Journal of the Neurological Sciences 317 (2012) 13–16

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Change in frequency of periodic limb movements during sleep with usage of continuous positive airway pressure in obstructive sleep apnea syndrome

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ARTICLE INFO

Article history:
Received 10 November 2011
Received in revised form 17 March 2012
Accepted 19 March 2012
Available online 11 April 2012

Keywords:
Periodic leg movements during sleep
Obstructive sleep apnea syndrome
Continuous positive airway pressure
Titration
Polysomnography
Sleep disorder

ABSTRACT

Periodic limb movements during sleep (PLMS) sometimes newly appear on the night of continuous positive airway pressure (CPAP) titration in patients with obstructive sleep apnea syndrome (OSAS). To ascertain the incidence and causative factors of this phenomenon, we investigated differences in its prevalence and the factors associated with newly appeared and persistent PLMS on CPAP titration night. We retrospectively analyzed polysomnographic data of 997 consecutive OSAS outpatients who had undergone overnight CPAP titration. On the basis of changes in periodic limb movements index (PLMI) values (cut off level ≥ 15/h) from baseline polysomnography (BPSG) to CPAP titration PSG, patients were assigned to one of four groups: persistent, CPAP-emergent, CPAP-disappeared, and non-PLMS. The rate of patients was 6.7% in the persistent group, 8.0% in the CPAP-emergent group, 4.0% in the CPAP-disappearance group, and 81.2% in the non-PLMS group. Multivariate logistic regression analysis revealed that a higher apnea–hypopnea index (AHI) on BPSG and ≥ 47 years of age appeared to be associated with the CPAP-emergent group. The results suggest that elderly patients with higher AHI at BPSG may present with CPAP-emergent PLMS.

1. Introduction

Periodic limb movements during sleep (PLMS), characterized by rhythmic movements of the limbs which can disturb nocturnal sleep and cause excessive daytime sleepiness [1], are often observed on the night of continuous positive airway pressure (CPAP) titration in patients with obstructive sleep apnea syndrome (OSAS) [2–4]. Such PLMS can be classified as persistent PLMS, in which PLMS is pathologically frequent on both baseline polysomnography (BPSG) and CPAP titration polysomnography (CPSG), and newly appeared PLMS on CPSG (CPAP-emergent PLMS). However, the prevalence and clinical characteristics of these types of PLMS as well as those of CPAP-disappeared PLMS, in which PLMS disappear on CPSG, remain unclear. The American Academy of Sleep Medicine (AASM) updated the sleep disorder classification in 2005 to include a revised definition of PLMS of 15 events/h on the periodic limb movements index (PLMI: number of PLMS divided by total sleep time) from the original 5 events/h [1]. In this study, using this revised definition, we investigated changes in PLMS from BPSG to CPSG in OSAS patients and estimated the prevalence as well as the associated factors for each of the PLMS categories.

2. Methods

A total of 1262 consecutive OSAS outpatients visiting our clinic between 2003 and 2009 were eligible for this study. Patients who had undergone both BPSG and subsequent CPSG were targeted for analysis if they met the following criteria: 1) apnea–hypopnea index (AHI) value of at least 20/h on BPSG (applicable value for induction of CPAP treatment in OSAS for Japanese health insurance coverage); and 2) clear improvement of OSAS with CPAP titration, as reflected by AHI change to < 10/h [4]. Patients using medications such as antidepressants, antipsychotics, and antihistamics, all of which can worsen PLMS, were excluded from the study [5]. As a result, data for 997 OSAS patients (mean age: 47.9 ± 12.7 years, mean BMI: 28.1 ± 4.8 kg/m^2, mean AHI: 46.4 ± 20.7 events/h) were analyzed. This study was approved by the Ethics Committees of the Neuropsychiatric Research Institute, and all

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0022-510X/$ – see front matter © 2012 Published by Elsevier B.V.
doi:10.1016/j.jns.2012.03.013

OSAS patients provided written informed consent for the results to be presented in a report.

The following PSG measurements were conducted using a digital PSG system (Alice version 4/5, Respironics, USA) with video-monitoring: electroencephalography (C3–A2, C4–A1, O1–A2, O2–A1), electrooculography (right/left), electrocardiography, chin electromyography, bilateral–anterior tibialis electromyography, nasal/oral airflow, thoracic/abdominal respiratory movements, and arterial oxygen saturation. Sleep stages and arousal index (ArI) were scored manually according to the Rechtschaffen and Kales criteria [6] and the American Sleep Disorders Association arousal criteria [7], respectively.

Respiratory events (apnea/hypopnea) were defined according to the AASM Chicago criteria [8]. PLMS was scored as a minimum of 4 consecutive anterior tibialis contractions on electromyography, each lasting 0.5–5.0 s with an interval of 5–90 s [1]. PLMS at the end of respiratory events defined according to the AASM criteria was not scored, but PLMS appearing ≥1–2 s before the end of the respiratory event was scored [9]. The attended CPAP titration was performed manually simultaneous with all-night PSG recording, and the level of titrated pressure was set to minimum to eliminate apnea/hypopnea events, oxygen desaturation, and snoring.

AHI and PLMI on BPSG and CPSG were calculated, and patients were divided into the following 4 groups based on the change in PLMI value from BPSG to CPSG (cut off ≥15) [1]: persistent group: PLMI ≥15 on both PSGs; CPAP-emergent group: PLMI <15 in BPSG but ≥15 in CPSG; CPAP-disappeared group: PLMI ≥15 in BPSG but <15 in CPSG; and non-PLMS group: PLMI <15 on both PSGs.

A chi-square test and a one-way factorial analysis of variance (ANOVA) or non-parametric Kruskal–Wallis test were used to compare demographic variables for the 4 groups. Within each group, we assessed the changes in PLMI from BPSG to CPSG using the Wilcoxon signed rank test. To investigate the factors associated with each PLMS group, logistic regression analysis was performed with explanatory categorical variables found to be significant on univariate analysis. Age was dichotomized at the median value of 47 years and cut-off values of BMI and AHI were set at 25 kg/m^2 [10] (criteria for the pathological obesity in Japanese) and 30/h [11] (threshold value for severe OSAS), respectively. Statistical significance was set at $p<0.05$. All analyses were performed using the SPSS statistical package (SPSS Inc., Chicago, IL).

3. Results

Most patients were classified into the non-PLM group (81.2%), followed by the CPAP-emergent group (8.0%), persistent group (6.7%), and CPAP-disappeared group (4.0%) (Fig. 1). The Kruskal–Wallis test revealed significant differences in both PLMI on BPSG and PLMI on CPSG among the 4 groups (PLMI in BPSG: $p<0.001$; PLMI in CPSG: $p<0.001$). The Wilcoxon signed rank test also revealed that PLMI was significantly increased from BPSG to CPSG in the persistent, CPAP-emergent, and non-PLM groups, but was significantly decreased in the CPAP-disappeared group (all $p<0.001$; Fig. 1).

One-way ANOVA revealed a significant difference in mean age among the 4 groups ($F(3, 996)=23.22$, $p<0.001$), and a post-hoc test showed that mean age was significantly lower in the non-PLMS group than in the other 3 groups (all $p<0.001$; Table 1). Sex distribution differed significantly among the 4 groups ($p=0.001$), whereas BMI did not differ among them ($p=0.166$). The Kruskal–Wallis test revealed significant differences in AHI and ArI on BPSG and in ArI on CPSG among the 4 groups (AHI on BPSG: $p=0.002$; ArI on BPSG: $p<0.001$; ArI on CPSG: $p<0.001$). A post-hoc test showed that AHI and ArI on BPSG were significantly higher in the CPAP-emergent group than in the other 3 groups (AHI: $p<0.01$; ArI: $p<0.001$), and ArI on CPSG was significantly lower in the non-PLM group than in the other 3 groups (all $p<0.05$). The Wilcoxon signed rank test revealed that the decreases in AHI and ArI values from BPSG to CPSG were significant in all 4 groups (AHI and ArI returned to normal values in all 4 groups) (all $p<0.001$; Table 1).

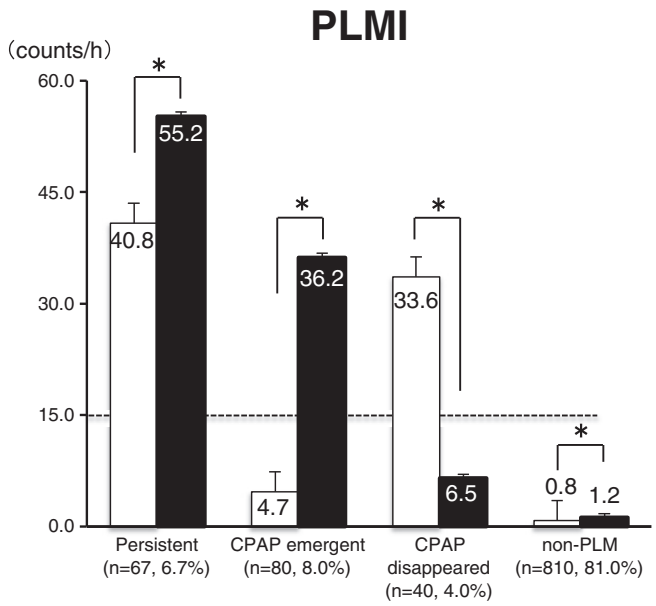

Fig. 1. Changes in PLMS according to the periodic limb movement index, from baseline PSG to CPAP titration PSG among 4 patient groups (n = 997). *p<0.05, Wilcoxon signed rank test between BPSG and CPSG. Percentages in parentheses represent the proportion of patients in each group in relation to the number of total subject patients.

Multivariate logistic regression analysis revealed significant associations of the CPAP-emergent group with higher age (≥47 years) and higher AHI (≥30/h) on BPSG (age: odds ratio (OR) = 1.69, CI = 1.05–2.71, p = 0.030; AHI: OR = 2.19, CI = 1.16–4.11, p = 0.015; Table 2). On the other hand, the persistent group was significantly associated with female sex and higher age (female sex: OR = 2.11, CI = 1.04–4.28, p = 0.039; age: OR = 3.82, CI = 2.08–7.01, p<0.001). The CPAP-disappeared group was significantly associated with female sex (female: OR = 2.44, CI = 1.03–5.79, p = 0.043). On the other hand, being female and higher age were negatively associated factors with the non-PLMS group (female: OR = 0.54, CI = 0.32–0.93, p = 0.023; age: OR = 0.39, CI = 0.28–0.55, p<0.001).

4. Discussion

To our knowledge, this is the first study to estimate the prevalence of PLMS categories in OSAS patients who undergo CPAP titration and to ascertain the associated factors for these groups in a relatively large sample.

The prevalence of PLMS has been estimated at 7.6% in the general population [12], which is similar to that of persistent PLMS in this study (6.7%). Moreover, persistent PLMS was significantly associated with higher age in this study, while non-PLMS was associated with lower age. These findings support that PLMS constitutes an age-dependent phenomenon in the general population [13]. Thus, persistent PLMS as seen in the present study is thought to be not so different from idiopathic PLMS.

As for sex, persistent PLMS and CPAP-disappeared PLMS were associated with being female, and non-PLMS was associated with being male. These findings are in line with the fact that restless legs syndrome (RLS), which shares a common pathogenesis with PLMS, is particularly common in women [1,14]

Of note, in the present study, the rate of CPAP-emergent PLMS was the same or just slightly higher than that of persistent PLMS, suggesting that CPAP-emergent PLMS is a relatively common phenomenon. As for the underlying mechanism of the frequent appearance of PLMS on CPAP titration, the “unmasking” of underlying idiopathic

Table 1
Descriptive variables for the 4 patient groups.

		All patients	① Persistent group	② CPAP-emergent group	③ CPAP-disappeared group	④ Non-PLMS group	P-value	Results of post-hoc test ($p<0.05$)
N (%)		997 (100)	67 (6.7)	80 (8.0)	40 (4.0)	810 (81.2)	–	–
Age (years)		47.8 ± 12.7	56.6 ± 11.9	51.6 ± 13.7	55.7 ± 15.2	46.3 ± 12.0	<0.001[a]	①,③,②>④
Sex (M/F)		923/74	56/11	74/6	33/7	760/50	0.001[b]	
BMI (kg/m^2)		28.1 ± 4.9	26.9 ± 3.2	28.6 ± 4.4	28.3 ± 5.9	28.1 ± 4.9	0.166[a]	
AHI (counts/h)	Baseline	46.5 ± 20.8	44.5 ± 16.8	55.1 ± 22.2	42.8 ± 15.4	46.0 ± 21.0	0.002[c]	②>④,①,③
	CPAP	3.1 ± 2.4	3.2 ± 2.0[d]	3.8 ± 2.7[d]	2.9 ± 2.5[d]	3.0 ± 2.4[d]	0.035[c]	②>④
ArI (counts/h)	Baseline	41.5 ± 20.2	41.8 ± 20.6	51.7 ± 23.5	37.4 ± 20.2	40.7 ± 19.6	<0.001[c]	②>①, ④,③
	CPAP	14.4 ± 7.8	18.6 ± 12.0[d]	16.1 ± 8.6[d]	17.6 ± 8.4[d]	13.7 ± 7.1[d]	<0.001[c]	①,③>④

Values are expressed as mean ± SD except for gender.
M: male, F: female, BMI: body mass index, AHI: apnea–hypopnea index, ArI: arousal index.
[a] One-way factorial analysis of variance (ANOVA) among 4 groups.
[b] Chi square test for 2 (gender) × 4 groups.
[c] Kruskal Wallis test among 4 groups.
[d] $p<0.05$ between BPSG and CPSG (Wilcoxon signed rank test).

PLMS through removal of respiratory events and its associated arousals when using CPAP should be considered [2,4]. The significantly higher values of AHI and ArI on BPSG in the CPAP-emergent group, compared with the other 3 groups, might partially support such a hypothesis. However, the values of these variables on CPAP were normalized similarly in all 4 groups. Also, given that the increase of PLMS on CPSG in the persistent group remained at 35.3%, the extreme elevation of PLMI on CPSG in the CPAP-emergent group (7.7-fold higher than the value on BPSG) could not be explained completely by an "unmasking effect" alone. Another possible explanation for the appearance of CPAP-emergent PLMS is night-to-night variability of PLMS [15]. However, the remarkable increase in PLMS in the emergent PLMS group cannot be simply explained by night-to-night variability.

Patients with severe OSAS are frequently complicated by hypertension mainly due to hyperactivity of the sympathetic nervous system brought about by frequent arousal responses and intermittent

Table 2
Results of multivariate logistic regression analyses on associated factors for the 4 groups (n = 997).

		N	Univariate OR	95%Cl	P-value	Multivariate OR	95%Cl	P-value
Persistent group								
Sex	Male	56	1		0.005	1		0.039
	Female	11	2.70	1.35–5.42			2.11	1.04–4.28
Age (years)	<47	14	1		<0.001	1		<0.001
	≥47	53	4.06	2.22–7.41		3.82	2.08–7.01	
BMI (kg/m^2)	<25	18	1		0.667	–		–
	≥25	49	0.884	0.51–1.55		–	–	
AHI on BPSG (events/h)	<30	17	1		0.745	–		–
	≥30	50	1.10	0.62–1.94		–	–	
CPAP-emergent group								
Sex	Male	74	1		0.978	–		–
	Female	6	1.01	0.43–2.41		–	–	
Age (years)	<47	30	1		0.025	1		0.030
	≥47	50	1.72	1.07–2.75		1.69	1.05–2.71	
BMI (kg/m^2)	<25	17	1		0.460	–		–
	≥25	63	1.23	0.71–2.15		–	–	
AHI on BPSG (events/h)	<30	12	1		0.013	1		0.015
	≥30	68	2.22	1.18–4.17		2.19	1.16–4.11	
CPAP-disappeared group								
Sex	Male	33	1		0.017	1		0.043
	Female	7	2.82	1.20–6.61		2.44	1.03–5.79	
Age (years)	<47	13	1		0.030	1		0.057
	≥47	27	2.11	1.07–4.13		1.94	1.98–3.84	
BMI (kg/m^2)	<25	11	1		0.672	–		–
	≥25	29	0.86	0.42–1.74		–	–	
AHI on BPSG (events/h)	<30	11	1		0.951	–		–
	≥30	29	0.98	0.48–1.99		–	–	
Non-PLMS group								
Sex	Male	760	1		0.002	1		0.023
	Female	50	0.45	0.27–0.75		0.54	0.32–0.93	
Age (years)	<47	438	1		<0.001	1		<0.001
	≥47	372	0.37	0.27–0.52		0.39	0.28–0.55	
BMI (kg/m^2)	<25	200	1		0.979	–		–
	≥25	610	1.00	0.69–1.43		–	–	
AHI on BPSG (events/h)	<30	230	1		0.053	–		–
	≥30	580	0.69	0.47–1.00		–	–	

95% CI: 95% Confidence Interval, BPSG: baseline polysomnography (PSG); OR: odds ratio Age: dichotomize at median value of 47 years old.
AHI on BPSG: cut off value was set at 30 events/h (criteria for severe OSAS).
BMI: cut off value was set at 25 kg/m^2 (criteria for pathological obesity in Japanese).

hypoxemia, and this pathological process cannot be normalized quickly with CPAP titration [16]. The increased sympathetic nervous activity (SNA) in these patients is thought to play a role in the formation of PLMS [17]. Given the significant associations of OSAS severity and age with CPAP-emergent PLMS in this study, the increased SNA due to OSAS and increased neurological or physiological vulnerability to PLMS due to aging [13] might additively contribute to the formation of this phenomenon. To verify this hypothesis, further study is necessary of the relationship between changes in markers of SNA and PLMS and the changes between BPSG and CPSG.

The present study has several limitations. First, the clinical significance of persistent and CPAP-emergent PLMS remains unclear, and further investigation is needed to evaluate subjective sleep disturbance possibly attributable to PLMS [1]. Second, we used the scoring rules of ASDA and ICSD-2nd, but did not use the scoring manual of AASM 2007 for assessing the data collected before the establishment of this scoring manual. Third, we examined acute changes in PLMS from BPSG to CPSG among OSAS patients, and further study is needed to investigate the long-term outcome of CPAP-emergent PLMS. Nevertheless, our results suggest that CPAP-emergent PLMS constitutes an OSAS severity- and age-dependent phenomenon. Therefore, our findings will likely provide practical merit since CPAP-emergent and persistent PLMS may cause residual excessive daytime sleepiness or increase the risk for developing hypertension after starting CPAP treatment.

Disclosure statement/funding sources for study

This study was supported by a Ministry of Education, Culture, Sports, Science and Technology grant.

Conflict of interest

All authors declare no conflicts of interest associated with this study.

Acknowledgements

This study was supported in part by a Research Grant for Nervous and Mental Disorders (21-4) from the Ministry of Health, Labour and Welfare of Japan.

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