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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.