Intravenous iron dextran for severe refractory restless legs syndrome

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ABSTRACT

Reduced brain iron is strongly associated with restless legs syndrome (RLS). Oral iron supplements are commonly recommended for RLS but are largely ineffective secondary to poor absorption and poor tolerability at required doses. Intravenous iron has been shown to increase brain iron content. Surprisingly only a few reports have ever presented data on the clinical effect of high dose intravenous iron for RLS.

We identified 25 subjects (age 53.2± 11.9, 7 male) that receive intravenous iron for RLS refractory to conventional treatments. We infused 1 gm of iron dextran over five hours using a standard protocol.

The age of RLS onset was 32.6± 13.0 years and 15 had a positive family history of RLS. Overall, this was a very severe and medically refractory group. Baseline ferritins ranged from 5 to 248 (mean 43.5± 58.0) and 20/25 had ferritins of less than 50.

Two subjects did not complete their entire infusion due to anaphylactic type symptoms but are included. Overall, 2 subjects reported complete amelioration of all RLS symptoms, 11 reported marked improvement, 2 moderate improvement, 3 mild improvement, and 6 reported no improvement. For those with improvement, the duration of effect was highly variable, mean 15.8± 17.7 weeks, range 1-60 weeks. Twelve subjects have had multiple infusions. Adverse events included two subjects with hypotension that required termination of infusion. Two had a rash within a week of infusion and one reported a headache.

Iron dextran can dramatically improve refractory RLS but results are inconsistent and not predicted by patient demographics. Although burdened by a higher rate of anaphylactic reactions, iron dextran may be superior to other IV iron preparations.

INTRODUCTION

Restless legs syndrome (RLS) is a common neurological condition clinically defined by: 1. an urge to move the legs, 2. improvement during movement, 3. worsening while at rest, and 4. worsening in the evening and night. 1 The condition is strongly genetic and multiple gene alleles are reported to increase the risk of RLS. 2, 3 However, the mechanistic association between these genes and RLS symptoms is not known in any case.

The most consistent pathologic finding in RLS is reduced brain iron, and alterations in CNS iron related proteins. 4, 5 The combined pattern of iron proteins is not fully understood, but suggests alteration in homeostatic mechanisms within the brain rather than reduced availability across the blood brain barrier. RLS is also seen as a consequence of systemic iron deficiency. 6 Treatment of RLS with iron was first reported in the 1950s but then largely forgotten. 7 More recently, open label reports suggest oral iron may improve RLS patients with systemic iron deficiency, although the a controlled trial of oral iron for RLS in subjects with normal serum iron indices did not show efficacy nor did it increase serum iron measures. 8 Single open label reports of intravenous iron for idiopathic RLS 9 and uremic associated RLS 10 showed some benefit. We report our long term results of intravenous iron dextran for idiopathic RLS.

METHODS

All patients were seen in the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic over the past 10 years. Patients were retrospectively identified from our patient database or records from the Baylor Infusion Center, or prospectively identified since 2008. Formal inclusion/exclusion criteria do not exist but all subjects had severe RLS (IRLS>25) and were refractory to multiple other treatment modalities. Low serum iron indices were not an inclusion requirement. All subjects underwent a standardized infusion totalling one gram of iron dextran over 4-5 hours, following a 50 mg test dose to assess for allergic reactions. Patients were allowed epinephrine and diphenhydramine if hypotension or other worrisome signs developed. Patients had a pre-infusion serum ferritin and some had a 4-8 week post infusion ferritins. As clinically justified additional identical 1 gm infusions were done. Demographics, previous treatments, subjective responses, and adverse events were noted. Descriptive statistics are done.

RESULTS

We identified 25 subjects (age 53.2± 11.9, 7 male) who received at least one infusion of intravenous iron dextran. Demographics are summarized in Table 1. The age of RLS onset was 32.6± 13.0 years and 15 had a positive family history of RLS. Overall, this was a very severe and medically refractory group. The mean IRLS was 33.0± 5.1, n=22 (some subjects were infused before development of the scale), and patients attempted 7.5± 2.7 medications prior to infusion, including 3.6± 1.4 different dopaminergic drugs. Baseline ferritins ranged from 5 to 248 (mean 43.5± 58.0) and 20/25 had ferritins less than 50.

Two subjects did not complete their entire infusion due to anaphylactic type symptoms but are included. Overall, 2 subjects reported complete amelioration of all RLS symptoms, 11 reported marked improvement, 3 moderate improvement, 3 mild improvement, and 6 reported no improvement. For those with improvement, the duration of effect was highly variable mean 15.8± 17.7 weeks, range 1-60 weeks. The time until clinical improvement was 4.5± 3.6 days. Thirteen subjects stopped or reduced their RLS medications after infusion.

Twelve subjects have had multiple infusions. Subsequent response varied and was both less and more robust in different patients. Reasons for not continuing infusions (13 total subjects) include relative lack of efficacy (9), not needed due to RLS improvement (4), allergic reaction (2) and high serum ferritin (2). Several subjects had more than one reason for not continuing.

Patients that responded robustly to IV iron (n=13) tended to have a family history of RLS compared to those with moderate or no response (9/13 vs. 5/12, p=0.23). No other factor (age, age of onset, sex, baseline ferritin, response to dopaminergic medications) even tended to predict overall response.

Summary of Demographics and Response

	Age at Infusion	Age at Onset	IRLS	SEX	Fam Hx RLS	Total Meds Tried	Dopamine Meds	Initial Dopamine Response (0-4)	Iron Binding %	Pre-Infusion Ferritin	Response (0-4)
1	53.4	30	33	F	N	8	4	2	14	14	4
2	50.9	40	34	F	Y	3	2	4	7	7	4
3	48.8	39	38	F	N	10	5	2		27	3
4	60.2	24	33	F	Y	8	5	3	20	20	3
5	47.4	30	36	M	Y	10	5	3		248	3
6	64.3	15	37	F	Y	10	5	4	25	25	3
7	61.3	30	28	F	Y	5	5	4	13	13	3
8	68.6	13	36	F	Y	8	3	4	4	4	3
9	32.3	24	36	F	Y	11	4	3	36	36	3
10	60.8	42	29	F	Y	10	5	2	9	9	3
11	61.9	50	35	F	Y	11	6	3	26	26	3
12	73.7	62	25	M	N	3	0			13	3
13	56.5	25	32	M	Y	5	2	4		42	3
14	52.3	50	17	F	Y	5	2	3	9	9	2
15	55.4	40	37	F	N	7	4	4		11	2
16	21.1	19	28	M	N	11	3	0		163	2
17	43.8	41	32	F	N	6	3	2		33	2
18	43.4	34		F	N	9	3	3	5	5	1
19	63.5	25	39	F	N	9	4	4		80	1
20	46.4	35		M	Y	3	2	2		12	0
21	36.6	30	34	F	Y	6	3	4		30	0
22	57.5	43	39	F	N	10	4	3			0
23	50.9	10	34	F	Y	8	4	3	27	28	0
24	53.1	48	35	M	Y	5	2	1	25	100	0
25	66.4	15	33	M	Y	8	4	4	28	89	0

DISCUSSION

We report mixed, but generally favorable open label results from1 gm of intravenous iron dextran in a group of highly refractory RLS patients. Importantly, we showed good clinical tolerability to subsequent infusions of a long period of time in some cases. We were unable to predict who would respond based on patient demographics, serum iron, or previous response to medications, although those with a positive family history of RLS tended to respond better.

High molecular weight iron dextran has higher rates of anaphylaxis compared to iron sucrose or sodium ferric gluconate. All preparations are able to increase serum iron; however iron dextran is retained longer and absorbed by macrophages better than the other preparations. This may be important, as iron therapy in theory for RLS requires CNS iron accumulation, which might require days, rather than the shorter time allowed by other iron preparations. Patients usually report a delay of at least three days before achieving any benefit, which would also suggest that the iron requires extended transport into the brain. Iron dextran is proven to increase brain iron based on imaging studies. 11 Iron access to the brain is extensively regulated and incompletely understood. 4 It may require a large serum "overload" over a period of time to shunt iron into the brain. This might not be achieved with oral iron.

This is an open label and largely retrospective report, and as such must be interpreted with caution. RLS trials show a marked placebo response, although this was a group refractory to many other treatments, which would suggest less placebo effect. Furthermore the delay in response, after an acute one day intervention, is suggestive of a biological response. Although we have not observed any clinical symptoms after creating abnormally high serum iron stores, free iron is known to be toxic, and potentially facilitates several maladaptive biochemical pathways. We have not evaluated any of these subjects for evidence of oxidative stress, or any other metabolic assessment other than serum ferritin. Therefore our report can not adequately assess long term safety.

REFERENCES

1. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4(2):101-119.
2. Winkelmann J, Schormair B, Lichtner P, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 2007;39(8):1000-1006.
3. Schormair B, Kemlink D, Roeske D, et al. PTPRD (protein tyrosine phosphatase receptor type delta) is associated with restless legs syndrome. Nature Genetics 2008;40(8):946-948.
4. Connor JR. Pathophysiology of restless legs syndrome: evidence for iron involvement. Current Neurology & Neuroscience Reports 2008;8(2):162-166.
5. Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003;61(3):304-309.
6. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age & Ageing 1994;23(3):200-203.
7. Nordlander NB. Therapy in restless legs. Acta Med Scand 1953;145(6):453-457.
8. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. European Neurology 2000;43(2):70-75.
9. Earley CJ, Heckler D, Allen RP. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. Sleep Med 2005;6(4):301-305.
10. Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. Am J Kidney Dis 2004;43(4):663-670.
11. Earley CJ, Heckler D, Allen RP. The treatment of restless legs syndrome with intravenous iron dextran. Sleep Med 2004;5(3):231-235.