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CASE REPORT

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Willis-Ekbom Disease, A Conundrum in Hemochromatosis: Case Report and Review of the Literature

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Abstract

Restless leg syndrome (RLS) also known as Willis-Ekbom Disease (WED) is a fairly common clinical entity traditionally associated with iron deficient states but emerging research hints at a more nuanced relationship. In this case presentation, a patient with hereditary hemochromatosis (HH) presented with RLS symptoms that worsened after phlebotomy. Diagnostic polysomnography revealed mild obstructive sleep apnea and significant periodic leg movements with associated arousals. With cessation of phlebotomy and initiation of nightly positive pressure, the patient's symptoms resolved. Review of the literature reveals similar associations between HH and RLS, and we hope this case raises awareness of an unexpected side effect of phlebotomy in these patients.

Keywords: Restless leg syndrome; Hemochromatosis; Hereditary hemochromatosis; Obstructive Sleep Apnea

Introduction

Restless Leg Syndrome (RLS)/Willis-Ekbom Disease (WED) is an incompletely understood clinical phenomenon that can significantly affect patients' quality of life. While it appears to have a genetic predisposition, it has also been linked to many other causes, with low iron levels being strongly associated with the presence of RLS. Hereditary Hemochromatosis (HH) is an inherited disorder of iron metabolism that leads to a global iron overload state. A standard treatment for HH is therapeutic phlebotomy. Here we present a patient with HH who developed significant nightly leg cramps that interrupted sleep after undergoing phlebotomy and was subsequently diagnosed with both RLS and Periodic Leg Movement Disorder (PLMD) as well as mild Obstructive Sleep Apnea (OSA).

Case Report

A morbidly obese 45 year old man (BMI=45) with a history of HH (homozygous C282Y), hypertension, and reflux presented with two months of worsening insomnia and non-refreshing sleep. He had no history of neurological problems or any illicit substance use. Home medications included Esomeprazole, Losartan, and Hydrochlorothiazide. He had undergone routine phlebotomy for the past 2 years to maintain ferritin levels ≤ 45 ng/mL for his hemochromatosis. He reported a sleep latency of 2 hours and frequent night time awakening due to "leg cramping" that improved with ambulation. Though he had no witnessed apneas, he did snore. Physical exam revealed a Mallampati IV airway, clear lung sounds, and no neurological deficits. Given the suspicion for both PLMD and Obstructive Sleep Apnea (OSA), a diagnostic attended polysomnogram was done that showed a Periodic Leg Movement (PLM) index of 154/hour and limb arousal index of 2.1/hour. Apnea-hypopnea index was 13/hour. CPAP titration study was performed approximately 1 month later with noted improvement in PLM index to 37/hour and limb arousal to 0.6/hour. With no interim phlebotomies and initiation of continuous positive airway pressure (CPAP) at 7 cm H_2O, he reported complete resolution of his RLS and insomnia symptoms 3 months later.

Discussion

Despite decades of research into RLS since its discovery in 1960, the diagnostic criteria remain clinical and essentially unchanged [1]. The exact pathogenesis of this syndrome continues to be elusive, but a clear inverse correlation with iron stores has been established. More recent histopathologic and imaging studies have shown that depletion of iron stores in dopaminergic neurons of the basal ganglia are strongly correlated with disease burden. The malfunction of these neurons in RLS helps explain why dopaminergic pharmacology is so effective initially in treating symptoms [2].

HH is known as an iron-overloaded state with significant morbidity caused by abnormal organ iron deposition. This case then raises an interesting question: if iron depletion in brain tissue causes RLS symptoms, how can a patient with hemochromatosis have the syndrome? One plausible explanation is the basal ganglia may be susceptible to iron depletion after venesection in these patients. Haba-Rubio et al. [3] noticed a similar unmasking of RLS symptoms in a patient undergoing phlebotomy for HH and MRI showed low iron signaling in the basal ganglia. A cross-sectional interview of hemochromatosis patients in Ireland found a remarkable 16% prevalence of RLS [4]. While there was a small subset of RLS patients with mild symptoms that preceded phlebotomy with high ferritin levels, patients in the cohort with more severe RLS were found to have lower serum ferritin levels at the time of the interview. Lanza et al. [5] reviews the latest research on the complex neurotransmission pathways surrounding RLS and agrees that a subset of patients clearly demonstrates disturbed dopaminergic response in response to reduced iron stores within the central nervous system. Much research remains to be done to tease out the underlying pathophysiology.

Our patient had certain sleep symptoms that could not clearly be attributed solely to his mild OSA. PAP therapy and cessation of phlebotomy markedly improved his symptoms, PLMs and limb arousal index. We believe the phlebotomies had a significant effect as the patient noted his symptoms waxed and waned in correlation to this intervention prior to any PAP initiation. However, CPAP may have had some effect as well as prior studies have shown a loose association between PAP therapy and improvement in RLS [6].

This case highlights the need to have a better understanding of the pathophysiology of RLS and the role of relative iron deficiency. Particularly, in patients with HH where such diagnosis would seem counter-intuitive, the clinician must consider RLS when patients develop associated sleep symptoms.

Additionally, this case questions the need to reassess the target iron levels that patients with HH may need, particularly if affected by RLS. Our patient had ferritin level targets of ≤ 45 ng/mL. Newer guidelines like those of the American Association for the Study of Liver Diseases (AASLD) recommend more lenient target ferritin levels of 50-100 ng/mL [7]. Such strategy may indicate a need for closer follow-up and perhaps less aggressive, but more frequent venesection.

We hope our case will encourage further investigation into this matter and additional reporting by clinicians that may have faced similar cases so as to further improve our understanding of this pathology.

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