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Case Report

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Restless Leg Syndrome: Role of Iron and Vitamin D Deficiencies

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ABSTRACT

Restless leg syndrome (RLS) is a common sensoriomotor neurological disorder. Its incidence increases with age. Despite its frequency, RLS can be underdiagnosed in clinical practice. Timely diagnosis of RLS, evaluation of exacerbating factors, management of symptoms, choosing appropriate treatments, and monitoring side effects, such as augmentation, all have clinical significance. Herein, we report a patient with severe RLS symptoms suffering from dopaminergic augmentation in whom excellent clinical improvement was achieved by tapering off the dopaminergic agent, treating iron deficiency anemia (an exacerbating factor), and providing vitamin D supplementation.

Keywords: Restless leg syndrome, augmentation, iron deficiency, vitamin D

INTRODUCTION

Restless leg syndrome (RLS) is a common sensoriomotor neurological disorder, with a prevelance of 6%-12% in the Western population. Clinically significant RLS requiring medical treatment affects 3% of the total adult population, and its incidence increases with age (1-3). Because the symptoms are subjective and there is no accompanying localizing physical deficit, this frequently seen disorder can be underdiagnosed in clinical practice. When diagnosed, the treatment itself has a risk of dopaminergic augmentation, which can also be underdiagnosed and incorrectly managed. Many factors have been shown to be associated with RLS; however, reduced central iron stores have the most powerful correlation with RLS clinicopathology (4). Also, although not yet present in the guidelines as a treatment option, serum vitamin D level has been shown to correlate with RLS symptoms (5, 6). Here, a geriatric patient with severe RLS is presented along with solutions to challenges encountered in the management of the symptoms of RLS and complications caused by dopaminergic treatment.

CASE PRESENTATION

An 81-year-old female was admitted with a severe complaint of an uncomfortable sensation in the legs, also with lesser severity in the arms and trunk, which was induced by rest and led to an urge to move. She was diagnosed with RLS 10 years ago. Her physician initially started pramipexole (0.250 mg) prior to bedtime, and then slowly increased the dose in the follow up and added gabapentin, because over time, she had worsening complaints that also occurred in the daytime. Although increased doses previously caused considerable improvement, these were not effective during the last three months. Since then, although she had taken the medicine at higher doses and at earlier times, the intensity of symptoms increased compared with when the medicine had first been administered. Restlessness occurred more quickly after rest and spread to her arms. In the meantime, her physician increased the pramipexole dosage to 0.75 mg twice a day. However, the patient reported that her complaints worsened with the increased pramipexole dosage; thus, she herself reduced the dosage to 0.50 mg twice a day 1 month ago, after which she reported partial relief.

On admission, neurological examination was normal. The symptoms were "very severe" according to the International Restless Legs Syndrome Study Group's restless legs syndrome rating scale (IRLSSGRS score: 34) (7). Laboratory tests revealed a low hemoglobin level of 5.9 g/dL (normal range: 10.8–14.2 g/dL) and ferritin level of 7.6 ng/mL (normal range: 4.6–204 ng/mL), with normal kidney and liver function. After transfusions of erythrocyte suspensions, oral iron supplementation was continued. The hemoglobin level increased to 11.9 g/dL and was stable at the follow up. After all, pramipexole was tapered off and gabapentin was switched to pregabalin. The patient's symptom severity decreased to mild (IRLSSGRS score: 9).

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Taking into account its possible effect on RLS symptoms, the patient's 25–OH–D3 vitamin level was measured and was found to be low (12 ng/mL, normal range 30–100 ng/mL), and replacement with 50.000 IU per oral once a week for 8 weeks was started. The patient reported total recovery (IRLSSGRS: 0) of RLS symptoms in just one month. After 3 months, the patient was still symptom free, taking 150 mg/day of pregabalin, 400 IU of vitamin D tablets and iron (11) capsules daily.

Written consent was obtained from the patient for publication of her medical information.

DISCUSSION

Restless leg syndrome, also called the Willis-Ekbom disease, is a common neurological sensoriomotor disorder characterized by an unpleasant or uncomfortable urge to move the legs; it occurs during rest, particularly in the evenings, and is transiently relieved by movement. As described in the International Restless Legs Syndrome Study Group's (IRLSSG) consensus diagnostic criteria (8), diagnosis primarily relies on clinical symptoms.

Many factors have been shown to be associated with RLS; however, reduced central iron store have the most powerful correlation with RLS clinicopathology. Because body iron stores (indicated best by the serum ferritin level) could correlate with the central nervous system's intracellular iron level, the relationship between serum ferritin and RLS symptoms was studied, and a decreased serum ferritin level (<50 mcgr/L) was found to be associated with RLS (4).

There are indirect evidences of dysregulation of the dopaminergic system in the pathogenesis of RLS, one of which is the clinical benefit of dopaminergic agents in this population. Dopamin agonists (DA) have been globally used as the first-line treatment for RLS. Pramipexole, ropinirole, and rotigotine have been approved by the FDA for moderate-to-severe RLS. During treatment with DAs, tolerance may occur; hence, the patient needs increasing doses of the drug or the addition of other medications.

However, the main problem in the long-term treatment with DAs is the dopaminergic augmentation. Augmentation is the drug-induced worsening of RLS symptoms in patients treated with dopaminergic agents and refers not only to loss of treatment efficacy but also the worsening of RLS beyond its severity at the time of treatment initiation (9). Diagnosis of augmentation can be challenging because it needs to be differentiated from the natural progression of RLS, its tolerance, end-of-dose rebound, and worsening caused by exacerbating factors (10).

When we consider the timeline of our case, in the first years of the disease, natural progression of RLS, tolerance to DA, and to a lesser extent, the end-of-dose rebound were the predominant factors for treatment failure. Later in the disease course, the patient had iron deficiency exacerbating RLS and finally augmentation.

One of the interesting points of our case is that severe RLS was the presenting symptom of severe iron deficiency anemia and not fatigue, palpitation, or shortness of breath, which caused the patient to seek medical care. Second, it demonstrates the importance of elimination of exacerbating factors while evaluating augmentation or treatment failure. The patient had been suffering from severe augmentation, which was tried to be overcome via dose increments that led to further worsening. Pramipexole dosage that the patient had used (1.5 gr per day) was twice the maximum dose recommended by the recent IRLSSG guidelines (10). If the iron deficiency had been discovered and treated earlier, the patient would have needed much lower doses of pramipexole, if ever, and augmentation would not occur.

Also, significant improvement after supplementation of vitamin D is noteworthy in our case. Although vitamin D deficiency is not reported as an exacerbating factor of RLS in the guidelines, it has been shown that vitamin D affects the nigrostriatal pathways, increases dopamine and its metabolites, and protects dopaminergic neurons against toxins (5). A pilot study by Wali et al. (6) indicated that correction of the vitamin D level improved RLS symptoms.

In the present case, full recovery was provided by treating the severe iron deficiency anemia (an exacerbating factor), tapering off the dopamin agonist, switching from gabapentin to pregabalin (an alfa 2delta ligand recommended by IRLSSG task for the treatment of RLS) (10), and finally by vitamin D replacement.

Patients with RLS can be attended by clinicians in different medical fields, such as pediatrics, obstetrics, hematology, neurology, or geriatrics. Timely diagnosis, evaluation of exacerbating factors, management of symptoms, choosing appropriate treatments, and monitoring side effects, such as augmentation, all are critical to prevent unnecessary investigations and/or inappropriate treatments.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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