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Original Article

The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: Association with ferritin levels

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ABSTRACT

Objectives: The aim of the study was to prospectively examine all patients with a diagnosis of RLS consulting a sleep disorders clinic and to assess RLS severity and augmentation and their associations, including ferritin levels.

Methods: Patients were stratified into patients with RLS as ancillary diagnosis, RLS sufferers without current augmentation and RLS sufferers with current augmentation. Work-up included RLS severity scales and blood biochemical variables including indices of iron metabolism.

Results: In an 18-month period, 302 patients with RLS (183 women, 119 men; mean age, 59.1 ± 13.7 years) were recruited. RLS was considered idiopathic in 291 patients (96.4%). Most patients (240, 79.5%) were RLS sufferers, whereas the remaining 62 (20.5%) had RLS as ancillary diagnosis. Nineteen out of 162 patients treated with dopaminergic agents (11.7%) had current augmentation. Almost one-third of all patients (31.1%) had ferritin levels <50 μg/l. Patients with an ancillary diagnosis of RLS had higher ferritin levels than RLS sufferers without current augmentation. The lowest ferritin levels were present in RLS sufferers with current augmentation 132.8 ± 98.0 μg/l vs. 100.6 ± 84.5 μg/l vs. 55.8 ± 43.6 μg/l; $p = 0.002$). Patients with augmentation did not differ from non-augmented patients regarding age, gender, RLS etiology, presence of previous augmentation, or any other documented comorbidity ($p > 0.05$).

Conclusion: The severity spectrum of RLS in this clinical cohort ranged from the ancillary diagnosis of RLS to augmented RLS. There was an inverse correlation between RLS severity and ferritin levels. Patients with current augmentation had the lowest ferritin levels. Our data further strengthen a putative role of low iron stores as a potential aggravator of idiopathic RLS. Moreover, low ferritin might represent a potential biomarker of RLS augmentation under dopaminergic therapy.

1. Introduction

Restless legs syndrome (RLS) is a common yet frequently underdiagnosed and under-treated sensorimotor disorder [1–4]. Approximately one-third of subjects with RLS are considered RLS sufferers [1,2,4]. Dopamine agonists are currently considered first line therapy in RLS [5]. The main long-term complication of dopaminergic therapy is augmentation [6]. Patients with augmentation experience a worsening of RLS symptoms despite therapy, with symptom severity exceeding the state before treatment. Augmentation is defined as a paradoxical response to RLS therapy or an earlier onset of RLS by 4 h or less if additional symptoms are present [7]. In long-term pharmacological studies, augmentation was found to occur in up to 72% of RLS patients treated with levodopa [8–10], but in a recent study only 10% of patients on levodopa discontinued treatment prematurely due to augmentation [11]. With dopamine agonists, augmentation was reported to occur less frequently, but prospective long-term data are lacking [11–16]. It has been hypothesized that augmentation might represent a hyper-dopaminergic state with a dysbalance between D1 and D2 receptor activation at the spinal cord level [17]. In addition, recent data suggest that RLS patients with lower ferritin levels at baseline are at higher risk of developing augmentation during dopaminergic treatment [18].

The aim of this study was to prospectively examine all patients with a diagnosis of RLS consulting a sleep disorders clinic and to assess RLS severity and augmentation and their associations, including ferritin levels.

2. Methods

2.1. Patient cohort and data collection

The sleep disorders clinic at the Department of Neurology of Innsbruck Medical University serves as a tertiary sleep disorders referral center serving for a population of about 2 million from western Austria and South Tyrol (Northern Italy). It is the only academic facility for diagnosis and treatment of sleep disorders in the

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abovementioned area. For this study, we recruited consecutive patients with the diagnosis of either idiopathic or symptomatic RLS who consulted our sleep disorders clinic, regardless of whether they presented with RLS or for other reasons (e.g. sleep-related breathing disorders, insomnia, excessive daytime sleepiness, etc), between August 2006 and February 2008. Diagnosis of RLS was based on the International RLS Study Group (IRLSSG) diagnostic criteria for RLS [6] and made by a neurologist experienced in RLS (B.H., B.F. or V.G.). A full sleep history and a detailed RLS interview were performed in all patients. Patients were stratified into patients with RLS as an ancillary diagnosis, RLS sufferers without current augmentation and RLS sufferers with current augmentation by expert rating. A diagnosis of ancillary RLS was given in case of either subjectively non-disturbing RLS symptoms or only sporadic RLS symptoms. We defined RLS sufferers as patients who consulted for clinically meaningful, bothersome RLS symptoms. Presence or absence of clinically meaningful augmentation was assessed according to published criteria [6,7]. After data collection, data were entered into a database for further analyses. This study was approved by the local ethics committee of Innsbruck Medical University and all patients gave written informed consent.

2.2. RLS interview and scales

Information about patients' demographic data, RLS etiology, RLS duration, relevant comorbidities, current RLS medication, and a history of previous or current oral iron substitution were obtained. The severity of RLS was assessed with the IRLS severity rating scale [19], the RLS-6 scales [20], and the clinical global impression [21]. Augmentation was diagnosed in a clinical interview according to published criteria [6,7] by physicians experienced in RLS and augmentation (B.H., B.F. and V.G.). Furthermore, the structured interview for the diagnosis of augmentation [22] was applied.

2.3. Laboratory evaluation

Blood biochemical variables including hemogram, C-reactive protein, electrolytes, creatinine, urea and indices of iron metabolism (iron, ferritin, transferrin, transferrin saturation) were performed at time of consultation in 291 patients. Because of the influence of inflammatory states on iron, ferritin and transferrin, patients with c-reactive protein (CRP) values >1.00 mg/dl ($n = 22$) were excluded from analysis. Moreover, two RLS patients with pathologically increased ferritin levels >500 μg/l of unknown cause were excluded from statistical analysis and transferred to further hematological evaluation.

2.4. Statistics

SPSS 12.0 was used for all statistical analyses. Data are given as means ± standard deviations or frequencies, as applicable. Patients were stratified into patients with the ancillary diagnosis of RLS, RLS sufferers without current augmentation and RLS sufferers with current augmentation. Normal distribution was investigated using the Shapiro–Wilk test. If data were not normally distributed, Mann–Whitney *U* test, Kruskal–Wallis Test or Fisher's exact test were used. A *p*-value below 0.05 was considered to indicate statistical significance.

3. Results

3.1. Patient cohort

From August 2006 to February 2008 a total of 302 consecutive patients with RLS were seen. Additional information on patients' age, sex, RLS etiology, exposure to clinic and current treatment, as well as RLS severity and comorbidities is provided in Table 1. Overall 177 (58.6%) of all patients were treated with RLS specific medication (168 monotherapy, 9 combination therapy). Of those, 162 (91.5%) received levodopa or dopamine agonists, another 10 (5.6%) were currently participating in double-blind placebo-controlled trials with dopamine agonists (see Table 2).

Mean ferritin values of the entire patient cohort were 104.2 ± 87.1 μg/l. Eighty-three (31.1%) had ferritin values <50 μg/l, 66 (24.7%) <40 μg/l, 47 (17.6%) <30 μg/l, 26 (9.7%) <20 μg/l and 9 (3.4%) <10 μg/l. Fourteen patients (4.6%) currently received oral iron substitution, 47 (15.6%) had a history of previous iron substitution. Interestingly, patients with a history of previous iron substitution had significant lower ferritin values at time of the investigation than RLS patients with no history of iron substitution (50.6 ± 41.5 vs. 114.2 ± 89.7; $p < 0.001$).

Table 1
Characteristics of the whole patient cohort ($n = 302$).

Variables	Whole patient cohort ($n = 302$)
Demographics	
Age, mean ± SD	59.1 ± 13.7
Women, *n* (%)	183 (60.6)
RLS etiology	
Idiopathic RLS, *n* (%)	291 (96.4)
Symptomatic RLS, *n* (%)	11 (3.6)
Exposure to clinic	
First time consultation at our center	130 (43)
Current RLS specific treatment	49 (37.7)
No RLS specific treatment	81 (62.3)
Follow-up consultation at our center	172 (57)
Current RLS specific treatment	128 (74.4)
No RLS specific treatment	44 (25.6)
Disease severity	
IRLS, mean ± SD	17.1 ± 9.1
RLS-6, mean ± SD	18.1 ± 10.6
GGI, mean ± SD	3.2 ± 1.3
Comorbidities	
Sleep related breathing disorders, *n* (%)	75 (24.8)
Narcolepsy, *n* (%)	6 (2.0)
Radiculopathy, *n* (%)	22 (7.3)
Polyneuropathy, *n* (%)	20 (6.6)
Migraine, *n* (%)	13 (4.3)
Epilepsy, *n* (%)	7 (2.3)
Parkinson disease, *n* (%)	4 (1.3)
Multiple sclerosis, *n* (%)	3 (1.0)
End-stage renal disease, *n* (%)	1 (0.3)

Table 2
Current RLS treatment of the whole patient population ($n = 302$).

Substance	*N* patients	Daily dosage mg/d (mean ± std)	Range (mg/d)
Dopamine agonists	128	73.5 ± 101.8	5–900
Pramipexole	85	0.4 ± 0.3	0.1–1.9
Rotigotine, open label trial	12	4.2 ± 1.7	1–7
Cabergoline	11	2.1 ± 0.7	1–3
Ropinirole	8	2.6 ± 3.3	0.3–10
Lisuride vs. placebo (trial)	7	NA	NA
Ropinirole XR vs. Ropinirole IR (trial)	3	NA	NA
Pergolide	2	0.5 ± 0	1
Levodopa (PRN permitted)	48	156.3 ± 111.4	50–600
Gabapentin	6	716.7 ± 577.6	300–1800
Opioids	4	NA	NA

On demand intake of levodopa was allowed for patients who did not have daily symptoms.

3.2. Comparison between RLS sufferers (without and with current augmentation) and patients with the ancillary diagnosis of RLS

Out of all patients, 240 (79.5%; 155 women, 85 men; mean age, 59.3 ± 14.0 years) consulted for clinically meaningful, bothersome RLS and were subsequently classified as RLS sufferers without current augmentation ($n = 221$) and RLS sufferers with current augmentation ($n = 19$). The majority of them (219, 91.3%) sought treatment for their RLS symptoms. The remaining 21 patients (8.7%) were seeking a diagnostic work-up only. In the RLS sufferer group, 165 (68.8%) were pre-treated, 75 (31.2%) were drug naïve. RLS was an ancillary diagnosis in 62 of all patients (20.5%; 28 women, 34 men; 58.1 ± 12.4 years). Of these patients, only 15 (24.2%) sought treatment on demand for their RLS, 12 (19.4%) were pre-treated on demand.

Although a significant proportion of the RLS sufferer group was pre-treated (68.8%), the difference between RLS sufferers and patients with RLS as an ancillary finding was significant in terms of symptom severity (IRLS severity score, 18.1 ± 9.4 vs. 13.3 ± 6.8; $p < 0.001$; RLS-6 scores, 18.8 ± 10.9 vs. 15.2 ± 8.7; $p = 0.014$; CGI, 3.3 ± 1.3 vs. 2.7 ± 0.9; $p < 0.001$). There was also a significant difference between both groups concerning the wish for RLS specific treatment (RLS sufferers vs. ancillary diagnosis of RLS, 219 out of 240 [91.3%] vs. 15 out of 62 [24.2%]; $p < 0.001$), the ratio of pre-treated patients (RLS sufferers vs. ancillary diagnosis of RLS, 165 out of 240 [68.8%] vs. 12 out of 62 [19.4%]; $p < 0.001$), and the frequency of previous iron substitution (44 out of 240 (18.3%) vs. 3 out of 62 (4.8%); $p = 0.009$). RLS sufferers had lower ferritin levels than patients with RLS as an ancillary finding (97.3 ± 83.0 μg/l vs. 132.8 ± 98.0 μg/l; $p = 0.008$). The same was true for both untreated subgroups (untreated RLS sufferers [$n = 70$] vs. untreated patients with an ancillary diagnosis of RLS [$n = 43$], 93.3 ± 80.1 μg/l vs. 128.3 ± 97.2 μg/l; $p = 0.031$).

3.3. Patients with current augmentation vs. patients without augmentation

Overall, 11.7% ($n = 19$, corresponding to a frequency of 6.3% in the whole sample) of all dopaminergic-treated patients ($n = 162$) had augmentation at time of investigation. Augmentation was present in 16.7% (8 out of 48) of patients treated with levodopa and in 11.0% (13 out of 118) of patients treated with dopamine agonists. There was no statistical difference in the frequency of augmentation in patients with levodopa compared to patients treated with dopamine agonists ($p = 0.406$). We also calculated the frequency of augmentation in patients treated with pramipexole which was the only subgroup large enough to allow for independent calculation. The frequency of augmentation in pramipexole was 10.6% (9 out of 85). Augmentation affected 11 women and 8 men with a mean age of 65.8 ± 12.5 years. Augmentation was diagnosed after a mean dopaminergic treatment duration of 34.9 ± 29.9 months. Patients with augmentation had significantly lower ferritin levels than patients without augmentation (55.8 ± 43.6 μg/l vs. 105.8 ± 89.3 μg/l; $p = 0.018$). Moreover, patients with augmentation had higher daily doses of levodopa (275.0 ± 148.8 mg/d vs. 134.2 ± 88.6 mg/d; $p = 0.001$), as well as higher daily levodopa equivalent doses (164.9 ± 156.9 mg/d vs. 81.8 ± 81.9 mg/d; $p = 0.018$) and a higher frequency of previous iron substitution (8 out of 19 [42.1%] vs. 39 out of 283 [13.8%]; $p = 0.004$). IRLS severity score was higher in augmented RLS than in non-augmented RLS (see Fig. 1). An inverse association of IRLS severity scores and serum ferritin levels was found in patients with the ancillary diagnosis of RLS, RLS sufferers without current augmentation and RLS sufferers with current augmentation (see Fig. 2).

Patients with augmentation did not differ from patients without augmentation regarding age, gender, RLS etiology, previous RLS augmentation, or any other documented comorbidity (for further data see Table 3).

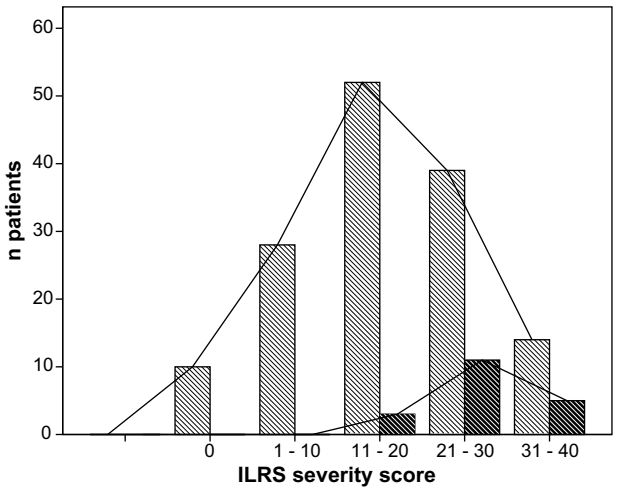

Fig. 1. Comparison of IRLS severity scores between treated patients with and without current augmentation(light bars, RLS patient without current augmentation; dark bars, patients with current augmentation).

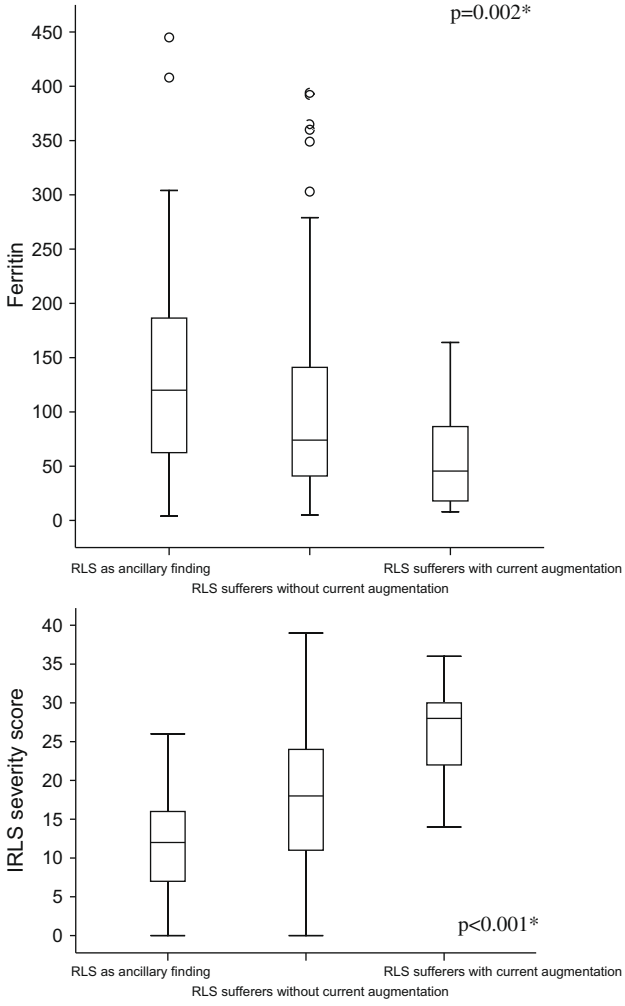

Fig. 2. Boxplot illustration of ferritin levels and IRLS severity scores across subtypes of RLS patients. (*p-values were calculated with the non-parametric Kruskal–Wallis test).

Table 3
Clinical characteristics of dopaminergic treated RLS patients with and without current augmentation (n = 162).

Variables	Patients with augmentation (n = 19)	Patients without augmentation (n = 143)	P
Demographics			
Age, mean ± SD	65.8 ± 12.5	62.5 ± 11.8	0.263
Women, n (%)	11 (57.9)	86 (60.1)	1.000
Clinical characteristics			
Idiopathic RLS, n (%)	17 (89.5)	138 (96.5)	0.191
Previous augmentation, n (%)	5 (26.3)	17 (11.8)	0.143
Disease severity			
IRLS, mean ± SD	26.0 ± 6.0	17.1 ± 9.6	<0.001
RLS-6, mean ± SD	25.1 ± 9.2	17.3 ± 11.1	0.002
GGI, mean ± SD	4.8 ± 0.8	3.1 ± 1.2	<0.001
SIDA			
N positive (%)	17 (89.5)	4 (2.8)	<0.001
Current treatment			
Dopamine agonists, n patients (%)	13 (68.4)	105 (73.4)	0.205
Pramipexole, n (%)	9 (47.4)	76 (53.1)	0.808
Ropinirole, n (%)	2 (10.5)	6 (4.2)	0.238
Pergolide, n (%)	1 (5.3)	1 (0.7)	0.221
Cabergoline, n (%)	1 (5.3)	10 (7.0)	1.000
Rotigotine, n (%)	0	12 (8.4)	0.363
Levodopa, n patients (%)	8 (42.1)	40 (28.0)	0.283
Levodopa equivalent dose, mg/d (mean ± SD)	164.9 ± 156.9	81.8 ± 81.9	0.018
Laboratory parameters			
Ferritin, µg/l (mean ± SD)	55.8 ± 43.6	105.8 ± 89.3	0.018
Hemoglobin, mg/l (mean ± SD)	13.9 ± 1.5	13.8 ± 1.3	0.742

SIDA, structured interview for the diagnosis of augmentation.

Eleven patients with current augmentation were on dopamine agonist monotherapy, six on levodopa monotherapy. Two patients were on a combined levodopa/dopamine agonist therapy at the time of augmentation (200 mg levodopa + 2 mg cabergoline per day, 200 mg levodopa + 0.27 mg pramipexole per day). Patients with current augmentation on levodopa had significantly higher total levodopa equivalent doses than patients with current augmentation on dopamine agonists (levodopa vs. dopamine agonists, 300 ± 167.3 mg/d vs. 64.3 ± 48.2 mg/d; $p < 0.001$). Augmentation in patients on levodopa did not differ from augmentation on dopamine agonists regarding age, gender, RLS etiology, IRLS severity scores, ferritin levels, RLS treatment duration, or any other documented comorbidity ($p > 0.05$).

4. Discussion

Our data show an inverse correlation between ferritin levels and RLS severity ranging from ancillary diagnosis of RLS to augmented RLS. Patients with ancillary diagnosis of RLS had the highest ferritin levels, whereas patients with augmented RLS had the lowest. Midbrain iron deficiency has been demonstrated in autopsy, imaging and cerebrospinal fluid studies in idiopathic RLS [23–28]. In recent genome-wide association studies, a common variant in an intron of BTBD9 on chromosome 6p21.2 was identified to be associated with RLS [29,30]. A 13% decrease of serum ferritin was reported per allele of this at-risk variant [30]. Moreover, a recent study showed that RLS patients with lower ferritin at baseline were at a higher risk of developing augmentation during the course of dopaminergic treatment [18].

In our patient group, the majority of patients were RLS sufferers. In only 20.5%, RLS was an ancillary diagnosis. On the other end of the spectrum, augmentation was present in 6.3% of the whole cohort and 11.7% of the treated patients. This demonstrates the broad spectrum of RLS ranging from ancillary to augmented RLS in a sleep disorders outpatient clinic. While the vast majority of patients who were RLS sufferers required RLS specific treatment, most patients with RLS as an ancillary diagnosis preferred to remain without medication. This is in line with a recent study in the general population indicating that only 20% of all individuals with RLS wish for specific treatment [31]. In order to account for these differences in RLS symptom severity, further studies should clearly distinguish between the epidemiological presence of RLS and clinical RLS. The vast majority of the patient cohort had idiopathic RLS, whereas only a small minority of 4% had symptomatic RLS. This confirms findings from a previous study that symptomatic RLS is rare in the general population [3].

Overall frequency of augmentation was high with 11.7% of all treated RLS patients who consulted our sleep disorders clinic in this 17-month interval. The relatively high frequency of augmentation may be partially explained by the fact that our sleep disorders clinic is a tertiary referral center with a patient population of more severe or therapy-refractory RLS. In RLS patients treated with dopamine agonists, the frequency of augmentation was 11.0%, which is similar to the reported augmentation rate in most long-term dopamine agonist trials [11–16]. In patients treated with levodopa, 16.7% were diagnosed with augmentation. This finding is much lower than that found in most published studies describing augmentation in up to 72% [9,10]. One possible explanation might be that the daily levodopa dosage used in our patient sample was relatively low with 156 mg [32]. There is only one recently published 30-week study which reported a lower frequency of augmentation in levodopa of 14.2% [11]. The low levodopa dosage used in our study may also potentially explain the fact that we saw similar augmentation rates in patients treated with levodopa and dopamine agonists. Furthermore, the only subgroup of dopamine agonists with a large enough sample size for independent statistical analysis was pramipexole, which is the only approved dopamine agonist for RLS in Austria. The frequency of augmentation in pramipexole was similar to that in dopamine agonists in general.

Almost one-third of the whole patient cohort had ferritin values <50 µg/l possibly indicating a need for iron substitution [33,5]. Moreover, 10% showed pathologically decreased ferritin levels <20 µg/l. The high frequency of low ferritin levels in RLS underlines the need for iron status evaluation in all patients with RLS as recommended by IRLSSG diagnostic guidelines (6) and is in line with the genetic link between iron regulation and RLS (30). In one early study, ferrous sulphate improved RLS in patients with ferritin levels <45 µg/l by 33%, whereas patients with ferritin levels >45 µg/l showed only a minor improvement of 10% compared to baseline RLS symptom severity [33]. Newer studies on intravenous iron therapy showed controversial results, which are still unexplained, although methodological differences (iron preparation, dose and frequency of substitution) are discussed [34,35]. Systematic data on iron substitution in augmented RLS are, so far, missing. Concerning the practical management of RLS, iron substitution should be considered before the initiation of RLS specific treatment in case of low ferritin levels below 45-50 µg/l [5,36] since a ferritin level <45 µg/l has been shown to detect 90% of patients with absent iron in bone marrow [37].

In patients with augmented RLS, levodopa and levodopa equivalent dosages were significantly higher than in patients without current augmentation. This supports the pathophysiologic concept of augmentation as a hyper-dopaminergic state with a relative dominance of the pronociceptive dopamine D1 receptor activation in comparison to the antinociceptive D2 receptor activation in augmentation [17]. A close interaction of iron metabolism and the dopaminergic system has been demonstrated in multiple studies

[38–42]. In iron-deficient anemic rats, iron deficiency was found to attenuate the dopamine reuptake mechanisms [39]. Moreover, nutritional iron deficiency causes a significant loss of iron in the caudate nucleus and a decreased dopamine D2 receptor density [40,41] which is also postulated in the current hypothesis of augmentation [17]. In another study, iron-deficient mice were shown to express a circadian sleep pattern similar to that found in RLS [43].

In summary, the results of our study not only further strengthen a putative role of low iron stores as a potential aggravator of idiopathic RLS, but also suggest that low ferritin represents a potential biomarker of augmentation under dopaminergic therapy.

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