CLINICAL VIGNETTE

Severe Restless Legs Syndrome in the Setting of Iron Deficiency and Chronic Blood Loss

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Introduction

Restless Legs Syndrome (RLS), also known as Willis-Ekbom Disease (WED), is a common sleep-related movement disorder characterized by an uncomfortable sensation in the legs associated with an urge to move the leg that usually improves with voluntary leg movement. One of the most common conditions associated with RLS is iron deficiency, with multiple studies demonstrating a correlation between low serum ferritin levels and the severity of RLS.[1] Treatment of symptoms often includes correction of ferritin levels as well as the use of pharmacotherapy for RLS. We report a rare case of severe RLS associated with iron deficiency in the setting of chronic blood loss secondary to esophageal varices.

Case Presentation

A 71-year-old male presented with a 20-year history of RLS. He has a history of depression on escitalopram as well as cirrhosis due to hepatitis C, complicated by recurrent bleeding esophageal varices. His symptoms were typical of RLS, characterized by an uncomfortable sensation in the lower legs which would only be mildly improved with movement of the leg and occurred exclusively in the evening. Over the last two years leading up to his presentation, he began to notice the onset of his RLS symptoms occurring during activities other than lying down in bed at night, including sitting in a movie theater as well as sitting on an airplane. Furthermore, he had started experiencing more severe symptoms at night-time which would interfere with sleep onset and subsequently caused him to develop a delayed sleep-wake phase.

During this time, his RLS medication regimen changed substantially. His symptoms had been controlled for many years on levodopa/carbidopa, after previously trying ropinirole, pramipexole, primidone, and gabapentin hydrochloride with no relief in his symptoms. By the time of his presentation, he was on a multi drug regimen which consisted of levodopa/carbidopa, pregabalin, baclofen, and a transdermal rotigotine patch.

Shortly before his presentation to sleep clinic, he had a colonoscopy and esophagogastroduodenoscopy due to subacute iron deficiency anemia. Esophageal varices, were found secondary to cirrhosis. He was taking oral ferrous sulfate which was eventually switched to IV iron infusions. After two iron infusions, his ferritin level remained low at 8. Gabapentin enacarbil was added to his medication regimen, which he tolerated well and which resulted in only mild improvement in his symptoms.

Discussion

According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), the diagnostic criteria for RLS include the hallmark features of the disease. An urge to move the leg, accompanied by an unpleasant sensation in the leg which improves with movement, occurs primarily at rest, and in the evening as opposed to during the daytime.[2] The causes of RLS are various and may be multifactorial, with iron deficiency being a more common etiology. As such, treatment of RLS often includes correcting ferritin levels less than 50 mcg/L. Though iron replacement alone does not always improve RLS symptoms, and often result in pharmacologic therapy with a dopaminergic agent or alpha-2-delta ligand. Prior to initiating pharmacotherapy, patients with RLS should be screened for iron deficiency and should receive iron supplementation when their serum ferritin is below 50 mcg/L.[3] Our patient's history of intermittent iron deficiency anemia due to recurrent bleeding esophageal varices in the setting of cirrhosis triggered episodes of worsening RLS symptoms. Consequently, frequent dose adjustments and the addition of adjunctive medications resulted in little to no improvement in his symptoms, as underlying iron deficiency persisted, and increased medications may exacerbated his symptoms.

Dopamine agonists, such as ropinirole and pramipexole, have been considered first line therapy for RLS. Our patient had previously tried both of these medications with no relief and eventually was started on levodopa/carbidopa which did provide relief for many years. Unfortunately, all of these medications have been associated with the development of augmenttation, a complication of long-term dopaminergic therapy.[4] In augmentation, RLS symptoms become more severe, appear earlier in the day, and may appear in previously unaffected body parts including the upper limbs.

Additionally, the natural progression of RLS is poorly understood, with a 30 to 60 percent spontaneous remission rate and up to two thirds of patients experiencing progressive symptoms over time.[5] This limited understanding of the natural history of RLS poses a challenge to the clinician, as augmentation in response to dopaminergic therapy may be difficult to differenti-

ate from natural progression of the disease. As a result, this often leads to modifications in the medication regimen which may lead to under-treatment of RLS symptoms or, conversely, worsening of augmentation. In our patient's case, the development of iron deficiency anemia, worsening of RLS symptoms in the presence of high doses of levodopa/carbidopa, and exacerbating factors including antidepressant therapy, are all pertinent factors that should be taken into consideration when treating patients with RLS.[6]

Conclusion

There is a need for further research to better understand the natural progression of RLS, the role of iron in the pathophysiology and treatment of RLS, and more potentially effective treatment options that extend beyond dopaminergic and alpha-2-delta ligand therapy.

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