Iron and The Restless Legs Syndrome

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Study Objectives: Using blinded procedures, determine the relation between serum ferritin levels and severity of subjective and objective symptoms of the restless legs syndrome (RLS) for a representative patient sample covering the entire adult age range.
Design: All patient records from the past 4 years were retrospectively reviewed to obtain data from all cases with RLS. All patients were included who had ferritin levels obtained at about the same time as a polysomnogram (PSG), met diagnostic criteria for RLS and were not on iron or medications that would reduce the RLS symptoms at the time of the PSG.
Setting: Sleep Disorders Center
Patients: 27 (18 females, 9 males), aged 29-81 years.
Interventions: None
Measurements and Results: Measurements included clinical ratings of RLS severity and PSG measures of sleep efficiency and periodic limb movements (PLMS) in sleep with and without arousal. Lower ferritin correlated significantly to greater RLS severity and decreased sleep efficiency. All but one patient with severe RLS had ferritin levels ≤50 mcg/l. Patients with lower ferritin (≤50 mcg/l) also showed significantly more PLMS with arousal than did those with higher ferritin, but the PLMS/hour was not significantly related to ferritin. This last finding may be due to inclusion of two 'outliers' or because of severely disturbed sleep of the more severe RLS patients.
Conclusions: These data are consistent with those from a prior unblinded study and suggest that RLS patients will have fewer symptoms if they have ferritin levels greater than 50 mcg/l.
Key words: Restless legs syndrome; iron; ferritin; periodic limb movements; polysomnogram; sleep

RESTLESS LEGS SYNDROME is a well defined sleep-related disorder characterized by abnormal sensations in the limbs, particularly the legs, associated with an urge to move the affected limb. The symptoms become worse both at night and when the patient is at rest, but are immediately relieved by walking.[1,2] Approximately 80% of RLS patients also suffer from the associated periodic limb movement of sleep disorder, in which involuntary movements of the lower legs occur every 20 to 90 seconds during sleep.[2] When lying in bed awake, similar periodic leg movements occur which, along with the sensory symptoms, make it hard for the patient to initiate sleep.[3] Sleep efficiency is reduced and RLS patients, in extreme cases, are prevented from sleeping more than 3 or 4 hours per night, as they must continually move their legs about to alleviate the irritating crawling sensations.

Ekbom,[4] who provided the first modern scientific definition for this syndrome, reported on the presence of iron deficiency in some patients with RLS. Other clinical findings have since further associated iron deficiency with RLS. The syndrome is seen frequently in certain groups where iron deficiency is common—for example, in pregnant women and anemic subjects.[5] Recently, RLS has also been described as being a common finding in patients with end-stage renal disease (ESRD), where anemia is always a feature[6]; moreover, treatment with erythropoietin, which reduces the anemia, also reduces the RLS symptom of the

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Table 1.—Basic RLS tetrad

Four clinical characteristics, ALL are required for a diagnosis of RLS

1.	Desire to move the limbs usually associated with paresthesias/ dysesthesias
2.	Motor restlessness during waking
3.	Symptoms are worse or exclusively present at rest (i.e., lying, sitting) with at least partial and temporary relief by activity
4.	Symptoms are worse in evening/night (note: a) must be true independent of differences in activity levels in the day and night and b) for currently very severe cases this may no longer be true but then must have been true when symptoms were milder.)

These are from the definition established by the International RLS Study Group and published in Movement Disorders, vol 10, 1995 (2)

periodic limb movements in sleep (PLMS).[7] Plasma iron and ferritin levels have also been found to be inversely correlated to the occurrence and severity of drug-induced akathesia, a movement disorder with several symptoms similar to RLS.[8,9]

Data from treatment of RLS further support a putative mechanism for the relation between iron and RLS. Dopaminergic agents have been shown to be dramatically effective, at least in initial treatment, and are, in general, more effective than the other major treatment medications of opiates or gabapentine.[10-12] This has led to the view that decreased dopamine activity may play a significant role in RLS. Although the underlying pathophysiology that would relate dopamine to RLS remains unclear, it is known that iron is involved in a rate-limiting step required to convert tyrosine into levodopa, which is subsequently decarboxylated to form dopamine. Low levels of iron may therefore effect RLS by lowering activity of the dopamine system.[13,14]

Despite these clinical and theoretical findings, little work has been done to directly explore the relationship of iron status to RLS. In particular, there has been only one study relating iron status to RLS, and that was an unblinded study limited to very elderly patients. In that study, serum ferritin levels—accepted as the single most important indicator of iron deficiency—were used as the primary measure.[15] Elderly RLS subjects (ages 70-87) showed lower serum ferritin levels compared to control subjects, and the ferritin levels were inversely correlated with the subjective report of severity of RLS symptoms.[16] That study, however, was never extended beyond the elderly. It also evaluated RLS severity only by unblinded subjective reports, without objective measurements.

The goal of the present study was to further characterize the iron relationship for the full age range of adults with RLS, using standard blinded procedures with both subjective and objective assessments of the primary symptoms of RLS.

METHODS

Subject Selection

At the sleep disorders center, a standard clinical polysomnogram (PSG), including measurement of the periodic leg movements in sleep (PLMS), was commonly used to confirm a diagnosis of RLS. Starting about 4 years ago, serum levels of iron, total iron-binding capacity (TIBC), percentage iron saturation (% iron sat), and ferritin were routinely obtained on all patients with a diagnosis of RLS. To develop a consecutive case series, all charts of patients from the past 4 years (ending April 1997) with a primary or secondary diagnosis of RLS were reviewed for this study. The study sample comprised all patients diagnosed with RLS who had polysomnograms and a complete iron evaluation within 6 weeks of the polysomnogram.

Patients had been diagnosed as having RLS by a board-certified sleep disorders specialist, based on clinical history outlined by the RLS international study group[2] (see Table 1), and an all-night polysomnogram (PSG) test showing either significant periodic limb movements in sleep (>15/hour) or significant periodic leg movements while lying awake and resting during the sleep period (>1/minute). Patients were excluded from the study if they were on any iron supplementation within 2 months of the study or were recently taking medications that might significantly alter the PSG results, including opiate or dopaminergic agents, clonazepam, gabapentine, and tegretol.

MATERIALS

The records were reviewed for the following patient characteristics: (1) gender; (2) age; and (3) RLS severity. The RLS severity was rated based on the usual earliest time after 12:00 noon that the patient experienced either motor or sensory RLS symptoms prior to starting any treatment: 1 for mild when onset was only at or after bedtime, 2 for moderate when onset was at or after 18:00, and 3 for severe when onset was before 18:00.[17] This is an established measure of RLS severity which has been used in prior studies, has been routinely obtained on all of our patients for at least the last 5 years, and has a blinded inter-rater agreement of 92% for trained clinician raters.[17] Data collection for RLS severity was obtained by trained clinician raters blinded to the iron and sleep data.

All patients had a standard all-night clinical PSG, which included recording sleep EEG (C3-A2, C3-O1), bilateral eye movements, respiratory effort (abdominal and thoracic), airflow (oral and nasal), submental EMG, and bilateral anterior tibialis EMG. Sleep was scored according to the Rechtshaffen and Kales criteria,[18] and the PLMS were identified during sleep using the modified Guilleminault criteria described by Coleman.[19] The dura-

Table 2.—Patient characteristics and related normal values for the laboratory used.

Patient Characteristics		Laboratory normal range (where appropriate)	Number of patients with abnormally low values
Number:	27	***	***
Age : Average (range)	62.7 (29 - 81)	***	***
Female to Male: Ratio(numbers)	18 : 9	***	***
PLM/hr: Average (range)	53.7 (2 - 193)	***	***
Ferritin(mcg/l): Average (range)	60.0 (5 - 229)	10 - 300	3
Iron (mcg/dl): Average (range)	70.3 (20-174)	male: 45-160 female: 30-160	2
Total Iron Binding Capacity (TIBC) mcg/dl Average (range)	355 (210-573)	260 - 450	1
% Iron Saturation Average (range)	21.4 (3.5-51.0)	11 - 46	4

note: Ferritin is a protein that provides storage of iron, Iron is the amount of iron in the sample, Total Iron Binding Capacity is the maximum amount of iron which could be in the sample, and % Iron Saturation, calculated as: (Iron/ TIBC) x 100, measures percentage of the maximum amount of iron actually used.

Table 3.—High- compared to low- ($\leq$ 50 mcg/l) ferritin groups: number of patients and averages of measurements.

Ferritin	Number	RLS Severity	Sleep Eff.	PLMS/hr	%PLMS Arsl	PLMS Arsl/hr
High >50	10	1.4	77.1	35.9	43.1	9.0
Low ²50	17	2.5	44.5	64.1	40.6	22.7
t test			-4.1	1.5	-0.22	1.76
one-tail, p			< 0.001	< 0.07	ns (>0.10)	< 0.05

't' test for difference between means could not be used on RLS severity since that was the criterion variable for determining the split into high and low ferritin groups. It could, however, be applied to the other data to test that the high ferritin group also showed significantly better sleep measurements than the low ferritin group, a directional hypotheses as indicated by the one-tail p values. The two-tail p values would be twice the one-tail values.

tion of the EMG increase for the movements must be 0.5-5.0 seconds, the inter-movement interval must be 5-120 seconds, and there must be at least three such movements in a series.

The following sleep variables were obtained independent of the clinical rating of severity: percentage sleep efficiency; number of PLMS per hour of NREM sleep; percentage PLM in NREM sleep with arousal; and number of PLMS in NREM sleep with arousals per hour. Since PLMS are suppressed in REM sleep, only the NREM sleep was considered for PLMS.

The measures of iron status were similarly obtained for all patients from serum tests for iron levels, ferritin levels, % iron sat, and TIBC.

Data Analyses

We hypothesized that lower ferritin relates to: (1) increased RLS severity; (2) increased periodic leg movements per hour (PLMS/hour); and (3) decreased sleep efficiency. We were also interested in an exploratory evaluation of the following secondary hypotheses: (1) lower ferritin relates to both increased number of PLMS with arousal/hour and increased percentage of PLMS associated with arousal; and (2) lower values of other serum iron measurements correlate with RLS severity, sleep efficiency, PLMS/hour, PLMS with arousal/hour, and percentage of PLMS with arousal.

The analyses of iron data in relation to outcome and subject variables were based on regression analyses. Statistical tests for the three primary hypotheses based on significant findings in a prior study[16] used 0.05 as the critical value (alpha) for type-I error. The Bonferroni adjustment to alpha was used for the exploratory analyses where there were 15 regressions calculated.

As an extension of the first primary hypothesis, it was expected that the relation between the ferritin levels and subjective RLS rating of severity would provide a critical value for separating the patients into high- and low-ferritin groups. It was further hypothesized that these groups would show significant differences in the objective sleep measurements with better sleep for the higher ferritin group. Since the hypothesized relationships were directional, one-tailed t-tests were used.

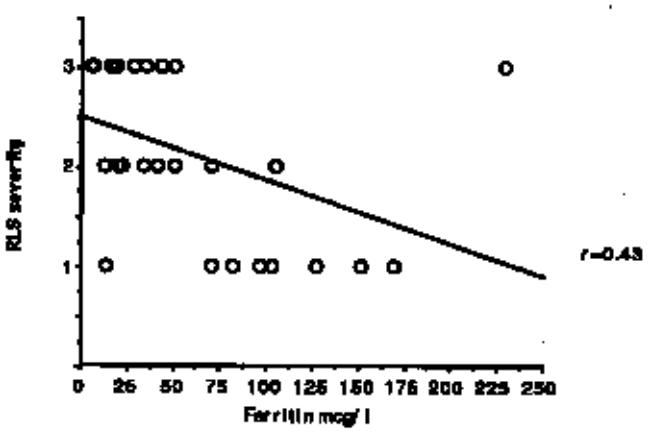

Figure 1.— Ferritin relation to subjective clinical rating of RLS severity

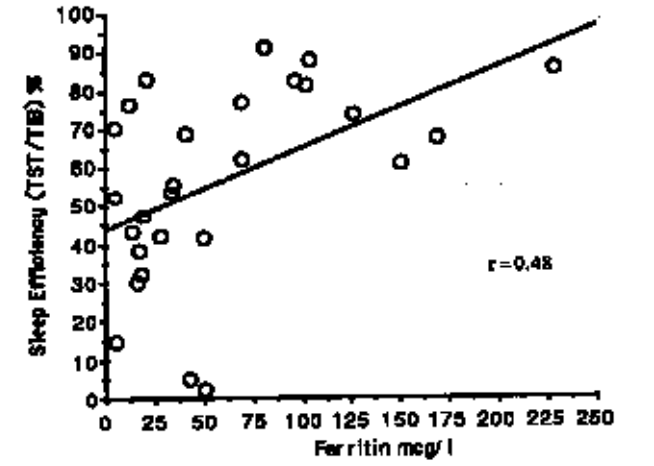

Figure 2.—Ferritin relation to sleep efficiency (Total Sleep Time as a percentage of Time in Bed).

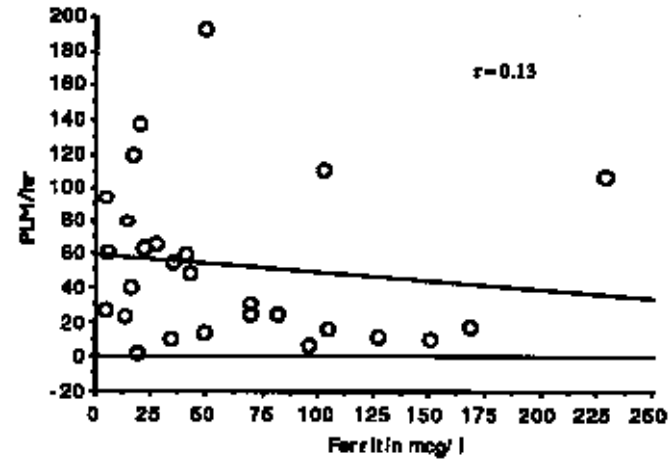

Figure 3.—Ferritin relation to PLMS/hr in NREM sleep.

RESULTS

Subjects

A total of 27 patients (18 females and 9 males) met the criteria for entry into the analyses. This represented 26% of all the RLS patients presenting for initial RLS treatment during this time period. Twenty-six patients were excluded because they did not have PSG evaluations owing to limitations imposed by insurance reimbursement. One patient was excluded for failing to stay to complete a full PSG. The remainder of the patients were excluded for not having ferritin levels determined within 6 weeks of the PSG, in most cases because of either insurance reimbursement limits on repeating tests or delays in evaluations after the PSG. The ferritin levels were obtained only because of the diagnosis of RLS and not because anemia was suspected for other reasons. Only three of the patients had abnormally low ferritin values, and only two had low iron values (Table 2). None of the patients in this sample who had been clinically diagnosed with RLS were rejected because of low PLMS rate. The ages of the subjects ranged from 29 to 81 years (mean=61.7; standard deviation=13.9). A summary of subject characteristics, including serum iron test results, is presented in Table 2.

Ferritin Relation to Subjective Rating of RLS Severity

Ferritin correlated significantly with RLS severity (r=0.43, p=0.02). The most-severe RLS symptoms occurred, with one exception, for patients with ferritin levels of 50 mcg/l or less (Fig. 1). The only exception was essentially an outlier who, despite high normal ferritin levels, had severe RLS; all other ferritin values for severe RLS were fairly evenly distributed at 50 mcg/l or below. Thus, considering >50 as high ferritin and ≤50 as low ferritin, 91% of severe, 75% of moderate and only 12% of mild RLS occurred with low ferritin.

Ferritin Relation to Objective PSG Sleep Variables

Ferritin correlated significantly with sleep efficiency (r=0.48, p=0.01), with sleep efficiency decreasing as serum ferritin decreased (Fig. 2). The minimum sleep efficiency for patients with high ferritin (>50) was 55%, compared to 2% for patients with low ferritin. The PLMS per hour did not show a significant relationship to the ferritin level (Fig. 3). If, however, the two outliers, both men with very high PLMS despite high ferritin levels, are removed from the analyses, the correlation is statistically significant (r=0.41, p=0.04).

Ferritin Relation to PLMS with Arousal and to Subject Variables

Ferritin levels were not found to be significantly relat-

Table 4.—Linear correlations ('r') from exploratory analyses of iron status measurements other than ferritin in relation to RLS severity and objective sleep variables.

	RLS Severity	Sleep Eff.	PLMS/hr	%PLMS Arsl	PLMS Arsl/hr
Iron	0.36	0.05	0.12	0.09	0.11
TIBC	0.29	0.11	0.26	0.10	0.10
% iron sat	0.51	0.10	0.04	0.18	0.02

all r values are not statistically significant (p>0.05) with Bonferroni correction for number of tests.

ed to either the percentage of PLMS with arousal or the average number of PLMS with arousal per hour of NREM sleep. Evaluating the relationship of ferritin to patient characteristics showed no significant correlation to the patient's age (r=0.29, p>0.10), but there was a gender effect. Females had significantly lower levels of ferritin (averages ± standard deviations: 44.3±47.1 vs 91.3±64.4, t=2.18, p<0.05). A multiple regression including both gender and ferritin showed that ferritin levels were still significantly related to RLS severity (partial F=5.46, p<0.03) and sleep efficiency (partial F=6.33, p<0.02), and that gender was not a significant factor in any of the regressions (partial F<0.21, p>0.2).

High- Compared to Low-ferritin Patient Groups

Using the ferritin level of greater than 50 mcg/l to define high ferritin showed that patients with low compared to high ferritin had significantly lower sleep efficiency (t=4.14, p=0.0002).

The low- compared to high-ferritin groups also showed statistical significance for greater PLMS with arousal/hour of NREM sleep (t=1.757, p=0.045). The PLMS/hour were much greater for the low-ferritin group, but this was not a significant difference (t=1.53, p=0.07) (see Table 3). The percentage of PLMS with arousal was about the same for the high- and low-ferritin groups.

Exploratory Analyses of Iron Status Variables Other than Ferritin

None of the other iron-status variables of iron, TIBC and % iron sat were significantly related to the subjective RLS severity rating or the objective sleep variables. The best correlation was between % iron sat and RLS severity (r=0.51, p>0.10 with Bonferroni correction for number of tests) (see Table 4).

DISCUSSION

The results from this study confirm two of our three primary hypotheses, ie, that low plasma ferritin correlates significantly with increased RLS symptoms and with decreased sleep efficiency. This blinded determination of subjective RLS symptoms confirms in a broad age range of adult patients the results of O'Keeffe's unblinded study, which was limited to patients over 70 years old.[16] It significantly extends O'Keeffe's findings by demonstrating that ferritin is also associated with other, more objective, measures of RLS symptoms. It is worth noting that for subjective ratings, the ferritin-severity correlation in this study of 0.43 is similar to O'Keeffe's correlation of 0.53. The findings are also consistent with past studies showing ferritin levels were inversely correlated to both the occurrence and subjective clinical rating of drug-induced akathesia, another dopamine-related disorder with symptoms similar to RLS.[8,9]

As in O'Keeffe's study, this study failed to find any significant correlation with serum iron levels. Moreover, in this study, the other iron-status indicators of TIBC and % iron sat were also not significantly related to any of the RLS assessments. The % iron sat, however, showed a remarkably strong—although not statistically significant—correlation to RLS severity (r=0.51, p>0.10); unlike ferritin, it did not show any indication of significant correlation with any of the objective sleep parameters. This result should, nonetheless, be considered in future studies. Overall further study of iron storage and transport in relation to significant features of RLS may prove useful for determining pathophysiology associated with RLS.

The sleep-efficiency results objectively confirm both our hypothesis and the relation of iron to a major complaint reported by RLS patients—disturbed sleep. The subjective sleep complaints of these patients center more on the inability to fall asleep or return to sleep than on the number of awakenings or the amount of movement while asleep. Sometimes the patients are even unaware of problems with leg movements while asleep. The sleep-efficiency measure is thus closer to the subjective complaints than is the assessment of PLMS. The values of sleep efficiency are also remarkably low in this population, with an average of 56.5% and a range of 2% to 91%. Three of the 27 patients had sleep efficiencies less than 15%. Given the clinical significance of this objectively measured symptom, the highly significant correlation with ferritin provides strong support for the clinical significance of lower ferritin levels.

Unexpectedly, this study did not confirm the hypothesized relationship between ferritin and PLMS/hour. There was a marked average difference in PLMS/hour between

high- and low-ferritin groups, but the variance was also great and the differences were not statistically significant. There are at least three possible explanations for the failure to confirm this hypothesis. First, there were two marked outliers with high PLMS rates and high ferritin. Without these outliers, there was a statistically significant relation between PLMS and ferritin. It is possible that they have a different etiology for their PLMS; however, there were no obvious subject variables accounting for this difference, except that both of these subjects were males. These outliers could also reflect the results of chance variation, particularly given the large night-to-night variability in PLMS rates[20,21]; a larger sample size is, therefore, needed to further evaluate this relationship. Second, it is possible that the more severely affected RLS patients have such profound movements that when they occur, they tend to lead to either an arousal or a full awakening, thereby reducing the PLMS rate. Finally, it seems possible that the reduced iron status, as reflected by ferritin levels, may exacerbate the sensory disturbance of RLS while awake more than the motor disturbance in sleep. This view would, however, not be consistent with the results from the dialysis patients, who show marked PLMS which are reduced significantly by treatments aimed at reducing the anemia associated with this condition.[7]

While these results strongly support a relationship between ferritin and the severity of symptoms for patients with RLS, they do not in any way indicate that ferritin provides a screening test for RLS. The ferritin values for the RLS patients were mostly in the low-normal range, so many individuals will have ferritins in this range but will not have RLS. Even among patients with RLS where the ferritin is related to severity, the relationship is far too variable to permit ferritin to be used as an assessment of the severity of RLS. The cost of the ferritin test (about $90) must also be considered when deciding how often to obtain this test.

The selection of the criterion of 50 mcg/l for the high-vs-low ferritin groups was obtained post hoc from the subjective reports of clinical severity, which showed that all of the subjects with severe RLS had ferritin levels of 50 mcg/l or less, except for one apparent "outlier" (Fig. 1). The statistical analyses of differences between these groups document that for this patient sample, this critical value for ferritin also produces expected significant differences in objective sleep parameters. A repeat study is needed to confirm this critical value, but the large significance obtained from these data strongly support the clinical utility of this criterion. Thus, these data suggest that the ferritin level needed to minimize RLS symptoms should be at least 50 mcg/l. This is considerably above the usual normal minimum of 10 mcg/l. While it is clear from these data and those of O'Keeffe that a ferritin below 50 mcg/l is associated with more-severe RLS, this does not demonstrate that increasing ferritin levels will lead to reduced symptoms. O'Keeffe, however, also reported a limited therapeutic trial with iron replacement in 15 patients, which showed clearly reduced RLS symptoms for patients whose initial ferritin (before iron replacement) was less than 45 mcg/l, but marginal benefit for those with initial ferritin of 45-100 mcg/l. The critical level he reports of 45 is similar to that of 50 mcg/l found in this study. These treatment data provide some further support for a causal relation between low ferritin and increased RLS symptoms. There is now a need for a blinded, placebo-controlled prospective study with iron replacement treatment in order to more completely characterize the relation of iron to RLS and to better determine the minimum desired ferritin for patients with RLS.

REFERENCES

1. Ekbom K. Asthenia crurum paraesthetica (irritable legs). Acta Med Scand 1944;118:197-209.

2. Walters A, Aldrich M, Allen R, Ancoli-Israel S, et al. Towards a better definition of the restless legs syndrome. Movement Disorders. 1995;10:634-642.

3. Montplaisir J, Godbout R, Boghen D, DeChamplain J, Young S, Lapierre G. Familial restless legs with periodic movements in sleep: electrophysiolog, biochemical, and pharmacologic study. Neurology 1985;35:130-134.

4. Ekbom KA. Restless legs syndrome. Neurology. 1960;10:868-873.

5. Norlander N. Therapy in restless legs. Acta Med Scan 1953;143:453-457.

6. Winkelman J, Chertow G, Lazarus J. Restless legs syndrome in end-stage renal disease. Am J Kid Dis. 1996;28 (in press):372-378.

7. Pressman M. PLMS and RLS in end stage renal disease. In: Allen R, ed. Course at 11th annual APSS meeting , Advances in Diagnosis and Treatment of the Restless Legs Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS). San Franciso: American Sleep Disorders Association; 1997.

8. Brown K, Glen S, White T. Low serum iron status and akathisia. Lancet 1987;1:1234-1236.

9. Barton A, Bowie J, Ebmeier K. Low plasma iron status and akathisia. Journal of Neurology, Neurosurgery, and Psychiatry 1990;53:671-674.

10. Allen RP, Kaplan PW, Buchholz DW, Earley CJ, Walters JK. Double-blinded, placebo controlled comparison of high dose propoxyphene and moderate dose carbidopa/levodopa for treatment of periodic limb movements in sleep. Sleep Res 1992;21:166.

11. Earley C, Allen R. Pergolide and carbidopa/levodopa treatment of the restless legs syndrome and periodic leg movements in sleep in a consecutive series of patients. Sleep 1996;19:801-810.

12. Kaplan P, Allen R, Buchholz D, Walters J. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep 1993;16:717-723.

13. Blake D, Williams A, Pall H, Fonseca A, Beswick T. Iron and akathisia. British Medical Journal 1986;292:1393.

14. Earley C. Word from the doctors: The importance of iron in restless legs syndrome. The Night Walkers Newsletter 1997.

15. Cook J, Skikne B. Iron deficiency: definition and diagnosis. Journal of Internal Medicine 1989;226:349-355.

16. O'Keeffe S, Gavin K, Lavan J. Iron status and restless legs syndrome in the elderly. Age and Aging. 1994;23:200-203.

17. Allen R, Earley C. Augmentation of the Restless Legs Syndrome with Carbidopa/levodopa. Sleep 1996;19:205-213.

18. Rechtschaffen A, Kales A, eds. A manual of standardized terminol-

ogy, techniques and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service/Brain Research Institute; 1968.

19. Coleman R. Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C, ed. Sleeping and waking disorders: indications and techniques. Menlo Park, Ca: Addison-Wesley; 1982:265-296.

20. Coleman R, Bliwise D, Sajben N, deBruyn L, Boomkamp A, Menn M, Dement W. Epidemiology of periodic movements during sleep. In: Guilleminault C and Lugaresi E, eds. Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution. New York, N.Y.: Raven Press; 1983: 217-229.

21. Bliwise D, Carskadon M, Dement W. Nightly variation of periodic leg movements in sleep in the elderly. Arch Gerontol Geriatr 1988; 7: 273-279.