difficulty in describing the abnormal symptoms that often vary from numbness, itch, cramps, pain, electric-like, burning, pins and needles, pulling, to aches, the International Restless Legs Syndrome Study Group (IRLSSG) reported updated consensus 2014 which clarifies the syndrome. According to the criteria, there are essential criteria which have to meet for the diagnosis of RLS. The first criterion is the urge to move the legs with or without accompanying uncomfortable, unpleasant sensations in the legs. The second and third ones are the worsening of the symptoms when rest or inactivity and partial or total improvement during the movement, at least as long as the activity continues. This urge to move the legs and accompanying unpleasant sensations during rest should only occur in the night, or worsen in the evening or night rather than the day. The last criterion is that all these symptoms should not solely account for as symptoms primary to another medical or a behavioral situation [4].

As it can clearly be noticed from the diagnostic criteria, RLS has a remarkable circadian rhythm in terms of symptoms more prone to occur at night rather than daytime. Actually, this clinical manifestation emphasizes the importance of dopaminergic dysfunction in the pathophysiology of RLS, in which symptoms occur or worsen at night due to the circadian rhythm of dopamine. The improvement of symptoms in patient receiving low-dose dopaminergic agents and the worsening with dopamine antagonists suggests the role of dopaminergic dysfunction in RLS [5,6]. Since the pathology of RLS is known to be multifactorial, central and peripheral nervous system excitability central iron status, glutamatergic, noradrenergic changes as well as the genetic background with the susceptible single nucleotide polymorphisms such as BTBD9, MEIS1 also play a role in the pathophysiology of the disease [5,7,8]. Decreased central iron is one of the important contributors of RLS pathophysiology whether the systemic iron levels are normal or decreased, which is shown to effect the functions of neuromelanin-containing and dopamine-producing cells [5].

Based on the circadian rhythm of dopamine, and symptoms are prone to occur at rest in the evening and night time, in particular, patients with RLS frequently suffer from sleep disturbances like insomnia. Since night time sleep problems commonly lead to day time sleepiness and concentration difficulties affecting the quality of life of patients, they need to be treated with non-pharmacological methods and/or pharmacological regimens on a patient specific basis. Prior to the consideration of pharmacological treatment, sleep hygiene is one of the most important non-pharmacological approaches that should be maintained in all patients with RLS. Factors leading to sleep deprivation and insomnia should all be avoided with adjusting the sleep and awakening times regularly with a sleep diary, dropping the

drugs that can cause insomnia, recommending the patient not to take stimulants including caffeine at the night time in a patient specific-manner [6]. Other non-pharmacological approaches such as pneumatic compression before usual symptom onset, vibrating pads, repetitive transcranial magnetic stimulation where available, can be considered. All patients should be examined for systemic iron deficiency, as well, and in case of iron deficiency anemia, they should be treated with oral iron preferably with vitamin C formulations. As a take home massage, one should keep in mind that pregnant women, patients with renal failure are more prone to iron deficiency, and need to be treated. Moreover, all possible secondary causes of RLS should be checked, and treated [9].

Pharmacological treatment can be considered in patients with moderate-to-severe RLS that leads to deterioration in the quality of life. The first-line treatment agents are reported as dopamine agonists or alpha-δ-calcium channel ligands either in mono-or combination therapy by the IRLSSG in 2013. Benzodiazepines, and opioids can also be an option, in pain dominant patients, particularly. During the overall treatment period, clinicians should keep in mind the possible complications of treatment including failure of response to treatment in terms of tolerance development, side effects, occurrence of dopamine dysregulation syndrome, rebound, and augmentation [9-11].

Since RLS is a chronic and bothersome condition that frequently needs a long-term therapy, and there are challenging treatment-based complications still, further research and studies are needed to understand more about the pathophysiology of the disease, and to find better management options without long term complications as augmentation, and the others.

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