Restless legs syndrome with augmentation successfully treated with IV iron

Vincent LaBarbera, MD; Lynn Marie Trotti, MD, MSc; David Rye, MD, PhD

Practical Implications

Consider IV iron infusions, when available, for the treatment of RLS augmentation in patients who have failed management of RLS with oral iron therapy, have severe symptoms, or are unable to tolerate oral iron supplementation.

Augmentation of restless legs syndrome (RLS) is iatrogenic worsening of symptoms that follows initial improvement on dopaminergic therapy.¹ With augmentation, symptoms become more intense, begin earlier in the day, and can spread to body parts previously unaffected. This is differentiated from tolerance (declining response to medication over time), in that symptoms during augmentation are worse than premedicated baseline symptoms. Augmentation increases patient discomfort, decreases quality of life, and is a troublesome clinical complication of treatment with dopaminergic agents.²

The severity of RLS at baseline and with augmentation is associated with low ferritin, reflective of a deficiency in mobilizable iron stores.¹ While oral and IV iron have been described as treatment of RLS,³ we are unaware of any studies assessing its efficacy for treating augmentation. Moreover, expert consensus opinion proposed by the International Restless Legs Syndrome Study Group proffers only guidelines on treating augmentation,⁴ absent controlled trials of any treatment modality.

Cases

All patients in this series were diagnosed with severe RLS and augmentation, based on the clinical constellation of symptoms meeting all primary criteria.² Supportive diagnostic criteria shared by these patients included initial beneficial response to dopaminergic agents of 10, 3, and 6 years, respectively, the presence of periodic limb movements of sleep, 2 patients documenting >10 per hour, and disruption of sleep onset/maintenance. Two of 3 patients acknowledged history of RLS in a first-degree family member. All 3 patients demonstrated iron deficiency absent identifiable bleeding diathesis from careful history and physical examination, and 2 underwent endoscopy/colonoscopy. Each patient was previously treated with oral iron. Two of the 3 patients failed oral iron repletion and 1 experienced intolerable side effects. Specific causes of poor gastrointestinal absorption (e.g., celiac disease) were not noted by the patients' gastroenterologist or primary care physician.

Patients received IV infusion of 2–4 courses of 125 mg ferric gluconate, with medication status preinfusion and postinfusion remaining constant, resulting in near-immediate relief from their augmentation symptoms (table).

DISCUSSION

To date, there have been no randomized controlled trials evaluating the treatment of RLS with augmentation; however, consensus expert opinion suggests multiple options to avoid and treat augmentation, including IV iron.⁴ We describe our positive experience in a small, unblinded, and uncontrolled series that shows that IV iron may be an effective and expeditious

From the Department of Neurology, Emory University School of Medicine, Atlanta, GA.

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Correspondence to: lbecke2@emory.edu

Table Demographic and clinical characteristics of 3 patients with augmenting restless legs syndrome (RLS) prior to and following treatment with IV ferric gluconate

	Patient 1		Patient 2		Patient 3	
Age, y/sex	81/F		71/F		66/F	
Race	Caucasian		Caucasian		Caucasian	
Family history of RLS	Yes		Yes		No	
PLMS documented	By history only		Yes		Yes	
Medication status^a	Pramipexole 0.5 mg, clonazepam 0.5 mg, fentanyl 50 mcg (patch), gabapentin 600 mg		Ropinirole 1 mg, alprazolam 0.5 mg		Ropinirole 2 mg, carbidopa/levodopa 50/200, clonazepam 3.5 mg, hydrocodone/acetaminophen 5/250 PRN	
Iron formulation/dose	Ferric gluconate, 125 mg × 2		Ferric gluconate, 125 mg × 3		Ferric gluconate, 125 mg × 4	
	Patient 1		Patient 2		Patient 3	
	Pre	Post	Pre	Post	Pre	Post
RLS severity scale (0–40)^b	36	7	>31	<10	>31	<10
Serum iron, µg/dL	23	36	13	50	60	95
Serum ferritin, ng/mL	7	37	14	49	48	256
Total iron binding capacity, µg/dL	454	374	529	398	319	312
Serum hemoglobin, g/dL	12.2	11.3	10.3	11.7	12.9	Not documented
Duration of benefit	3 wk		2 mo		3 mo	

Abbreviation: PLMS = periodic limb movements of sleep.

^aMedication status remained constant prior to and immediately following IV iron infusions.

^bSeverity assessed by the International Restless Legs Syndrome Study Group rating scale.

treatment. The patients were prescribed ferric gluconate, chosen for its availability at our site. Subsequently, benefit of ferric carboxymaltose on RLS without augmentation has been demonstrated.⁵ The duration of benefit is consistent with that reported for IV iron therapy of RLS without augmentation.⁵

Iron deficiency monitoring is often under the purview of the primary care physician. However, it is increasingly common for specialists to be the first to measure iron parameters. Ferritin measurement of <50–75 ng/mL is considered indicative of the need for iron supplementation in the RLS literature.⁴ Ferritin measurement is complemented by serum iron, total iron binding capacity, and transferrin saturation, because ferritin is an acute phase reactant.

While our experience suggests IV iron to be an encouraging treatment option for augmentation, differentiation of disease progression and augmentation remains challenging.² A potential limitation to our experience is that iron deficiency in the absence of dopaminergic treatment may result in RLS symptoms severe enough to mimic augmentation, despite pathophysiologic differences between those exposed and not exposed to dopaminergics. While iron deficiency has been proposed to affect RLS expressivity via upstream factors influencing availability of synaptic dopamine (e.g., iron is a cofactor for tyrosine hydroxylase, which converts tyrosine to dopamine, and oral iron deficiency reduces dopamine transporter number in rat models), overabundance of dopamine in the CNS favors postsynaptic D1 receptor stimulation, D1-related pain, periodic limb movements while awake, and temporospatial spread of symptoms.⁶ Although oral supplementation failed to replete 2 patients, and 1 experienced intolerable diarrhea, the selection criteria for patients who might benefit from

IV iron—based upon clinical characteristics and serologic measures of iron metabolism—remain ill-defined. Our 3 patients with augmenting RLS exhibited a wide range in peripherally derived measures of iron, from unambiguous iron deficiency with anemia (case 2) to modestly low serum ferritin (case 3). Yet IV iron provided nearly immediate relief in each instance. Given published safety data of IV iron,⁷ lack of current evidence-based treatment for augmentation, and the potential for placebo effect, controlled studies of IV iron for augmentation are warranted.

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V. LaBarbera: case series concept and design, acquisition of data, drafting/revising manuscript. L.M. Trotti: critical revision of the manuscript for important intellectual content. D. Rye: case series concept and design, critical revision of the manuscript for important intellectual content.

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