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CLINICAL VIGNETTE

Pharmacologic Exacerbation of Periodic Leg Movements

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Abstract

Periodic Leg Movements of Sleep (PLMS) are a common finding on nocturnal polysomnograms (PSGs), and can pose a diagnostic challenge for the primary care physician when treating patients with sleep disturbances. PLMS are associated with different medical diseases, can be secondary to medications, and can be an intrinsic movement disorder. We describe a patient who developed medication induced PLMS resulting in severe maintenance insomnia. Identification and discontinuation of the offending medication produced a complete resolution of the patient's sleep disturbance. A brief literature review on common causes of secondary PLMS and Restless Leg Syndrome will be discussed.

Case Summary

A 25yr female without significant medical problems came to establish care with her Primary Care Physician (PCP) with the chief complaint of maintenance insomnia. Two months prior she developed nocturnal awakenings which occurred 2-4 times a night. Her usual bedtime was 10 PM and she denied difficulty falling asleep, or having any leg discomfort prior to falling asleep. Her nocturnal awakenings were spontaneous and they resulted in significant daytime fatigue and cognitive impairment. She did report that her boyfriend recently noted that she frequently moved and kicked her legs during her sleep, which disturbed his sleep on occasion. She denied having any other significant movements in her sleep such as sleep walking or seizure like activity.

She had recently moved to Los Angeles and had some anxiety adjusting to her new location and career, and was prescribed escitalopram by a previous physician. During this visit she was offered reassurance, and her maintenance insomnia was attributed to her psychosocial

stressors, and she was continued on escitalopram. The rest of her past medical history and physical exam was unremarkable. Her only other medication was an oral contraceptive which she had been taking for over 2 years. Basic laboratory testing including a CBC, Metabolic Panel, TSH, and Sexual Transmitted Disease panel were all within normal limits.

She returned two months later with persistent maintenance insomnia and a PSG was ordered. The PSG data revealed the following pertinent findings:

- increased arousal index = 19/hour
- increased PLMS index = 15/hour
- increased PLMS arousal index = 6/hour
- increased Wake After Sleep Onset = 70 minutes (normal <20 minutes)
- normal sleep latency = 20 minutes
- no evidence of sleep apnea or seizure activity

Based upon her PSG findings, it was suspected that her PLMS were secondary to her medications, and her escitalopram was gradually titrated off over a three week period which resulted in complete resolution of her sleep disturbance. Iron studies were ordered which revealed a ferritin level of 34. She was prescribed iron supplementation, however she self discontinued the iron because of it caused significant constipation, and because she felt that her sleep was back to normal. A follow up telephone call 3 months later revealed no sleep disturbance.

Discussion

PLMS are stereotypic and repetitive movements of the legs usually consisting of dorsiflexion of the ankle or the great toe, and sometimes of the knees. PLMS are a polysomnographic finding

and not a clinical disorder in themselves¹. On the other hand, Periodic Leg Movement Disorder (PLMD) is a clinical disease and is diagnosed if the frequent PLMS also cause a sleep disturbance and cannot be explained by another primary disorder. PLMD is a diagnosis of exclusion. Where PLMS is a common finding in the general population with a rate of 8%, primary PLMD is considered an uncommon disease². Patients with clinically pathological PLMS complain of sleep onset and/or sleep maintenance insomnia. They are generally unaware of the frequency and disruptive nature of their limb movements when asleep, and often the bed partner is affected more than the patient³.

RLS and PLMS and PLMD, while separate entities, are often mentioned together in the medical literature because their exacerbating triggers, diagnosis, and treatments have considerable overlap. RLS is a clinical diagnosis where the chief symptom is an urge to move the legs to relieve an uncomfortable sensation. These uncomfortable leg symptoms are usually present only at night and are relieved by leg movements only to return a short time later. PLMS on PSG is present in 85% of patients with RLS, and so is a suggestive but not specific finding for RLS⁴. Unlike PLMS and PLMD, RLS is a clinical diagnosis, and a polysomnogram is not required to make the diagnosis.

PLMS are associated with several different medical conditions (Table 1) such as RLS, low iron stores, and others. Several common medications can also cause secondary PLMS, the most common of which are Selective Serotonin Reuptake inhibitors (SSRIs) and Tricyclics (Table 2)⁵. The exact pathogenesis for PLMS is unknown but dopamine and iron metabolism impairment is thought to have a central role. Dopamine agonists relieve PLMS and RLS, and conversely dopamine antagonists and low iron states tend to exacerbate these conditions.

Treatment options for PLMS causing sleep disturbances include lifestyle modifications and pharmacotherapy. However, one of the most important principles in evaluating patients with sleep disturbance with PLMS is to first rule out secondary causes of PLMS. Life style modifications include reducing alcohol, nicotine, and caffeine products which have been know to exacerbate PLMS. Iron stores should be checked and iron supplementation offered to target ferritin levels above 50. For the primary care

physician pharmacotherapy options include dopamine agonists (Ropinirol and Pramipaxol) and gabapentine products. Gabapentin enacarbil is a new extended release version of gabapentin which is FDA approved for RLS, and also likely to work for PLMD.

Summary

PLMS are a common finding on PSGs and it is important to understand their causes when treating patients with sleep complaints. PLMS is a test finding where as PLMD and RLS are distinct clinical entities that require some form of treatment. Awareness of commonly prescribed drugs that can cause PLMS, while often under appreciated, will help the primary care physician in treating their patients with sleep complaints. In our case report, correctly identifying the secondary cause of PLMS was crucial in restoring normal sleep.

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Table 1

Medical Conditions Associated with PLMS

-Restless Leg Syndrome -Low Iron Levels (Ferritin <50) -Sleep Apnea -Diabetic Neuropathy -Neurological Disorders - Parkinsons, Multiple Sclerosis, - REM Behaviour Disorder, - Narcolepsy -Severe Chronic Kidney Disease

Table 2

Medications Associated with Secondary PLMS

SSRI's	Escitalopram Citalopram Fluoxetine
SNRI's	Venlafaxine
Tricyclics/ Tetracyclics	Amitriptyline Nortriptyline Mirtazapine
Antiemetics	Metoclopramide Compazine

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