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Research Article

Continuous Positive Airway Pressure Treatment can Unmask Periodic Limb Movements in Patients with Obstructive Sleep Apnea

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Abstract

To test the hypothesis that obstructive sleep apnea (OSA) can mask concurrent periodic limb movements during sleep (PLMS), which becomes evident or worsens after treatment with continuous positive airway pressure (CPAP), the present study investigated the frequency of PLMS during polysomnography (PSG) for OSA diagnoses and for CPAP titration in consecutive patients with OSA. A total of 142 consecutive patients (29 women and 113 men; mean age of 53±10 years; body mass index of 31±6 kg/m^2) referred to PSG for OSA diagnostic (PSG1) and CPAP titration (PSG2) on two different nights were retrospectively evaluated. The frequency of patients with PLMS index>5 events per hour of sleep was 13 (9%) in PSG1 and 18 (13%) in PSG2. Only four patients had PLMS index>5 in both PSGs. A decrease of the PLMS index was observed in two of the four patients who sustained PLMS index>5 in PSG2 compared to PSG1. These findings showed that the CPAP treatment can unmask but not exacerbate PLMS in patients with OSA.

ABBREVIATIONS

OSA: Obstructive Sleep Apnea; PLMS: Periodic Limb Movements During Sleep; Plmsi; Index of Periodic Limb Movements During Sleep; CPAP: Continuous Positive Airway Pressure; PSG: Polysomnography; EMG: Electromyogram; BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; AHI: Apnea-Hypopnea Index; Spo_2: Oxyhemoglobin Saturation

INTRODUCTION

Periodic limb movements during sleep (PLMS) are characterized by repetitive, involuntary, highly stereotyped movements, most frequently observed in the lower extremities [1]. PLMS could be associated with significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning [2], and this association is classified as Periodic Limb Movement Disorder by the International Classification of Sleep Disorders [1].

The exact prevalence is not known, but PLMS has been reported in both children and adults [1-3] and may be seen concurrently with different sleep disorders [4-7], including obstructive sleep apnea (OSA) [8-14].

Moreover, some studies reported that PLMS are more likely to occur or worsen during continuous positive airway pressure (CPAP) titration in patients with OSA [8-14].

To test the hypothesis that OSA can mask concurrent PLMS, which becomes evident or worsens after treatment with CPAP, the purpose of the present study was to investigate the frequency of PLMS during polysomnography (PSG) for OSA diagnoses and for CPAP titration in consecutive patients with OSA.

MATERIALS AND METHODS

We retrospectively evaluated consecutive patients referred to the Sleep Institute - AFIP for two overnight in-lab PSGs: first PSG (PSG1) for diagnosis of OSA and second PSG (PSG2) for CPAP titration, during the period from March 2003 to March 2007. PSGs were performed using EMBLA S7000 equipment (Embla Systems, Inc., Broomfield, CO, USA) and included the recording of the electroencephalogram (C3-A2, C4-A1, O2-A1, O1-A2),

electrooculogram, chin and tibial anterior electromyogram (EMG), electrocardiogram (modified V2 lead), airflow (nasal cannula and oronasal thermistor), respiratory efforts (chest and abdominal respiratory-inductive-plethysmography effort belts), oxyhemoglobin saturation (SpO2), body position, and snoring. Sleep stages scoring was performed according to the Rechtshaffen & Kales criteria [15]. Respiratory events were evaluated according to the task force of the American Academy of Sleep Medicine [16]. Arousals [17] and PLMS [18] were scored according to the criteria of the American Sleep Disorders Association. The PLMS associated with respiratory events during sleep were excluded, i.e., an apnea or hypopnea and a PLMS were assumed to be associated with each other if they overlapped or if the end of one event and the beginning of the other event were within 0.5 seconds or less of each other, regardless of which event was first.

Patients were divided into two groups according to the values of the PLMS index (PLMSi): below and above five events per hour of sleep. The full night CPAP titration protocol included: (1) all patients received a hands-on demonstration of CPAP equipment, careful mask fitting, and acclimatization prior to titration; (2) starting CPAP was 4 cm H_2O and pressure was increased by at least 1 cm H_2O with an interval of no less than 5 minutes until the following obstructive respiratory events were eliminated: apneas, hypopneas, respiratory effort-related arousals, and snoring; (3) maximum CPAP was 20 cm H_2O; (4) If the patient woke up and complained that the pressure was too high, the pressure was restarted at a lower pressure, chosen as one that the patient reports was comfortable enough to allow return to sleep. All CPAP titrations were done with device Resmed VPAP™ III.

The Epworth Sleepiness Scale (ESS) [19] was applied on the night of each PSG before electrodes hook up.

Statistical assessment: The Kolmogorov-Smirnov normality test was performed to verify the variables distribution. Numerical variables followed a normal distribution were presented as means and standard deviations. Student's t test for dependent samples and for independent samples was performed. Logistic regression analysis was used for evaluate the effect of the PSG variables during CPAP titration on PLMSi>5. Delta AHI and delta SpO_2 nadir was used. The significance value was $p < 0.05$. The sample size was estimated in N=34, calculated for GPower 3.1.2 software. The analyzed parameter was PLMSi with effect size d=1.18, p<0.05, observed power: 0.95, using Student's t test for dependent samples.

RESULTS

The PSG of 142 patients (29 women and 113 men) with a mean age of 53±10 years (range: 33 to 86 years), body mass index (BMI) of 31±6 kg/m^2 (range: 19.5 to 49.1 kg/m^2) and ESS score of 12±6 (range: 0 to 24) were evaluated.

The frequency of patients with PLMSi>5 events per hour of sleep was 13 (9%) in PSG1 and 18 (13%) in PSG2. Only four patients had PLMSi>5 in both PSGs. Figure 1 shows the comparison between the values of the PLMSi from both PSG1 and PSG2 in 18 patients who had PLMSi>5 on PSG2. A decrease of PLMSi values was observed in two of the four patients who sustained PLMSi>5 in PSG2 compared to PSG1.

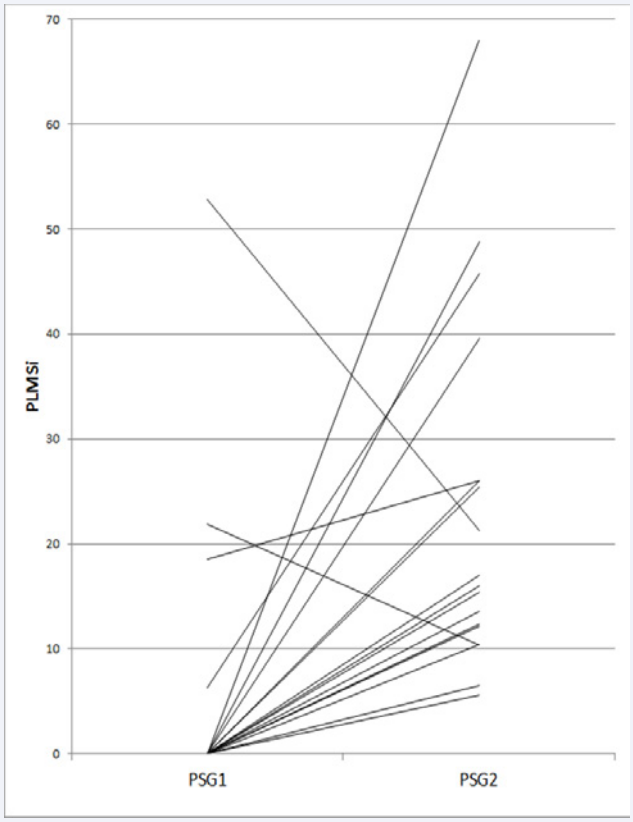

Figure 1 Comparison between the values of the periodic leg movements index (PLMSi) observed in polysomnography for the diagnosis of obstructive sleep apnea (PSG1) and for CPAP titration (PSG2) of the 18 patients who had PLMSi above five events per hour sleep in PSG2.

Comparing data from the patient group with PLMSi<5 and the group with PLMSi>5 (Table 1), in both PSGs, no significant differences were found for age, BMI, ESS score and variables of PSG, with the exception of PLMSi ($p < 0.01$) and decreased sleep efficiency in the group PLMSi>5 in PSG1 (80 ± 13% vs. 67±14%, respectively; $p = 0.008$). We observed high AHI values regardless of PLMi values.

Table 2 compares data from PSG1 and PSG2 in the patients who presented PLMSi>5 during the PSG2 (N = 18). Significant differences were found only in the apnea-hypopnea index (AHI) (40±55 vs. 19±22, $p = 0.002$) and in the SpO_2 nadir (72±14 *vs.* 85±5%, $p = 0.002$), as expected with CPAP treatment.

A logistic regression model evaluating the patients group with PLMi>5 showed the effect of SpO2 nadir after adjustment for pressure titration CPAP and gender (Table 3).

DISCUSSION

The present study showed that CPAP treatment can unmask but not exacerbate PLMS in patients with OSA, but the variability of this phenom should be considered. The frequency of PLMS was increased with CPAP treatment, but patients who presented

Table 1: Comparison between the groups of patients with a periodic leg movements index (PLMSi) lower and higher than five events per hour of sleep during polysomnography for the diagnosis of obstructive sleep apnea (PSG1) and for CPAP titration (PSG2) (mean ± standard deviation).

	PSG1			PSG2		
	PLMSi<5 N=129 (91%)	PLMSi>5 N=13 (9%)	P	PLMSi<5 N=124 (87%)	PLMSi>5 N=18 (13%)	P
Age, years	53±10	56±10	0.37	55±10	58±13	0.26
BMI, kg/m2	30±6	29±5	0.31	31±6	33±7	0.29
ESS score	12±6	10±4	0.14	12±7	12±7	0.86
Sleep latency, minutes	17±21	19±11	0.51	16 ± 14	15±11	0.62
REM latency, minutes	118±76	170±85	0.05	103±72	117±102	0.58
Sleep Efficiency, %	80±13	67±14	0.008	78±13	76±11	0.56
S1, %	6±5	8±6	0.26	6±4	5±4	0.79
S2, %	62±13	62±16	0.92	54±12	54±15	0.91
S3 + 4, %	14±10	14±11	0.84	20±9	20±12	0.89
REM sleep, %	17±7	15±7	0.31	20±9	21±12	0.86
PLMS index, events/h	2±2	32±18	0.003	2±2	23±17	<0.001
Arousal index, events/h	35±6	39±37	0.66	14±12	17±11	0.39
AHI, events/h	45±24	45±23	0.95	18±13	19±16	0.78
SpO2 nadir, %	75±14	79±8	0.15	84±9	85±3	0.49

Abbreviations: BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; S: Sleep Stage; AHI: Apnea-Hypopnea Index; Spo_2: Oxyhemoglobin Saturation

Table 2: Comparison of data from polysomnography for the diagnosis of obstructive sleep apnea (PSG1) and for CPAP titration (PSG2) of patients with a periodic leg movement index (PLMSi) above five events per hour of sleep during the PSG2 (N=18) (mean ± standard deviation).

	PSG1	PSG2	P
Sleep latency, minutes	23.4±27.5	14.9±11.1	0.23
REM latency, minutes	119.7±79.4	117.1±102.2	0.93
Sleep Efficiency, %	76.7±12.6	76.1±11.0	0.88
S1, %	6.3±4.4	5.4±3.8	0.50
S2, %	56.2±14.0	53.8±14.9	0.63
S3 + 4, %	19.1±11.8	19.5±12.4	0.92
REM sleep, %	18.2±7.6	20.6±12.0	0.48
PLMS index, events/h	5.5±13.5	23.3±16.9	0.003
Arousal index, events/h	23.5±15.7	16.7±11.7	0.19
AHI, events/h	40.2±22.5	18.8±16.5	0.002
SpO2 nadir, %	72.3±14.4	84.7±5.35	0.002

Abbreviations: S: Sleep Stage; AHI: Apnea-Hypopnea Index; Spo_2: Oxyhemoglobin Saturation

Table 3: Effect of full night CPAP titration on periodic limb movements.

	B	Wald	Sig.	Exp(B)	95% CI. for EXP(B)	
					Lower	Upper
Male gender	3.46	6.84	0.009	31.81	2.38	424.78
Delta SpO_2 nadir,%	0.04	4.08	0.04	1.04	1.00	1.09
Delta AHI	0.02	3.47	0.06	1.02	0.99	1.04
CPAP Pressure	0.14	3.17	0.07	1.15	0.98	1.36
Constant	-7.12	11.79	0.001	0.001		

-2 Log likelihood: 95.008; Cox & Snell R Square: 0.11; Nagelkerke R Square: 0.20
Abbreviations: AHI: Apnea-Hypopnea Index; Spo_2: Oxyhemoglobin Saturation

PLMS before and after CPAP exhibited decreased PLMSi after treatment.

Our data support the findings of Fry and coworkers [8], which showed that PLMS is common in patients with OSA and more prevalent during CPAP treatment than during baseline recording. This increase was attributed to the correction of respiratory events during sleep by CPAP, allowing for the manifestation of coexisting PLMS. They suggested that the absence of PLMS during an initial PSG diagnostic consistent with OSA does not preclude the occurrence of PLMS after successful treatment of the OSA.

Some authors [11] suggested that the both PLMS and respiratory events could have a common central generator based on some evidence: functional magnetic resonance imaging demonstrated that the red nucleus and the brainstem are stimulated during PLMS in patients with restless legs syndrome and PLMS, leading to the hypothesis that they could be the primary generators of this disorder [20]. Additionally, the repetitive nature of limb movements, occurring with a periodicity of 20 to 40 seconds, has supported the hypothesis of an underlying pacemaker in the central nervous system [21]. Likewise, OSA is characterized by repetitive episodes of upper airway obstruction that occur during sleep and the period between two successive apneas is the sum of the duration of the apnea plus the duration of inter apneic ventilation. The duration of apnea seems to be dependent on arousal caused by mechanoreceptor stimulation due to increased respiratory effort in a try to overcome upper airway obstruction. The duration of ventilation between respiratory events depends on the duration of the arousal. The periodicity of apneas could be dependent on the interaction of respiratory and sleep/wake regulatory mechanisms. These mechanisms could be modulated by a central generator that can explain the intra and inter-subject variability related to the duration of apnea and the duration of ventilation between the apneas. Thus, the frequency of approximately 30 to 40 seconds observed between respiratory events would have the same degree of magnitude as the periodicity of PLMS. However, the results showed by Carelli and coworkers [11] do not support the hypothesis of a common central generator being at the origin of OSA and PLMS. Data from that study showed that the periodicity of respiratory events was different from the periodicity of PLMS in OSA patients, before as well as after CPAP treatment.

Briellmann and colleagues [10] proposed that PLMS occurring in patients with OSA have a heterogeneous origin. They investigated the relationship between OSA and leg movements during sleep by categorizing leg movements into subgroups based on periodicity and the duration of inter-movement intervals and proposed that PLMS may be unmasked in some cases by CPAP treatment of OSA. In others patients, the presence of arousal due to incomplete CPAP treatment of OSA may itself cause PLMS, requiring optimization of CPAP for the PLMS to be eliminated. A similar suggestion was proposed by Seo & Guilleminault [14], who showed that PLMS does not disappear with the elimination of respiratory events, but with the elimination of flow limitation and the associated instability of NREM sleep. A limitation of the present study was that the esophageal pressure was not used to show the respiratory effort during sleep to confirm the complete absence of airflow limitation after CPAP adjustment in those patients with severe OSA.

The differential diagnosis of these two sleep disorders is difficult in the untreated OSA patient, given the presence of leg movements linked with arousal occurring post-apnea. The recording of the tibial EMG while CPAP treatment allows the diagnosis of PLMS and can explain the persistence of daytime sleepiness.

Another limitation of the present study was its retrospective nature. Besides, our data evaluated only one night of PLMSi with CPAP treatment. It could also reflect a limitation of the present study since an individual inter-night PLMS variability was previously observed [22], which should be considered in the clinical evaluation.

Although it is relatively well established the beneficial effect of treatment of OSA with CPAP [23,24], indeed, physicians should be aware that PLMS may be a possible cause of sleep disturbance and daytime fatigue complaints after beginning treatment with CPAP in OSA patients. To fully manage and treat this condition, more data are needed to understand the frequency and severity of this issue, in addition to identifying the causes of these conditions and potential treatment approaches. Potential research should include prospective studies utilizing multi-night PSG to assess the extent of PLMS on CPAP therapy, the assessment of night and daytime symptoms as a result of the PLMS, and the investigation of comorbidities.

CONCLUSION

The present study showed that CPAP treatment can unmask but not exacerbate PLMS in patients with OSA, but the variability of this phenomenon should be considered. The frequency of PLMS was increased with CPAP treatment but patients who presented PLMS before and after CPAP exhibited decreased PLMSi after treatment.

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