Variability of Periodic Leg Movements in Various Sleep Disorders: Implications for Clinical and Pathophysiologic Studies

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**INTRODUCTION**

PERIODIC LIMB MOVEMENTS IN SLEEP (PLMS) ARE CHARACTERIZED BY PERIODIC EPISODES OF REPETITIVE, STEREOTYPED LIMB MOVEMENTS AND ARE A COMMON FINDING IN SLEEP LABORATORY INVESTIGATIONS.1,2 With advancing age, PLMS are observed even in nonsymptomatic adults, ie in persons without sleep/wake disturbances.3,4 PLMS occur frequently in patients with restless legs syndrome (RLS), narcolepsy, sleep apnea syndrome, insomnia, and rapid eye movement sleep behavior disorder.5 A PLMS index (the number of PLMS per hour of sleep) above 10 per hour is often used as a cut off for differentiating normal from elevated values. About 67% of RLS patients reveal a PLMS index higher than 10 per hour during a single night of polysomnographic recording.6

Previous studies investigating “nocturnal myoclonus” (a term used formerly for PLMS) have reported a random variability of PLMS across consecutive nights in elderly healthy subjects and in subjects with sleep complaints.7,8 Up to now, no study has dealt with PLMS variability in different sleep disorders. However, this issue has clinical relevance because PLMS are thought to disturb sleep, especially those movements that are associated with arousal. Consequent daytime fatigue has been reported previously in adults,10 although it is still matter of debate whether such a relationship exist.11,12 The measurement of PLMS is also frequently used for assessing treatment efficacy in studies investigating the effects of pharmacologic substances in RLS and PLMS-related insomnia.

Regarding the above considerations, we retrospectively evaluated polysomnographic and PLMS parameters in consecutive patients investigated in the sleep laboratory. The aim of the study was to assess the variability of PLMS in various sleep disorders.

**METHODS**

**Patients**

Data from all patients monitored for PLMS during 2 successive nights over a period of 34 months (N = 145) were evaluated retrospectively. A low number of PLMS or PLMS associated with arousals in 1 of the nights was not an exclusion criterion. All patients were tested for the use of benzodiazepines, opioids, cannabinoids, amphetamines, cocaine, and barbiturates by urinalysis, and, consequently, 30 patients were excluded due to positive results of the urinalysis or due to intake of substances influencing sleep (neuroleptics, hypnotics, antidepressants). All RLS patients were untreated. Patients with psychiatric disorders were either untreated (n = 9) or on stable psychiatric medication (n = 14, taking antidepressants that could possibly influence sleep) for at least 4 weeks before polysomnography. No other patients received psychiatric or other medication that may have influenced sleep or PLMS. One hundred fifteen patients were included in the final evaluation. The patients were grouped into 5 diagnostic categories.

Disclosure Statement

This is not an industry supported study. Drs. Hornyak, Feige, Voderholzer, and Riemann have indicated no financial conflicts of interest.

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tion, laboratory data, and polysomnographic findings. Each patient was assigned to only 1 diagnostic category. The groups comprised (1) patients with RLS, n = 42, mean age: 58 ± 13 years (± SD); (2) patients with insomnia secondary to a psychiatric disorder, n = 32, mean age: 52 ± 11 years; (3) patients with primary insomnia, n = 23, mean age: 45 ± 13 years; (4) patients with sleep apnea syndrome, n = 13, mean age: 52 ± 13 years; and (5) patients with narcolepsy n = 5, mean age: 42 ± 21 years.

The diagnosis of RLS was assessed according to the criteria of the International Restless Legs Syndrome Study Group.13 The severity of RLS symptoms was estimated by an experienced clinician on an arbitrary scale from 1 to 7 (1: mild symptoms, 7: severe symptoms) and was based on the frequency and severity of RLS complaints. The mean score was 3.6 ± 1.9 (± SD). Primary insomnia was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Third Edition.-R criteria.

Polysomnographic and PLMS Recordings

Polysomnographic assessments included electroencephalogram (C3-A2, C4-A1), electrooculogram, submental electromyogram, electrocardiogram, and superficial electromyogram of both anterior tibial muscles. Oronasal air flow, thoracic and abdominal breathing efforts, and transcutaneous oximetry were monitored in all patients. Patients with sleep-disordered breathing (apneas-hypopneas index > 10 per hour of sleep) were excluded from the study. Polysomnographic recordings were performed from 11:00 PM (“lights out”) to 7:00 AM (“lights on”). Sleep recordings were visually analyzed by experienced raters according to Rechtschaffen and Kales criteria.14 Arousals were scored as described by the American Sleep Disorders Association.2 PLMS were scored according to standard criteria,15 ie, they were scored only if they were part of a series of 4 or more consecutive movements lasting at least 0.5 seconds, with an intermovement interval of 4 to 90 seconds. PLMS were scored as associated with arousal if the arousal followed the beginning of the leg movement within an interval no longer than 3 seconds. Total sleep time was calculated as time spent in any sleep stage during the recording, and sleep efficiency was calculated as the percentage of total sleep time during the time in bed. The arousal index was defined as the number of arousals per hour of sleep. Regarding the frequency of PLMS, the following indexes were calculated: (1) the PLMS index, which gives the number of all PLMS per hour of total sleep time, and (2) the PLMS arousal index, which considers only PLMS associated with arousals per hour of total sleep time.

### Table 1—Polysomnographic Characterization of Patient Groups

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sleep efficiency, %</th>
<th>Total sleep time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Night 1</td>
<td>Night 2</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>67 ± 17</td>
<td>73 ± 15**</td>
</tr>
<tr>
<td>Insomnia due to psychiatric disorders</td>
<td>69 ± 19</td>
<td>81 ± 12***</td>
</tr>
<tr>
<td>Primary insomnia</td>
<td>74 ± 13</td>
<td>81 ± 12*</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>80 ± 12</td>
<td>82 ± 11</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>86 ± 5</td>
<td>88 ± 7</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Asterisks indicate significant differences between the first and second night (Wilcoxon signed-rank test): *P <.05; **P <.01; ***P <.001.

### Statistical Analysis

Since the data points were not normally distributed, statistical analyses were performed using the Wilcoxon signed-rank test for paired comparisons. Correlations were calculated according to Spearman. The level of significance (2-tailed if not indicated otherwise) was set at P ≤ .05.

### RESULTS

**Sleep Parameters and PLMS Measures**

Sleep efficiency and total sleep time showed a first-night effect in patients with RLS, primary insomnia, and insomnia secondary to a psychiatric disorder (Table 1). The arousal index was significantly different between the first and second night in patients with insomnia secondary to a psychiatric disorder (Table 1). The PLMS index and the PLMS arousal index did not differ significantly between nights in any of the groups (Table 2), and both the PLMS index and the PLMS arousal index were reliable across nights for the entire group (Spearman-rho for the PLMS index: 0.853, P < .001; Spearman-rho for the PLMS arousal index: 0.830, P < .001).

### Variability of PLMS Indexes

Although the PLMS index and PLMS arousal index did not systematically change from the first to the second night, both indexes showed considerable intrasubject variability between nights. Table 2 shows differences in the absolute values for PLMS indexes and PLMS arousal indexes between night 1 and night 2. The most pronounced differences appeared in patients with RLS (Figure 1a). Patients with sleep disturbances not related to RLS also showed some variance of PLMS but not to the extent seen in RLS patients (Figure 1b). The difference between both groups was significant for both the PLMS index and the PLMS arousal index (Mann-Whitney test, P < .000). According to the PLMS index, a difference of more than 10 per hour from 1 night to the next occurred in 31 patients (27%). Twenty of the 31 were patients with RLS, 5 with insomnia secondary to a psychiatric disorder, 3 with primary insomnia, and 3 with sleep apnea syndrome. A difference in the PLMS index greater than 25 per hour between both nights was present in 10 patients with RLS and in 1 patient with insomnia related to a psychiatric disorder. Regarding the PLMS arousal index, data revealed a difference between values from both nights of more than 5 per hour in 22 patients, 19 of them diagnosed with RLS. Of the 9 patients showing a difference of more than 10 per hour, 8 presented with RLS.

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In the clinical practice, cut-off values are frequently used for differentiating elevated PLMS indexes. Using a cut-off value of 10 per hour for the PLMS index, 10% of the RLS and 16% of the non-RLS patients would be assigned to different categories (“normal” vs “clinically relevant”) if PLMS recordings had been performed on only 1 night. Using a cut-off value of 5 per hour for the PLMS arousal index, 19% of RLS patients and 10% of the non-RLS patients would change from one category to the other.

DISCUSSION

We found a considerable variability of the PLMS index across the 2 investigated nights (absolute difference between nights > 10/h) in 27% of the whole patient population. The intraindividual variance occurred most frequently and to the highest extent in patients with RLS.

Our finding regarding the variability of PLMS indexes in patients with sleep disorders other than RLS is in line with results of previous studies investigating community-dwelling elderly with or without sleep complaints or elderly individuals with disturbed sleep. These studies have described a considerable night-to-night variation of PLMS or of the movement index in the polysomnogram, which did not seem to be related to symptoms of disturbed sleep. In the largest study investigating PLMS in RLS patients to date, Montplaisir et al performed polysomnography on 133 RLS patients, 49 of whom were monitored across 2 consecutive nights to assess the diagnostic reliability of PLMS recordings. Although the authors of this study noticed the variance in PLMS and stated that the percentage of elevated PLMS indexes increased when 2 recording nights were considered, they did not investigate this phenomenon any further. A high and frequent PLMS variability comparable to the one we found, particularly in the group of patients with RLS, has not yet been reported.

Our data may theoretically be biased by the way patients were selected. We evaluated consecutive patients who were investigated with 2 nights of PLMS recordings in the sleep laboratory. Since RLS patients disproportionately contribute to the pool of persons afflicted with PLMS, most 2-night PLMS recordings

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PLMS index, no./h</th>
<th>PLMS arousal index, no./h</th>
<th>Absolute differences between nights 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Night 1</td>
<td>Night 2</td>
<td>Night 1</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>35.9 ± 27.7</td>
<td>37.9 ± 31.3</td>
<td>13.3 ± 11.4</td>
</tr>
<tr>
<td>Insomnia due to psychiatric</td>
<td>13.2 ± 16.2</td>
<td>14.2 ± 19.3</td>
<td>3.6 ± 5.2</td>
</tr>
<tr>
<td>disorders</td>
<td>7.7 ± 15.8</td>
<td>6.5 ± 15.4</td>
<td>2.1 ± 5.6</td>
</tr>
<tr>
<td>Primary insomnia</td>
<td>10.3 ± 11.9</td>
<td>9.9 ± 9.6</td>
<td>1.9 ± 1.7</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>20.5 ± 30.1</td>
<td>23.0 ± 29.7</td>
<td>3.1 ± 2.9</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. The differences between the PLMS index and PLMS arousal index are calculated in absolute values, ie, not regarding whether the index decreased (would refer to a negative value) or increased (would refer to a positive value) in the second night.

In the clinical practice, cut-off values are frequently used for differentiating elevated PLMS indexes. Using a cut-off value of 10 per hour for the PLMS index, 10% of the RLS and 16% of the non-RLS patients would be assigned to different categories (“normal” vs “clinically relevant”) if PLMS recordings had been performed on only 1 night. Using a cut-off value of 5 per hour for the PLMS arousal index, 19% of RLS patients and 10% of the non-RLS patients would change from one category to the other.

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Figure 1a—Periodic limb movements of sleep (PLMS) index over 2 consecutive nights in patients with restless legs syndrome (RLS) (n = 42). PLMS index in the first night: 35.9 ± 27.7/h; PLMS index in the second night: 37.9 ± 31.3/h (mean ± SD).

Figure 1b—Periodic limb movements of sleep (PLMS) index over 2 consecutive nights in patients with sleep disorders other than restless legs syndrome (RLS) (n = 73). PLMS index in the first night: 11.5 ± 16.6/h; PLMS index in the second night: 11.7 ± 17.8/h (mean ± SD).
were done on RLS patients, leading to an unequal distribution of the population in the different diagnostic categories. However, from our viewpoint, the high variability of PLMS seen in RLS seems not so much to be a methodologic bias but, rather, appears to be related to the disorder itself.

The mechanism behind and the relevance of PLMS variability is unknown, and the pathophysiology of PLMS is also not understood. The question of whether PLMS are an epiphenomenon or are related to the pathophysiology of RLS and other sleep disorders has yet to be resolved conclusively. Generally, PLMS are hypothesized to be a potential marker of impaired central dopaminergic function. Electrophysiologic studies concerning PLMS suggest a brainstem disinhibition resulting in an abnormal hyperexcitability along the spinal cord. Magnetic resonance imaging studies of patients with RLS have demonstrated an activation of the red nuclei and the brain stem during periodic leg movements in awake subjects and decreased iron concentrations in the substantia nigra and in the putamen, indicating an alteration of dopaminergic mechanisms. The involvement of striatal structures in RLS and PLMS has not yet been elucidated conclusively. Two working groups found no differences between healthy subjects and RLS patients for regional blood-flow values derived from [18]FDG positron emission tomography scans or the binding constants in [18]F-dopa scans. Other groups have described a mild reduction of [18]F-dopa uptake and of D2-receptor binding in the putamen and the caudate nucleus. A recent study reported on reduced nocturnal urinary dopamine excretion in otherwise healthy subjects with PLMS. From the clinician’s view, PLMS appear to be strongly related to dopaminergic pathways, since dopaminergic substances have been found to be highly effective in treating PLMS.

The results of our study have implications for clinical and possibly also for pathophysiologic investigations. Firstly, the high variability of PLMS indexes should be considered if the PLMS recording is performed to support clinical diagnosis, to assess effects of a specific drug on PLMS in an individual case, or to evaluate the efficacy of a substance on PLMS in clinical trials. Using mean values of 2 nights of PLMS recordings can provide a higher diagnostic reliability and sensitivity. Secondly, one could speculate that the variability of PLMS probably reflects an intrinsic instability of central dopaminergic activity, which may bear relevance on studies investigating the pathophysiology of PLMS. An instability of monoaminergic or dopaminergic function has been reported, for example, during maturational changes and in children with orthostatic dysregulation, although there are, on the other hand, data indicating that dopaminergic activity and its behavioral manifestation may be complex and not linearly correlated. Hypothesizing that such a relationship exists, we believe that the fluctuations of dopaminergic function, as indicated by PLMS variability, should be taken into account in research studies.

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