Establishing the Law of Parsimony in a Case of Restless Legs Syndrome

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Restless legs syndrome (RLS) is a common movement disorder characterized by uncomfortable sensations in the lower limbs relieved by limb movements. Clinical studies have established a possible association between RLS and vitamin B12 deficiency but not a causal one. RLS has rarely been reported as an isolated neurological manifestation of vitamin B12 deficiency. In this case report, we described a 24-year-old young man with RLS who responded poorly to symptomatic therapy. The etiological evaluation suggested vitamin B12 deficiency secondary to pernicious anemia. The patient responded rapidly to vitamin B12 supplementation and clinical manifestations of RLS resolved, suggesting a possible causal relationship.

INTRODUCTION

Restless legs syndrome (RLS) is characterised by uncomfortable sensation in the legs with an urge to move the limbs, precipitated by rest and relieved with activity.¹² With a prevalence of 5%–15% in adults, RLS remains largely unrecognized and heavily reliant on clinical criteria.

The specific pathogenesis of RLS is not yet fully understood. The postulated mechanisms include iron deficiency, dopaminergic dysfunction, single nucleotide polymorphisms in RLS risk specific genes.³ Neuropsychiatric manifestations commonly associated with vitamin B12 deficiency include myelopathy, neuropathy and cognitive impairment. Furthermore, vitamin B12 deficiency coupled with elevated homocysteine has been linked with neurodegenerative diseases.²³ However, the studies focusing on vitamin B12 deficiency as a causative factor for development of RLS are scarce. We describe a patient with RLS as the sole presenting feature of vitamin B12 deficiency which showed complete resolution with vitamin B12 supplementation alone.

CASE REPORT

A 24-year-old young man complained of painful nocturnal sensations in both of his lower limbs that disturbed his sleep for the past 3 months. Walking provided some comfort but the symptoms returned when the patient lay down in a supine position. These symptoms tended to start a few minutes after lying in bed and would last for hours. The patient experienced sleep disruption but did not have any daytime symptoms. He was diagnosed with RLS, with a score of 25 on the Restless Legs Syndrome Rating Scale, indicating high severity. No abnormalities were detected upon neurological examination. Laboratory testing including complete blood count; liver, renal, and thyroid functions; serum vitamin D, folate, and iron levels; and nerve conduction studies all returned normal results. As per the updated algorithm for the management of RLS,¹ the patient was started on gabapentin 300 mg per day. Additionally, pramipexole was initiated at 0.125 mg and titrated up to 0.5 mg per day. Following 1 month of treatment, the patient reported no improvement. Further investigation revealed a serum vitamin B12 level of 45 pg/mL (reference range: 150 to 950 picograms per milliliter (pg/mL). Treatment with intramuscular hydroxocobalamin was commenced at 1,500...
micrograms daily for 7 days, and then, on alternate days for a week. Thereafter, the patient was maintained on a weekly dose for 1 month, and then monthly for 6 months. The treatment regime resulted in complete symptomatic improvement at the one-month follow-up (Restless Legs Syndrome Rating Scale score of 0). At 3 months, other medications (gabapentin and pramipexole) were discontinued, and the patient’s serum vitamin B12 level measured 1,200 pg/mL. An investigation into the etiology of vitamin B12 deficiency revealed a positive serum intrinsic factor antibody level of 115 units and positive serum parietal cell antibodies, confirming pernicious anemia.

**DISCUSSION**

RLS may be idiopathic (primary) or secondary to iron deficiency, diabetes mellitus, liver and renal diseases, inflammatory bowel diseases, pulmonary disease, and gastric surgery. In the only attempt of its kind, a prospective study from India identified 44 patients with RLS and studied their characteristics based on the presence or absence of vitamin B12 deficiency. RLS with co-existent vitamin B12 deficiency demonstrated specific features, such as shorter duration of symptoms, negative family history of RLS, prompt response to vitamin B12 supplementation, and successful taper of dopamine agonists without symptom relapse (unlike patients of RLS without B12 deficiency). In that study, the mean vitamin B12 level among the deficient patients was 148 pg/mL, and 15% had both ferritin and vitamin B12 deficiencies. Our patient had severe vitamin B12 deficiency but normal serum ferritin levels. Vitamin B12 deficiency is common in India. Low vitamin B12 levels alone has not demonstrated a causal association with RLS among Indian patients. However, patients with RLS have been found to have low vitamin B12 levels that proportionally correlated with symptom severity. A US study of pregnant women found that low serum folate was associated with RLS rather than vitamin B12 deficiency. Similarly, a German study found no differences in the vitamin B12 levels of healthy controls and patients with RLS. This discrepancy may be due to differences in the ethnicity and dietary patterns of the studied populations. For a causal relationship to be established, the presence of a temporal effect, previous associations, sustained improvement, and no alternative explanation for the improvement should be present. Our patient did not experience any symptomatic relief from standard RLS treatment including dopamine agonists and gabapentin. Instead, he responded exclusively to vitamin B12 supplementation.

The inhibition of methylation reactions due to vitamin B12 deficiency can lead to decreased production of many enzymes involved in dopamine metabolism, which may explain the development of RLS when vitamin B12 is deficient. Furthermore, elevated levels of inflammatory cytokines that are detected in patients with severe RLS are reduced by vitamin B12 supplementation. Interestingly, our patient did not present with other classical manifestations of Vitamin B12 deficiency, such as subacute combined degeneration of the spinal cord, peripheral neuropathy, neuropsychiatric symptoms, or optic neuropathy. Thus RLS may be an early and isolated feature of vitamin B12 deficiency. Vitamin B12 replacement at this stage may have circumvented the development of other serious vitamin B12 deficiency-induced sequelae.

Classically associated with iron deficiency, RLS can be independently associated with vitamin B12 deficiency. Moreover, RLS may be an early isolated manifestation of vitamin B12 deficiency. As such, we recommend vitamin B12 screening in patients who present with RLS. Furthermore, to prevent augmentation of the disabling symptoms, we suggest circumventing long-term treatment with dopamine agonists.

**Ethics Statement**

Written informed consent has been obtained from the patient for possible publication.

**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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**Author Contributions**


**Funding Statement**

None

**Acknowledgments**

None

**REFERENCES**
