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Original Article

Is there a polysomnographic signature of augmentation in restless legs syndrome?

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ABSTRACT

Objective: Augmentation of restless legs syndrome (RLS) is a potentially severe side-effect of dopaminergic treatment. Data on objective motor characteristics in augmentation are scarce. The aim of this study was to investigate in detail different variables of leg movements (LM) in untreated, treated, and augmented RLS patients.

Methods: Forty-five patients with idiopathic RLS [15 untreated, 15 treated (non-augmented), 15 augmented] underwent RLS severity assessment, one night of video-polysomnography with extended electromyographic montage, and a suggested immobilization test (SIT).

Results: Standard LM parameters as well as periodicity index (PI) and muscle recruitment pattern did not differ between the three groups. The ultradian distribution of periodic leg movements (PLM) in sleep during the night revealed significant differences only during the second hour of sleep ($P < 0.05$). However, augmented patients scored highest on RLS severity scales ($P < 0.05$) and were the only group with a substantial number of PLM during the SIT.

Conclusion: This study demonstrates that polysomnography is of limited usefulness for the diagnosis and evaluation of RLS augmentation. In contrast, the SIT showed borderline differences in PLM, and differences on subjective scales were marked. According to these results, augmentation of RLS is a phenomenon that predominantly manifests in wakefulness.

1. Introduction

Restless legs syndrome (RLS) is a common sensorimotor disorder characterized by an urge to move the legs, accompanied by unpleasant sensations in the legs, and occurring predominantly during periods of rest in the evening or night [1]. RLS affects ~10% of the general population [2] and in 2.7% of the population the disorder has a moderate-to-severe negative health impact [3]. Levodopa and dopamine agonists are efficacious for the treatment of RLS, but carry a relevant risk of causing augmentation on the long term [4–7]. Augmentation is a worsening of RLS symptom severity during RLS treatment. Features of augmentation include an earlier onset of symptoms, a shorter latency to symptoms at rest, a spread of symptoms to other body parts (e.g. the arms), a shorter duration of the treatment effect, and a paradoxical response to changes in medication (i.e. increase of symptom severity after an increase of the daily medication dosage, decrease of symptom severity after a dose decrease) [4,8]. Recent studies have shown that augmentation is present in 11.7% in a clinical series of RLS [9] and a community-based study showed that up to 21% of RLS patients under dopaminergic treatment suffer from augmentation [5]. The pathophysiology of augmentation is not fully understood. Current concepts consider augmentation to reflect a hyperdopaminergic state, in which pronociceptive D1 receptors are believed to be stimulated to a greater extent than antinociceptive D2 receptors, which may generate pain as well as periodic leg movements (PLM) [10]. It is assumed that PLM and motor activity in general increase during augmentation [8]; however, there has been no systematically controlled video-polysomnographic (vPSG) study focused on leg muscle activation in augmentation.

The present study aimed to perform a controlled analysis of the characteristics of motor activity in RLS augmentation by vPSG and suggested immobilization test (SIT).

2. Methods

2.1. Study population and design

For this study, RLS patients according to standard criteria [1] were prospectively examined at the sleep laboratory of Innsbruck Medical

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University. Only patients with idiopathic or familiar RLS after exclusion of possible RLS mimics, as proposed by Hening et al. [11], were eligible. Three groups of RLS patients were included: (1) untreated RLS, (2) treated RLS without current augmentation, and (3) treated RLS with current augmentation. In the following, the terms 'untreated', 'treated (non-augmented)' and 'augmented' are used for these groups. The presence of augmentation was determined in a clinical interview according to current standard criteria [8]. Any other disease or medication that might have an impact on motor activity during sleep [e.g. rapid eye movement sleep behaviour disorder or relevant untreated sleep apnea syndrome (apnea hypopnea index (AHI) > 10/h)] represented exclusion criteria. The recruitment aim set for this study was 15 patients in each group. Evaluation of subjects included clinical history, demographic data, neurological examination, RLS-specific scales and questionnaires (see below), a SIT and vPSG. The study had been approved by the ethical committee of Innsbruck Medical University and all participants gave written informed consent.

2.2. RLS scales and questionnaires

The International RLS Study Group Rating Scale (IRLS, total score) [12], the RLS-6 Scales (RLS-6) [13], and the Clinical Global Impression (CGI, item 1) [14] were administered to assess severity of RLS symptoms. To analyse the involved body parts, item 4 of the Augmentation Severity Rating Scale (ASRS) [15] was applied.

2.3. Polysomnography with multiple electromyography recording

Every patient underwent one night of vPSG. The recording included electroencephalography (EEG montage in accordance with the 2007 American Academy of Sleep Medicine criteria) [16], electrooculography (EOG), respiration using nasal airflow (thermocouple and nasal pressure cannula), and thoracic and abdominal respiratory effort, and one-channel electrocardiography (ECG). In addition to conventional PSG electromyography (EMG) of chin and bilateral tibialis anterior muscles, multichannel EMG of upper and lower extremity muscles (bilateral biceps bracchii, triceps bracchii, rectus femoris, biceps femoris and gastrocnemius muscles) was recorded.

EMG signals were recorded with a sampling rate of up to 1000 Hz, high-pass filtered at 50 Hz and low-pass filtered at 300 Hz. Baseline EMG amplitude of the relaxed tibialis anterior muscle was ±2 μV (non-rectified signal). Leg movements (LM) and PLM were recorded according to criteria of the World Association of Sleep Medicine (WASM) [17]. EMG of both tibialis anterior muscles was recorded using surface electrodes placed symmetrically on the middle of the muscles with an inter-electrode distance of 2–3 cm. Sleep stages were scored in 30 s epochs using standard criteria [16].

2.4. Analysis of PLM and related variables

In accordance with the aim of this study, the main focus was the analysis of LM and PLM, which was performed in several established and new ways. LM and PLM were analysed manually according to WASM criteria [17]. The LM and PLM indices were calculated for time in bed (TIB), total sleep time (TST), total wake time (TWT), and hour of sleep.

2.4.1. Periodicity index (PI)

The PI is calculated as the number of LM intermovement intervals (IMI) occurring in a sequence of three IMIs with a duration between 10 and 90 divided by the total number of IMIs [18].

Table 1
Demographic variables.

	Untreated ($n = 15$)	Treated (non-augmented) ($n = 15$)	Augmented ($n = 15$)	*P*-value
Age (median/range) (years)	60 (21–73)	58 (26–72)	60 (38–75)	0.471
Gender (F/M)	10/5	9/6	10/5	0.056
RLS duration (median/range) (years)	9 (1–25)	16 (4–37)	20 (1–61)	0.050
Medication				
Polytherapy	NA	0	9	
Substances				
Levodopa	NA	1	10	
Dopamine agonist				
Pramipexole	NA	10	5	
Ropinirole	NA	4	2	
Rotigotine	NA	0	1	
Opioids				
Tramadol	NA	0	1	
α2δ Ligands				
Gabapentin	NA	0	1	

RLS, restless legs syndrome; NA, not applicable.

2.4.2. Muscle recruitment in periodic leg movements in sleep (PLMS)

In addition to the standard LM and PLM analysis, every single PLMS was analysed with regard to: (i) the number of involved muscles, and (ii) identification of the first contracting muscle. For these issues, surface EMG of bilateral biceps bracchii, triceps bracchii, rectus femoris, biceps femoris, and gastrocnemius muscles was recorded in addition to the standard tibialis anterior muscle. We calculated the 'PLMS spread index', which reflects the proportion of PLMS in which at least two more leg muscles than the tibialis anterior are contracted. This index can vary between 0 (in every PLM less than two leg muscles other than the tibialis contracted) to 1 (in every PLM at least two additional leg muscles are contracted).

2.5. Suggested immobilization test

A SIT with a duration of 60 min was conducted before every sleep study. In variation from Michaud et al. [19]. subjects were sitting in a reclining chair in a comfortable position with flected legs in a semi-flexed position. The instructions before the test were to keep the voluntary movements to a minimum for the entire test. Every 15 min the patients were asked to mark their urge to move and leg discomfort on a visual analogue scale (VAS). For each patient the SIT total PLM index is reported as well as the total value (sum of each 15 min value divided by five) on the VAS for the categories 'urge to move' and 'leg discomfort' and the value of every single 15 min period. To illustrate the evolution of symptoms, values of VAS and PLM were plotted across a time axis. For patients who could not complete the SIT the last observation on VAS carried forward was used for analysis; for calculation of the PLM index for patients prematurely ending the test, the number of PLM was calculated for a 60 min period (i.e. number of PLM divided by number of minutes finished multiplied by 60).

2.6. Statistical analysis

Statistical analyses were performed using SPSS 20 (IBM Corp., Armonk, NY, USA). Data are given as frequencies, mean ± standard deviation (SD), median and range, or as mode. Normality testing was performed with the Shapiro–Wilk test. Group comparisons were performed using the χ^2-test for categorical variables, and analysis of variance (ANOVA) or Kruskall–Wallis test for quantitative variables depending on distribution. $P < 0.05$ was considered significant.