Sleep Board Review Questions: The Restless Sleeper

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A 50 year old female is being evaluated at the Sleep Clinic for difficulty falling asleep. She reports having unpleasant sensation in her legs causing an urge to move when she lies down to go to sleep. She feels better when she gets up and walks around. She is a restless sleeper and usually finds her bed-sheets on the floor in the morning. She does not have any other medical history. Her physical exam is normal.

Which of the following studies would be most helpful in diagnosis and management of this patient?

1. Nerve conduction study
2. Nocturnal polysomnography (PSG)
3. Serum ferritin level
4. Suggested immobilization test (SIT)

Correct!
3. Serum ferritin level

Restless legs syndrome (RLS) is a sensorimotor disorder. Symptoms usually involve the lower extremities but have also been reported in upper extremities. Hence, the more appropriate term is 'restless limb syndrome'. There are four characteristic features (1,2):

1. Urge to move legs, usually accompanied by uncomfortable and unpleasant sensations.
2. Urge to move and unpleasant sensations begin or worsen during rest or inactivity.
3. Urge to move and unpleasant sensations partially or totally relieved by movement.
4. Urge to move and unpleasant sensations occur or worse in the evening or night.

RLS is present in 4-15% of people in general population (2). Women are twice as likely as men to manifest symptoms of RLS, with multiparous women having higher risk for RLS compared with nulliparous women. It is the most common movement disorder in pregnancy, affecting 13% to 26% of pregnant women, and it tends to worsen as pregnancy progresses (3).

Diagnosis of RLS is based on the characteristic history. Sleep study or laboratory testing is not required to establish diagnosis. Supportive criteria include response to dopaminergic agents, periodic limb movements of sleep (PLMS) or during wakefulness (PLMW) seen on polysomnography, and family history of RLS. About 80% of patients with the RLS experience periodic limb movements of sleep (PLMS) and this can result in arousals, leading to sleep maintenance insomnia (4). However, PLMs are not necessary for diagnosis of RLS.

Dopamine agonists alleviate RLS symptoms and dopamine antagonists may exacerbate them. This supports the hypothesis that RLS is due to dopamine deficiency or decreased dopamine activity (5). Specific imaging studies have had mixed results, although dopamine deficiency in the nigrostriatum area of the brain is the likely culprit. Studies have shown increased tyrosine hydroxylase (the rate limiting enzyme in dopamine synthesis) concentrations in the substantia nigra, decreased numbers of D2 dopamine receptors in the putamen, and increased concentrations of 3-O-methyldopa in the cerebrospinal fluid (6). That led to believe that there is an upregulation of dopaminergic transmission and postsynaptic desensitization to dopamine.

RLS can be idiopathic or secondary. Idiopathic disease seems to have a strong genetic component, with a family history in 18% to 59% of patients. RLS may be associated with a variety of conditions, most often iron deficiency and uremia. Ferritin levels <50 mg/L (112 pmol/L) have been associated with increased symptom severity, decreased sleep efficiency, and increased PLMS with arousals in patients with RLS. Magnetic resonance imaging and autopsy specimens of substantia nigra have shown that brain iron stores are reduced in patients with RLS (7). Iron is an essential cofactor for tyrosine hydroxylase and seems to have a crucial role in dopamine metabolism. Iron

replacement therapy should be considered in patients with low ferritin level along with an appropriate work-up for the cause of iron loss. Absolute iron levels have not been correlated with RLS severity.

Medications such as anti-psychotics, anti-emetics (metoclopramide, prochlorperazine), anti-histamines (diphenhydramine), anti-depressants (selective serotonin reuptake inhibitors), nicotine, alcohol and caffeine are associated with worsening of RLS. Estrogen use and obstructive lung disease are associated with a higher incidence of RLS (8). There is an increased prevalence of RLS in type 2 diabetes and polyneuropathy only partially explains the relation between the two disorders (9). RLS, in turn, is associated with insomnia, depressive symptoms, anxiety and reduced quality of life (10). RLS may also be causally associated with cardiovascular disorders, but more data are needed to better understand this relationship (11).

Suggested Immobilization Test (SIT) is a research tool to diagnose RLS and is not commonly used clinically. It is designed to quantify sensory and motor manifestations of RLS during wakefulness and has high sensitivity and specificity (12).

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