Normal Ferritin in a Patient with Iron Deficiency and RLS

Susan Mackie, M.D.; John W. Winkelman, M.D., Ph.D., F.A.A.S.M.

Brigham and Women's Hospital, Boston, MA

A 58-year-old woman presented with restless legs syndrome (RLS). RLS had been present for 12 years and was initially problematic only at bedtime. Treatment with ropinirole 0.5 mg each night resulted in complete resolution of symptoms at that time. In recent years, symptoms had grown more severe and extended earlier in the day, prompting an increased dosage of ropinirole. At the time of presentation, she was taking 0.5 mg ropinirole at noon and 1 mg at bedtime. Despite this, she experienced discomfort as early as 10 a.m., escalating throughout the afternoon. She also reported considerable difficulty with sleep onset and maintenance, with 5-6 awakenings each night due to RLS, one of which was often prolonged (up to 3 hours).

Review of systems was notable for loud snoring and "tired" mood with low energy and poor concentration. Medical history included anxiety, for which she was being treated with sertraline; uterine cancer, recognized due to dysfunctional uterine bleeding and treated with a hysterectomy; and hyperlipidemia. Social and family history were unremarkable. Her only

medications were ropinirole as above, sertraline 150 mg, and simvastatin 40 mg. Physical examination was normal apart from a BMI of 48 (normal: 18-25), indicative of obesity. Polysomnography demonstrated reduced sleep efficiency (64%) due to several prolonged awakenings. It also showed severe obstructive sleep apnea (OSA) with an apnea-hypopnea index of 32/h. Serum iron studies were obtained:

- Ferritin: 85 ng/mL (normal: 12 ng/mL to 250 ng/mL)
- Iron: 28 µg/dL (normal: 26 µg/dL to 98 µg/dL)
- TIBC: 298 µg/dL (normal: 262 µg/dL to 474 µg/dL)
- Transferrin saturation: 9% (normal: 20% to 50%)

QUESTION

In addition to treatment of sleep apnea, what further evaluation or management do you recommend?

ANSWER

Iron supplementation is indicated. Although ferritin is within the normal range and above the cut-off generally used for iron supplementation in RLS (i.e., > 50 ng/mL), the transferrin saturation is abnormally low.

Oral ferrous sulfate 325 mg twice daily was begun. Six weeks later repeat iron studies showed:

- Ferritin: 125 ng/mL
- Iron: 125 µg/dL
- TIBC: 322 µg/dL
- Transferrin saturation: 39%

Accompanying this normalization of iron measurements, the patient reported complete resolution of daytime RLS symptoms. Because of this improvement (which was noted prior to initiation of treatment for OSA), the earlier dose of ropinirole was stopped. Nocturnal symptoms were also substantially alleviated, and the patient reported fewer overnight awakenings.

DISCUSSION

There is broad consensus that iron status should be evaluated in all patients with RLS.¹ Many clinicians believe that serum ferritin > 50 ng/mL is an adequate marker of iron sufficiency, and recently published practice parameters for the treatment of RLS do not mention measurement of other iron markers.² However, hematologists nearly universally recommend that ferritin not be used as a lone assay of iron status. Ferritin is increased in a number of conditions unrelated to iron status. This may cause a falsely normal value in an individual with truly low iron stores. Thus, an opportunity to ameliorate symptoms using iron supplementation may be missed. The ratio of serum iron to total iron binding capacity (a.k.a. transferrin saturation) may reveal decreased iron stores in such situations despite a falsely normal ferritin. Transferrin saturation < 20% is indicative of iron deficiency.

Ferritin is an acute phase reactant and as such, inflammation increases ferritin independent of any true effect on iron stores. Therefore, ferritin is most likely to be spuriously normal in the setting of inflammation. On the other hand, and in contrast to iron deficiency, the inflammatory state is distinguished by normal transferrin saturation. Thus, a low value is indicative of true iron deficiency.

Obesity, commonly observed in sleep medicine clinics, is perhaps the most common inflammatory state. Although seldom associated with overt anemia, obesity has been consistently associated with the elevated ferritin levels characteristic of inflammation.³

Obesity is also a risk factor for both iron deficiency and RLS.^{4,5} Iron deficiency among obese RLS patients may therefore be especially common. As in this patient, ferritin is likely to be a misleading indicator of iron status in this group.

Iron deficiency is a known risk factor for augmentation during treatment with dopamine agonists.⁶ Augmentation is an iatrogenic worsening of RLS due to the medication, frequently characterized by shorter time to symptom onset at rest or migration of symptoms earlier in the day. Augmentation may have been a factor in this patient's recent intensification of symp-

toms. If ferritin alone had been measured, the contribution of iron deficiency to this process would have been overlooked.

In addition to obesity, several other conditions that are common among RLS patients and pertinent to this patient deserve mention in this context. Obstructive sleep apnea, major depressive disorder, and chronic partial sleep deprivation have all been associated with increased levels of serum inflammatory markers. These problems are nearly ubiquitous in sleep medicine clinic, and all may be under-recognized by a clinician focused on treatment of RLS.

In this patient, obesity, obstructive sleep apnea, incompletely treated mood symptoms, and sleep deprivation due to RLS may all have contributed to normal ferritin despite iron deficiency. Low iron stores were, in turn, likely contributing to augmentation. In addition to identification and treatment of iron deficiency, adjustment of dopaminergic therapy to include multiple daily doses or a continuous release formulation could be helpful in this circumstance. Down-titration of the SSRI medication could also be of benefit. Objective documentation of symptoms before and after treatment interventions using a validated measure such as the International Restless Legs Scale (IRLS) is appropriate. Although the IRLS was not obtained in this patient, clinical interview confirmed that supplemental iron alone was sufficient to facilitate reduction in the ropinirole dose in this instance.

In light of the myriad subtle conditions in which ferritin alone may be falsely reassuring, clinicians are encouraged to evaluate iron status in all patients with RLS using both ferritin and transferrin saturation. This approach minimizes false negative conclusions about iron deficiency and maximizes the opportunity to provide symptom relief with iron supplementation alone.

PEARLS

1. Iron status should be evaluated in all patients with RLS.
2. In addition to ferritin, it is helpful to obtain transferrin saturation, which is the ratio of serum iron to TIBC.
3. Supplemental iron is recommended if ferritin is < 50 ng/mL or transferrin saturation is < 20%.

CITATION

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Address correspondence to: Susan Mackie, 1505 Commonwealth Avenue, 5th Floor, Brighton, MA 02135; Tel: (617) 783-1441; Fax: (617) 783-1458

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