Original article

Periodic limb movements and sleepiness in obstructive sleep apnea patients

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Abstract

Background and purpose: The aim of this study was to assess the possibility that periodic limb movements during sleep (PLMS) could play an additive role in the sleepiness associated with obstructive sleep apnea syndrome (OSAS) before treatment, or could account for residual sleepiness in successfully CPAP-treated patients.

Patients and methods: In order to test this hypothesis, we compared objective sleepiness, assessed by the Multiple Sleep Latency Test (MSLT) and subjective sleep propensity, assessed by the Epworth Sleepiness Scale (ESS), in a clinical series of 57 patients consecutively diagnosed with OSAS (apnea/hypopnea index, 53.3 ± 26.15), before and after 1 year of treatment with CPAP.

Results: Twenty-two patients (38.5%) had significant PLMS (at least 5 PLMS/h of sleep; mean 52.9 ± 53.9) in absence of apneas (with CPAP). The two groups (with and without PLMS) were similar in gender distribution, BMI, apnea/hypopnea index or CPAP level. Patients with PLMS were older than those without PLMS. Sleepiness measurements following OSAS diagnosis and after 1 year of CPAP treatment were similar in patients PLMS compared to those without significant PLMS. There was no correlation in the PLMS patient group between the PLM index, Epworth Sleepiness Scale score and mean latency in the MSLT.

Conclusion: In this study we did not find a link between PLMS and increased objective or self-evaluated sleepiness in OSAS patients, before or after treatment with CPAP.

Keywords: Periodic limb movements during sleep; Obstructive sleep apnea syndrome; Excessive daytime sleepiness; CPAP

1. Introduction

Periodic limb movements during sleep (PLMS) are frequently found in polysomnograms, appearing as repetitive episodes of muscle contraction, 0.5–5 s in duration, separated by an interval of typically 5–90 s [1]. The occurrence of PLMS at rates of five or more per hour of sleep is regarded as abnormal and is supportive of the diagnosis of periodic limb movement disorder (PLMD) if associated with hypersomnia or insomnia [2]. PLMS are considered responsible for sleep fragmentation, and a complaint of excessive daytime sleepiness (EDS) in these patients is often regarded as a consequence of PLMS. However, PLMS are present in up to 6% of the general population [3] and in more than 45% of adults aged 65 years or older [4,5], and can be detected in asymptomatic individuals. Coleman et al. [6] demonstrated that in patients with primary insomnia and PLMS, there was no correlation between the PLMS index and the mean sleep latency in the MSLT. Moreover, in a study of patients with several sleep disorders associated with PLMS [7], the index of PLMS associated with arousals did not differentiate patients with EDS from those without. In a recent study, Chervin [8] tested the association between the rate of PLMS and the severity of EDS in a clinical series of 1124 patients with suspected or confirmed sleep disordered breathing (SDB). Surprisingly, increased leg movements were associated with decreased objective sleepiness (but explained less than 1%
of the variance) and showed no association with subjective sleepiness or sleep propensity. Thus, the extent to which PLMS contribute to excessive daytime sleepiness is controversial [9], and some authors consider PLMS simply as a polysomnographic observation without functional significance [10].

PLMS are a common finding in patients with obstructive sleep apnea syndrome (OSAS). Their appearance or enhancement during continuous positive airway pressure (CPAP) has also been reported [11]. In this study we investigated the sleepiness associated with PLMS in a group of unselected OSAS patients, before and after 1 year of CPAP treatment. Our hypothesis was that PLMS could play an additive role in the sleepiness of these patients before treatment, or account for residual sleepiness in successfully CPAP-treated OSAS patients.

2. Methods

2.1. Patients

Data from 57 consecutively diagnosed OSAS patients, treated with CPAP during 1 year, were retrospectively analyzed. Patients were referred to our laboratory for clinical indications between January and December 2000. Patients suffering from other associated sleep disorders (including those with restless legs syndrome (RLS)) or taking medication influencing sleep or PLMS were excluded from this study. Patients who refused CPAP treatment or failed to comply with treatment were not included (as their follow-up data were not available). The compliance rate at 1 year was 87%. Nocturnal polysomnography followed our standard procedures: the first night was an adaptation night, the second consisted of a diagnostic polysomnographic recording and the third night served for CPAP titration under polysomnographic supervision. As prior to treatment it is difficult to differentiate intrinsic leg movements from secondary movements non-specifically associated with the arousal at the end of the respiratory event, only data from the third night were considered for PLMS analysis.

After the first night patients underwent an MSLT, an objective measure of the severity of sleepiness, and completed an Epworth Sleepiness Scale (ESS0), a validated self-evaluation of sleep propensity [12]. The MSLT followed standard methods for collection [13] and each patient’s mean latency (MSLT0) was calculated as to time, averaged across five nap attempts, from ‘lights off’ to the first epoch of stage 1 sleep. We also considered for analysis the number of positive naps (MSLTn0), i.e. the number of nap attempts during which the patient fell asleep.

CPAP compliance was periodically checked during the 1-year period (visits at home were scheduled as follows: 1 week after the beginning of the CPAP treatment, once a month during the first 3 months, every 3 months until the end of the period). Additional visits were realized if there were specific problems related with treatment (e.g. mask change, need of humidifier).

The follow-up evaluation was performed after 1 year of home treatment with CPAP at the fixed pressure. After one night spent at our laboratory, we repeated the MSLT (MSLT1, MSLTn1) and the ESS (ESS1) and calculated the CPAP compliance at home, from the engine time-counter, to obtain a global mean objective use per day. A polysomnography was done, under CPAP treatment and continuous supervision, in order to detect eventual respiratory events.

2.2. Polysomnographic recordings

Sleep was assessed using two EEG channels (C3-O1 and C3-A2), two electro-oculograms and a chin electromyogram, according to standard criteria [14]. Ventilation during sleep was recorded with a pneumotachograph (Rudolph 3700) or with nasal and oral thermistors; respiratory effort was assessed by means of an esophageal latex balloon linked to a pressure transducer (Validyne DP45) or with a thoracoabdominal stain gauge; and arterial oxygen saturation with a pulse oxymeter (Biox 3700; Ohmeda) using a finger probe. Surface electrodes were applied to the skin on both anterior tibialis muscles to detect muscle activity during sleep; the right and left legs were recorded separately. Patients monitored with an esophageal balloon at baseline were also monitored with an esophageal balloon at follow-up. Signals from the whole night were digitized and stored using a recording system developed in our laboratory. Offline visual scoring of sleep stages and respiratory events was performed on a computer monitor. PLMS were scored according to ASDA criteria [1] in order to establish an index of these events per hour of sleep during the CPAP nights. Care was taken to differentiate these well-defined PLMS from phasic activity in REM sleep. Leg movements that occurred as part of general body movements in association with EEG arousals following residual respiratory events at the initial phase of CPAP titration were not scored as PLMS.

The procedure for CPAP titration was as follows: increase by 1 mb step every minute until apneas were eliminated and increase by 1 mb step every 5 min until hypopneas, flow limitation and snoring were eliminated, and esophageal pressure swings (when available), from end-expiratory to peak-inspiratory pressure, were reduced to below 10 mb.

3. Results

The age of the 57 patients ranged from 27 to 76 years at the time of the OSAS diagnosis (mean, 54.6 ± 11.2 yr); 44 were males (77.1%). At the first period, their mean body mass index (BMI) was 33.2 ± 7.1 kg/m². The mean apneahypopnea index (AHI) was 53.3 ± 26.1. The mean
minimal $\text{SaO}_2$ was 85.1 ± 12.4% and the calculated CPAP level was 9.5 ± 2.11 mb.

At follow-up after 1 year of home CPAP, the mean objective use of CPAP was 5.5 ± 2.04 h/day. The mean BMI was not significantly changed (33.5 ± 7.1 kg/m²; $P$ = n.s.) and no significant residual respiratory events were observed with CPAP during the control polysomnography. Only minor CPAP level adjustments were made in some patients, essentially to eliminate snoring (mean change of CPAP pressure: −0.1 ± 1.7 cmH₂O). Globally, sleepiness was improved, by both subjective and objective assessment, compared to the first period: ESS score was 8.3 ± 4.3 vs 11.6 ± 4.8 ($P < 0.001$), the mean latency at the MSLT1 was 16.5 ± 4 vs 13.3 ± 5 min ($P < 0.001$) and the number of positive naps (MSLTn1) was 1.7 ± 1.6 vs 2.8 ± 1.7 ($P < 0.001$) (Table 1).

During the second recorded night, when the optimal CPAP pressure was reached, 23 patients (38.5%) had a PLMS index > 5. The mean index was 44.7 ± 39.5 PLMS/h sleep compared to 0.07 ± 0.44 in the group without significant PLMS index ($P < 0.0001$). Both groups, with and without PLMS, were similar in gender distribution, BMI, AHI and CPAP level, but patients with PLMS were older (58.8 ± 11.3 vs 52 ± 10.5 yr; $P = 0.03$). At the follow-up evaluation, after 1 year of home CPAP, the mean index of PLMS, in the PLMS group, was 50 ± 56.2. In the group without significant PLMS at the first evaluation, two patients showed a PLMS index > 5 at the follow-up (30 and 12.1, respectively) and were excluded from subsequent analysis. The mean index of PLMS in this group was then 0.6 ± 1.57. The home CPAP use during the year following OSAS diagnosis was similar in both groups (Table 2).

Sleepiness was not substantially different between the two groups, but the group with PLMS showed a tendency to be less somnolent. At the first evaluation, before CPAP therapy, the mean sleep latency in MSLT0 was 14.7 ± 4.46 min in the group with PLMS and 12.43 ± 5.4 min in the group without PLMS ($P = 0.05$). The group with PLMS slept a mean of 2.5 ± 1.7 of the five nap attempts, and the group without PLMS slept a mean of 3.11 ± 1.75 ($P = 0.1$). The ESS score (ESS0) was 10.5 ± 3.05 in the group with PLMS and 12.34 ± 5.6 in the group without PLMS ($P = 0.06$).

At the follow-up evaluation after 1 year of CPAP treatment the ESS1 score was 7.73 ± 5.3 in the group with PLMS and 8.71 ± 4.8 in the group without PLMS ($P = 0.19$). The mean sleep latency in the MSLT1 was 17.4 ± 3.69 min for the group with PLMS and 15.94 ± 4.14 for the group without PLMS ($P = 0.09$). The mean positive MSLT nap (MSLTn1) was 1.3 ± 1.5 in the group with PLMS and 2.1 ± 1.73 in the group without PLMS ($P = 0.05$).

The change in the ESS score between the two evaluations (ESS1 − ESS0) was −2.7 ± 4.7 for the group with PLMS and −3.6 ± 6.8 for the group without PLMS ($P = 0.29$). The change in the mean MSLT sleep latency (MSLT1 − MSLT0) was 2.7 ± 5 min for the PLMS group vs 3.5 ± 4.2 min in the group without PLMS ($P = 0.27$). The change in the number of positive MSLT naps (MSLTn1 − MSLTn0) was −1.1 ± 2.1 for the PLMS group vs −1.1 ± 1.8 ($P = 0.41$), for the group without PLMS.

Some patients had few PLMS and, theoretically, could have obscured an association between sleepiness and PLMS in other patients. When comparing 14 patients with a PLMS index > 5 with the patients with a PLMS index ≤ 5 there were no differences in the ESS (ESS0 = 11 ± 2.6

<table>
<thead>
<tr>
<th>variable</th>
<th>Period 0 (n=57)</th>
<th>Period 1 (n=57)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>33.2 ± 7.1</td>
<td>33.5 ± 7.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>CPAP (mb)</td>
<td>9.5 ± 2.1</td>
<td>9.2 ± 2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>MSLT min</td>
<td>13.3 ± 5.1</td>
<td>16.5 ± 4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSLTn</td>
<td>2.8 ± 1.7</td>
<td>1.7 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESS</td>
<td>11.6 ± 4.8</td>
<td>8.3 ± 4.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Period 0, first polysomnographic evaluation at the OSAS diagnosis; Period 1, follow-up evaluation, after 1 year of home CPAP; BMI, body mass index; CPAP, level of continuous positive airway pressure; MSLT min, mean sleep latency on a Multiple Sleep Latency Test; MSLTn, number of positive naps during MSLT; ESS, score on the Epworth Sleepiness Scale.

Table 2

<table>
<thead>
<tr>
<th>PLMS, n=22 (38.5%)</th>
<th>No PLMS, n=35 (61.5%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.8 ± 11.3</td>
<td>52 ± 10.5</td>
</tr>
<tr>
<td>%Male</td>
<td>81.80%</td>
<td>74.20%</td>
</tr>
<tr>
<td>BMI</td>
<td>32.9 ± 6.9</td>
<td>33.4 ± 7.4</td>
</tr>
<tr>
<td>AHI</td>
<td>58.2 ± 31.9</td>
<td>50.2 ± 21.7</td>
</tr>
<tr>
<td>Mean min$\text{SaO}_2$</td>
<td>82 ± 19</td>
<td>87.1 ± 4.5</td>
</tr>
<tr>
<td>CPAP level</td>
<td>9.8 ± 2.2</td>
<td>9.3 ± 2</td>
</tr>
<tr>
<td>CPAP use</td>
<td>5.3 ± 2.2</td>
<td>5.6 ± 1.9</td>
</tr>
<tr>
<td>ESS0</td>
<td>10.5 ± 3</td>
<td>12.3 ± 5.6</td>
</tr>
<tr>
<td>MSLT0 min</td>
<td>14.7 ± 4.4</td>
<td>12.4 ± 5.4</td>
</tr>
<tr>
<td>MSLT0n</td>
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<td>3.1 ± 1.7</td>
</tr>
<tr>
<td>ESS1</td>
<td>7.7 ± 3.5</td>
<td>8.7 ± 4.7</td>
</tr>
<tr>
<td>MSLT1 min</td>
<td>17.4 ± 3.6</td>
<td>15.9 ± 4.1</td>
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<tr>
<td>MSLT1n</td>
<td>1.3 ± 1.5</td>
<td>2 ± 1.7</td>
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<tr>
<td>$\Delta$ESS</td>
<td>−2.7 ± 4.7</td>
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<tr>
<td>$\Delta$MSLTn</td>
<td>−1.1 ± 2.1</td>
<td>−1.1 ± 1.8</td>
</tr>
</tbody>
</table>

No PLMS, patients with PLMS index < 5 PLMS/h of sleep; PLMS, patients with PLMS index > 5 PLMS/h of sleep; BMI, body mass index; AHI, apnea/hypopnea index; Meanmin$\text{O}_2$, mean minimal oxygen saturation. CPAP, level of continuous positive airway pressure; CPAP use, mean utilisation CPAP at home/day. ESS0, Epworth Sleepiness Scale score before CPAP treatment; MSLT0 min, mean sleep latency on a Multiple Sleep Latency Test before CPAP treatment; MSLT0n, number of positive naps during MSLT before CPAP treatment; ESS1, Epworth Sleepiness Scale score after CPAP treatment; MSLT1 min, mean sleep latency on a Multiple Sleep Latency Test after CPAP treatment; ESS1, Epworth Sleepiness Scale score after CPAP treatment; MSLT1n, number of positive naps during MSLT after CPAP treatment; $\Delta$ESS, ESS1 − ESS0; $\Delta$MSLT min, MSLT1 − MSLT0; $\Delta$MSLTn, MSLT1n − MSLT0.

* Excluded two patients with PLMS index >5/h of sleep during the control polysomnography at the follow-up evaluation.

with PLMS and 12.34 ± 5.6 in the group without PLMS ($P = 0.06$).
vs 12.3 ± 5.6; ESS1 = 8.2 ± 4.1 vs 8.7 ± 4.7; \( P = \text{n.s.} \),

MSLT (MSLT0 = 15 ± 4.6 vs 12.4 ± 5.4 min; MSLT1 = 17.2 ± 2.7 vs 15.9 ± 4.1 min; \( P = \text{n.s.} \)) or MSLTn (MSLT0 n = 2.2 ± 1.8 vs 3.1 ± 1.7, MSLT1 n = 1.5 ± 1.4 vs 2 ± 1.7; \( P = \text{n.s.} \)).

Bivariate correlation analysis using Pearson correlation coefficient was used to determine the correlations between PLMS index and clinical and sleepiness variables. PLMS index was related to age \( (r = 0.6 \text{ for the first evaluation and } r = 0.68 \text{ for the follow-up evaluation; } P < 0.01) \), and PLMS index during the control polysomnography was correlated with PLMS index during the first evaluation \( (r = 0.8; P < 0.001) \), but no correlation was found with BMI, AHI, CPAP level, CPAP use, ESS, MSLT or MSLTn.

4. Discussion

The main goal of our study was to explore the role of PLMS in sleepiness in OSAS patients, before and after CPAP treatment. The overall conclusion that can be drawn from our results is that, in these patients, the presence of PLMS is not associated with increased sleepiness, as measured by the MSLT or by the ESS.

In the present study we analyzed data from polysomnographic recordings in patients diagnosed with OSAS before and after 1 year of CPAP treatment. This choice permitted us to differentiate clearly the sleepiness associated with respiratory events and PLMS-related sleepiness. As shown by the absence of difference between groups at the first evaluation, PLMS seems not to play an additive role in respiratory event-related sleepiness. Assuming that PLMS persisted during the year following OSAS diagnosis (suggested by their persistence at the control polysomnography), PLMS seem not to be responsible for residual sleepiness, as pointed out by the absence of difference in sleepiness measurements in both groups at follow-up evaluation.

Our results are in accordance with previous reports. Mendelson [7] examined 67 patients with PLMD. He did not find a significant correlation between the PLMS arousal index (PLMS with EEG changes occurring simultaneously or 1 s following the leg movement) and either the MSLT mean sleep latency or subjective sleepiness. The PLMS arousal index did not differentiate those patients who entered with chief complaints of insomnia or sleepiness, and there was no significant difference in the PLMS arousal index in those who reported that they did or did not awaken refreshed in the morning. In addition, he examined 518 OSAS patients and found 10% having a PLMS arousal index > 5 (mean 17 ± 2). These patients were less sleepy, as assessed by the MSLT. In the entire OSAS group there was a statistically significant, but quantitatively small positive correlation between the PLMS-arousal index and the mean sleep latency in the MSLT.

Among patients with suspected or confirmed SDB, Chervin [8] showed that increased numbers of PLMS were not associated with increased sleepiness in the MSLT or ESS. His data suggested that even in patients with more severe SDB, the rate of PLMS showed a small, but significant association with less severe objective sleepiness.

It must be pointed out that these two studies were carried out in the initial evaluation of OSAS patients, when movements secondary to the arousal which occurs at the end of the respiratory event could be misinterpreted as a PLMS.

However, the belief that PLMS can cause sleepiness is widely prevalent [15], and it is expressed in the International Classification of Sleep Disorders [2].

It is possible that the absence of correlation between the index of PLMS and the measure of sleep propensity results from the difficulty of quantifying sleepiness. Sleepiness is probably not a unitary concept and can reflect essentially different states. The MSLT and the ESS are considered as the gold standards in the assessment of sleepiness and certainly offer valuable information, but they do not grasp all aspects of sleepiness [16,17].

The absence of correlation between the index of PLMS and sleepiness does not mean that PLMS is without clinical significance. The autonomic response during PLMS, such as cardiac activation [18] and the increases in systolic blood pressure [19] would be conducive to long-term cardiovascular consequences, particularly in a risk population such as apneic patients, but this assertion needs further investigation. PLMS would also interfere with the sleep of the patient’s partner. Recording of leg movements is necessary to distinguish PLMS from other involuntary movements in sleep that warrant treatment and vigilance (e.g. REM sleep behavior disorder) and to document PLM during wakefulness and sleep in RLS. PLMS could be associated with central hypoventilation, and if anterior tibialis EMG is not recorded, PLMS could be misinterpreted as respiratory-related leg movements [20].

Our study has several limitations. One of the limitations is that EEG arousals associated with PLMS were not scored and a PLMS arousal index was not calculated. As the question that we wished to ask was if PLMS per se were responsible for daytime sleepiness, we evaluated all PLMS independent of the presence or absence of EEG arousals. Therefore, the relationship between PLMS and arousal is not truly understood. It has been shown that arousals often precede rather than follow the movements [21], and they are still present after suppression of leg movements with L-dopa [22], suggesting that leg movements are not the cause of the arousals, but rather a phenomenon associated with an underlying arousal disorder, or that they reflect a physiologic mechanism that maintains sleep in the face of arousing stimuli such as the cyclic alternating pattern [23]. However, even PLMS without visible arousals show changes in EEG spectral activity and heart rate [18]. These data suggest that arousals are probably not the only parameter of activation to
consider when evaluating sleep disruption presumably associated with PLMS, because it has been shown that stimuli that produce measurable cardiovascular disturbances without cortical EEG activation appear sufficient to produce daytime sleepiness [24]. According to its guidelines, the MSLT was performed following an all-night polysomnography. Although this night was the adaptation night, we do not think that this fact could affect the results. It has been shown that the results of MSLT and other measures of daytime sleepiness are not influenced by whether or not the subjects had polysomnography the night prior to MSLT [25]. In our study CPAP titration was performed by well-trained technicians to eliminate apneas, hypopneas, flow limitation and snoring. However, while esophageal pressure monitoring during polysomnography was not systematically used, we cannot formally exclude the presence of leg movements associated with respiratory event related arousal (RERA) [26]. CPAP titration that suppresses apneas, hypopneas and snoring may not necessarily be adequate to eliminate increased upper airway resistance [11], and it has been suggested that the increased PLMS reported with CPAP could be due to the conversion of frank apneas to RERAs [26]. However, this fact could contribute to additional sleepiness in the PLMS patient group, a finding that is not observed in our sample. In the same sense, during CPAP titration, there is a period of time before the optimal pressure is reached in which respiratory events persist, and leg movements could be the result of this. Care was taken not to include leg movements at the end of remaining respiratory events as PLMS, but a bias cannot be excluded toward a higher number of events for both groups at baseline by this fact.

In conclusion, in this study we found that PLMS is a frequent phenomenon in OSAS patients, but we could not show a link between PLMS and increased objective or self-evaluated sleepiness in successfully treated patients before or after CPAP treatment.

References