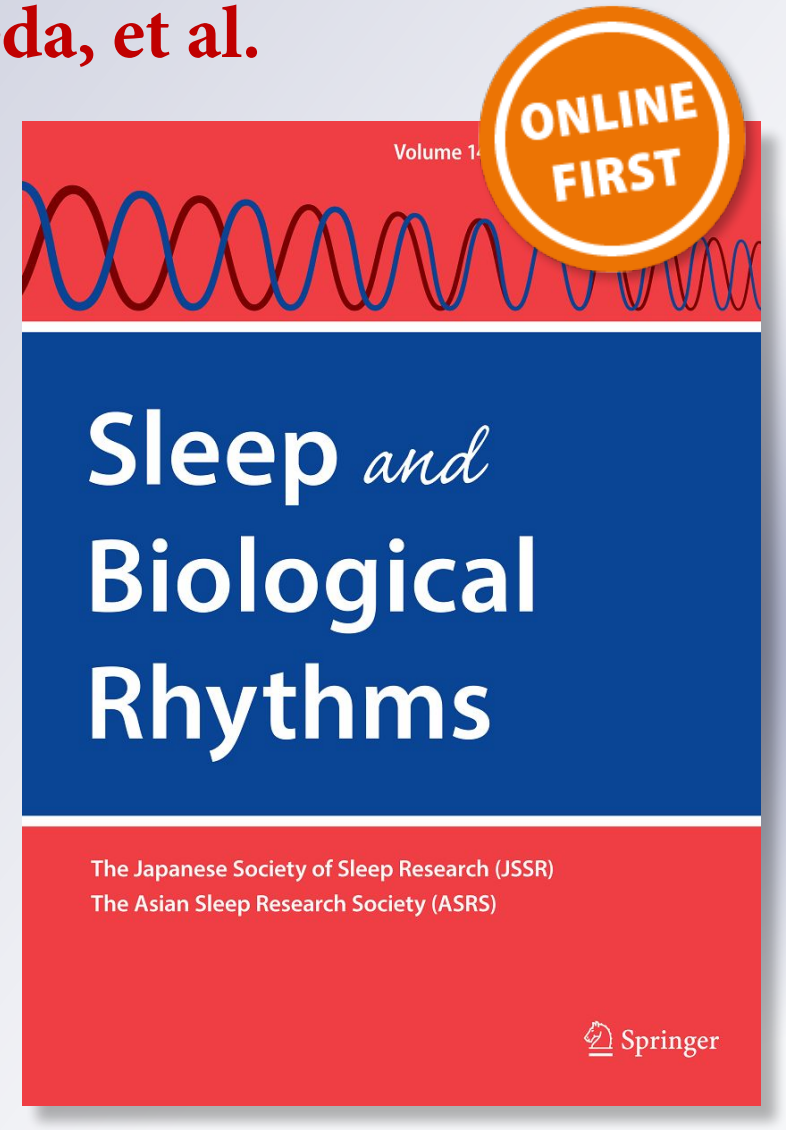
Possible effect of periodic limb movements during sleep on the sleepiness of patients with sleep disordered breathing

Masatoshi Hirata, Seiichi Nakata, Mahmood A. Hamed, Noboru Iwata, Yoichi Nishimura, Miyoko Nishiura, Yoshihiro Imaeda, et al.

Sleep and Biological Rhythms

ISSN 1446-9235

Sleep Biol. Rhythms
DOI 10.1007/s41105-015-0043-5



Springer

Sleep Biol. Rhythms
DOI 10.1007/s41105-015-0043-5

ORIGINAL ARTICLE

Possible effect of periodic limb movements during sleep on the sleepiness of patients with sleep disordered breathing

Masatoshi Hirata[1] · Seiichi Nakata[2] · Mahmood A. Hamed[2] · Noboru Iwata[2] · Yoichi Nishimura[2] · Miyoko Nishiura[1] · Yoshihiro Imaeda[1] · Fumihiko Yasuma[3] · Masaaki Matsunaga[4] · Hiroshi Yatsuya[4]

Received: 23 February 2015 / Accepted: 6 December 2015

Abstract We aimed to conduct a cross-sectional study in order to investigate the effect of periodic limb movements during sleep (PLMS) on daytime sleepiness in patients with sleep disordered breathing especially those with obstructive sleep apnea syndrome (OSAS), diagnosed by polysomnography (PSG). Our subjects included 233 male patients who visited our institute during the 25-month period between June 2012 and June 2013. We scored the number of Periodic Limb Movements per hour as the Periodic Limb Movements Index (PLMI) on standard PSG, and considered that periodic limb movements during sleep was present in the patients with PLMI >15/h. Non-PLMS group included those patients with PLMI ≤15/h. To assess the sleepiness of participants, we used Japanese version of the Epworth Sleepiness Scale (JESS) and Japanese version of the Pittsburgh Sleep Quality Index. We compared the sleep parameters and sleepiness indicators between patients with PLMS and age, apnea–hypopnea index (AHI), and body mass index-matched non-PLMS control groups. JESS scores were higher in patients with PLMS than in non-PLMS in both low AHI (<15/h) and high AHI (≥15/h) strata. However, the difference was statistically significant only in high AHI stratum ($P = 0.399$ and 0.001, respectively). In conclusion, PLMS was associated with increased JESS especially in patients with moderate-to-severe OSAS. Although the magnitude of the difference in those with AHI <15/h was smaller and statistically insignificant in the present study, this issue warrants further investigation by enrolling more patients with AHI <15/h.

Keywords Japanese version of the Epworth Sleepiness Scale · Obstructive sleep apnea syndrome · Periodic limb movements during sleep · Sleep disordered breathing · Sleepiness

Introduction

Periodic limb movements during sleep (PLMS) is a frequent finding in polysomnography (PSG), defined as repetitive episodes of leg muscles' contraction for 0.5–10 s, separated by free interval of 5–90 s [1]. Limb movements were not scored if they occurred within 0.5 s preceding or following an apnea or hypopnea [1]. The occurrence of PLMS at a rate of >15/h of sleep is regarded as pathological [2]. PLMS is a common variety among sleep-disordered breathing (SDB) representing about 20–30 % [3]. PLMS rarely appears below age 50 years, and its frequency increases with aging [4]. Coleman et al. [5] demonstrated that in patients with primary insomnia and significant PLMS, there was no correlation between the Periodic Limb Movements Index (PLMI) and mean sleep latency in the Multiple Sleep Latency Test (MSLT). In patients with sleep disorders with significant PLMS [6], Mendelson reported that the PLMS-related arousals did not differ between patients with and without excessive daytime sleepiness (EDS). Chervin [7] tested the association between the rate of PLMS and the severity of EDS in 1124

✉ Seiichi Nakata
seisay@fujita-hu.ac.jp

[1] Department of Clinical Laboratory, Second Affiliated Hospital, Fujita Health University, Nagoya, Japan

[2] Fujita Health University, Second Hospital, Otolaryngology, Nagoya, Japan

[3] Department of Internal Medicine, National Hospital Orgaization Suzuka Hospital, Suzuka, Japan

[4] Department of Public Health, Fujita Health University, Toyoake, Japan

Published online: 28 December 2015

patients with suspected or confirmed SDB, and found that the increased leg movements were correlated with decreased objective sleepiness without any association with subjective sleepiness or sleep propensity. Thus, the contribution of PLMS to symptoms of daytime sleepiness in SDB patients is controversial [8].

Therefore, the purpose of this study was to examine the association of PLMS with daytime sleepiness in patients with sleep-related complaints.

Methods

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and approved by the local institutional review board. Written informed consent was obtained from all participants.

Patients

A cross-sectional study of 233 male (median age 44.6 years, range 30–59 years) patients suspected of having obstructive sleep apnea syndrome (OSAS) with snoring or sleep-related complaints, who visited the Second Affiliated Hospital, Fujita Health University during the 25-month period between June 2011 and June 2013 was conducted. The patients who had narcolepsy with cataplexy ($n = 2$), restless leg syndrome ($n = 2$), hypersomnia ($n = 1$), parasomnia ($n = 0$) and insomnia ($n = 0$) diagnosed from an interview, results of PSG and MSLT and according to criteria of International Classification of Sleep Disorders III [2] were excluded from the total of 233 patients, leaving 228 subjects for the present study. All PSG recordings were not including continuous positive airway pressure titration.

PSG and subjective sleepiness

We conducted standard PSG with various physiological electroencephalogram parameters (C4-A1, F4-A1 and O2-A1) of the reference electrode derivation principle, electrooculogram, chin/anterior tibial electromyograms, nasal/mouth-breathing airflow analysis by thermistor and pressure sensors, chest wall/abdominal motion analysis by strain gauge, snoring sound analysis by microphone, oxygen saturation analysis by pulse oximetry, and electrocardiogram in an electrically shielded room for sleep study. We calculated the Apnea Hypopnea Index (AHI) using the alternative substitution rule, 3 % Oxygen Desaturation Index, arousal index, and PLMI as the number of Periodic limb movements (PLM) per hour according to the American Academy of Sleep Medicine manual for the scoring of sleep and associated events [1]. To assess the subjective sleepiness, we used Japanese version of the Epworth Sleepiness Scale (JESS) score (as study of drowsiness) [9] and Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) (as evaluation of sleep quality) [10].

Definition of PLMS and selection of the control group

We defined the PLMS group as that with participants having a PLMI >15/h and the non-PLMS group as that with participants having a PLMI ≤15/h. Control subjects for PLMS were selected from the non-PLMS by pair-matching of 10-year age interval, AHI and body mass index (BMI). This was done separately in patients with <15/h and ≥15/h of AHI (Fig. 1). Specifically, we identified 17 patients with PLMS among total 228 studied patients, 6 of them had AHI <15/h. We selected non-PLMS controls from the remaining 211 patients. Namely, we selected 12 age, AHI, and BMI-matched controls from 72 non-PLMS patients with AHI <15/h and 22 controls from 139 non-PLMS patients with AHI ≥15/h.

Statistical analysis

Patients' characteristics and PSG data were presented as median and inter-quartile ranges as shown in Tables 2 and 3. To compare patient characteristics between PLMS and non-PLMS groups, we used Mann–Whitney U test. A matched pair comparison of JESS between PLMS and non-PLMS groups was conducted by two-way analysis of covariance taking PLMS and matching variable as factors and adjusting for AHI as the covariate. All P values were two sided, with $P < 0.05$ was considered as statistically significant. All statistical analyses were conducted using the SPSS statistical package for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

Fig. 1 Pair-matching between PLMS and non-PLMS group. *AHI* apnea hypopnea index, *BMI* body mass index, *PLMS* periodic limb movements during sleep

Results

Means for age, BMI and AHI of the patients were 44.6 years, 25.9 kg/m^2, and 31.5/h, respectively (Table 1). Mean PSQI-J and JESS were 6.9 and 10.8, respectively. Although there was a statistically significant correlation between PLMI and AHI (Spearman $r = -0.247$, $P < 0.001$), the distribution of PLMI is skewed, and the relation does not seem clear as indicated by the small correlation coefficient (Fig. 2).

As expected from the definition, in both AHI <15/h and AHI ≥15/h strata, the PLMS-related arousal index and PLMI were significantly higher in the PLMS group compared with non-PLMS group (Tables 2, 3). However, only in the AHI ≥15/h stratum, the JESS score was statistically significantly higher in the PLMS group compared with non-PLMS group. The difference remained significant even after adjustment for AHI (13.1 vs. 8.0, $P = 0.002$) (Table 4). The mean JESS of PLMS group was not statistically significantly different from that of non-PLMS group although it appeared higher in the PLMS group than in the non-PLMS group (9.2 vs. 7.6, $P = 0.388$).

Table 1 Characteristics of the subjects

	Male ($n = 228$) Mean (range)
Age (years)	44.6 (30–59)
BMI (kg/m^2)	25.9 (18.1–43.6)
AHI (events/h)	31.5 (0.8–106.0)
PLMI (events/h)	3.3 (0.0–75.0)
3 %DSI (events/h)	27.6 (0.5–109.1)
Nadir SpO_2 (%)	79.4 (32.0–95.0)
Arousal index (events/h)	30.3 (3.2–105.8)
PSQI-J scores	6.9 (0–18)
JESS scores	10.8 (0–24)

AHI apnea hypopnea index, *BMI* body mass index, *DSI* oxygen desaturation index, *JESS* Japanese version of the Epworth Sleepiness Scale, *PLMI* periodic limb movements index, *PSQI-J* Japanese version of the Pittsburgh Sleep Quality Index, *SpO_2* oxygen saturation

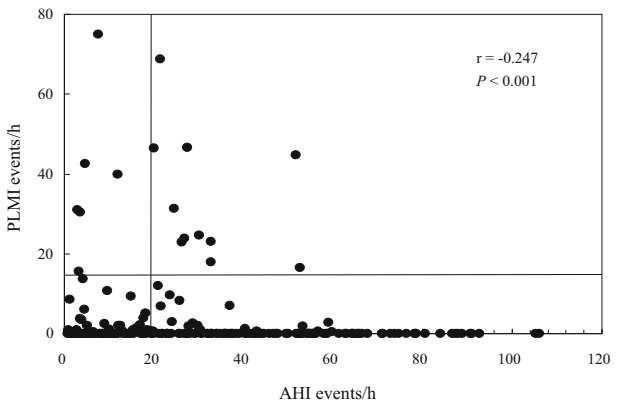


Fig. 2 Relation between AHI and PLMI, Spearman $r = -0.247$, $P < 0.001$. *AHI* apnea hypopnea index, *PLMI* periodic limb movements index

Discussion

In the present study, we found higher JESS points in PLMS compared to non-PLMS especially in subjects with AHI ≥15/h. Although this is a cross-sectional study and no inferences about causality is possible, how could a significant PLMS in OSAS patients affect daytime sleepiness? This may be explained by the latent sleepiness in PLMS which appears to have a potentiating effect on sleep apnea resulting in the increase of the daytime sleepiness of OSAS patients. In contrast to our results, Al-Alawi et al. [11] suggested that patients with both OSAS and PLMS were not sleepier than those with OSAS alone. In addition, Chervin [7] reported that the rates of PLMS showed no association with sleepiness or sleep propensity. In other words, significant PLMS did not influence sleepiness in either study. On the other side, Kapur et al. [12] showed that the intensity of sleepiness in patients with moderate-to-severe SDB was modified, not only by respiratory disturbance, sleep fragmentation, and insomnia, but also by the PLM activity as a comorbid condition, which is consistent with our findings. Vernet et al. [13] reported that the patients with excessive sleepiness had more PLM (without arousal), if they were compared to OSAS patients with and without residual excessive sleepiness. Though the role of PLMS on the genesis of daytime sleepiness is unclear as described above, our results could strengthen the speculation that PLMS affects sleepiness in OSAS patients.

In the present study, we found that PLMS is present in 17 (7.5 %) of 228 male patients aged 30–59 years, whereas it was estimated as 7.6 % [14] and 6.7 % [15] in other studies. These other studies' results are quite similar to our results.

Difference in JESS was bigger in those with AHI ≥15/h and statistically significant in the present study. However, PSQI-J was not significantly different between PLMS and non-PLMS groups. This lack of difference may be because PSQI-J cannot be used to evaluate the severity of sleepiness, but simply the quality of sleep.

A few limitations of the current study should be mentioned. First, there is a problem of night-to-night variation [16, 17]. Since our study consisted of only one night of PSG, there is a possibility that some individuals with elevated PLMS were not identified during the single overnight visit. It might also be likely that a first night effect in the

Table 2 Comparison of the sleep parameters between PLMS and non-PLMS groups in patients with AHI <15/h

	PLMS group ($n = 6$) Median (interquartile range)	Non-PLMS group ($n = 12$) Median (interquartile range)	P value*
Age (years)	48.0 (42.5–50.5)	46.0 (42.8–51.3)	0.9626
BMI (kg/m^2)	21.7 (20.0–22.9)	22.1 (21.8–22.6)	0.3254
AHI (events/h)	4.2 (3.4–6.9)	5.0 (3.8–8.2)	0.3490
PSQI-J scores	6.0 (5.3–7.5)	6.5 (5.8–8.0)	0.8883
JESS scores	10.0 (9.3–10.8)	6.5 (3.8–12.0)	0.3993
3 %DSI (events/h)	4.0 (1.7–6.5)	3.3 (1.5–4.8)	0.7787
Nadir SpO_2 (%)	90.5 (88.5–91.0)	89.0 (88.0–92.0)	0.9626
%SPT (%)	88.2 (85.9–93.8)	88.7 (80.3–92.0)	0.4537
REM, %TST	16.8 (14.3–17.5)	17.9 (10.7–20.1)	0.8514
StageN1 (%TST)	33.8 (19.6–46.6)	29.0 (17.8–38.9)	0.3993
StageN2 (%TST)	45.2 (35.8–61.5)	50.8 (40.5–53.3)	0.9254
StageN3 (%TST)	1.8 (0.0–4.6)	5.8 (1.3–12.9)	0.1744
T-arousal index (events/h)	13.2 (6.8–23.9)	10.1 (6.4–12.5)	0.3490
R-arousal index (events/h)	7.0 (5.0–8.9)	7.3 (5.8–10.5)	0.7787
P-arousal index (events/h)	1.9 (0.8–13.9)	0.1 (0.0–0.1)	0.0007
PLMI (events/h)	35.6 (30.6–42.0)	0.0 (0.0–0.0)	0.0007

AHI apnea hypopnea index, *BMI* body mass index, *DSI* oxygen desaturation index, *JESS* Japanese version of the Epworth Sleepiness Scale, *P-arousal index* periodic limb movements during sleep-related arousal index, *PLMI* periodic limb movements index, *PLMS* periodic limb movements during sleep, *PSQI-J* Japanese version of the Pittsburgh Sleep Quality Index, *R-arousal index* respiratory-related arousal index, *REM* rapid eye movement, *SpO_2* oxygen saturation, *SPT* sleep period time, *T-arousal index* total-arousal index, *TST* total sleep time

* Mann–Whitney *U* test

Table 3 Comparison of the sleep parameter between PLMS and non-PLMS groups in patients with AHI ≥15/h

	PLMS group ($n = 11$) Median (interquartile range)	Non-PLMS group ($n = 22$) Median (interquartile range)	P value*
Age (years)	45.0 (42.0–53.5)	45.0 (42.0–53.8)	0.9999
BMI (kg/m^2)	28.1 (25.0–28.6)	25.5 (22.7–27.9)	0.1087
AHI (events/h)	27.4 (25.4–32.8)	34.4 (24.8–42.2)	0.3797
PSQI-J scores	8.0 (5.0–8.0)	6.5 (4.3–10.5)	0.5286
JESS scores	13.0 (12.5–15.0)	7.5 (4.3–10.8)	0.0014
3 %DSI (events/h)	23.7 (17.2–30.9)	25.0 (19.8–36.3)	0.4337
Nadir SpO_2 (%)	75.0 (74.5–79.0)	80.5 (77.3–84.8)	0.1521
%SPT (%)	87.1 (83.1–91.6)	89.1 (83.0–96.2)	0.4162
REM (%TST)	14.5 (13.4–20.5)	18.2 (11.8–21.1)	0.7916
StageN1 (%TST)	39.4 (32.3–53.5)	50.6 (29.5–60.8)	0.3821
StageN2 (%TST)	42.3 (28.1–46.0)	34.7 (25.0–43.0)	0.1732
StageN3 (%TST)	2.8 (0.0–4.5)	3.3 (0.1–5.6)	0.5023
T-arousal index (events/h)	32.4 (28.5–36.5)	32.4 (20.8–37.6)	0.6843
R-arousal index (events/h)	25.5 (23.2–31.9)	31.4 (19.6–36.1)	0.8937
P-arousal index (events/h)	1.3 (1.0–2.8)	0.0 (0.0–0.1)	0.0002
PLMI (events/h)	24.6 (23.1–45.6)	0.0 (0.0–0.0)	<0.0001

AHI apnea hypopnea index, *BMI* body mass index, *DSI* oxygen desaturation index, *JESS* Japanese version of the Epworth Sleepiness Scale, *P-arousal index* periodic limb movements during sleep-related arousal index, *PLMI* Periodic Limb Movements Index, *PLMS* periodic limb movements during sleep, *PSQI-J* Japanese version of the Pittsburgh Sleep Quality Index, *R-arousal index* respiratory-related arousal index, *REM* rapid eye movement, *SpO_2* oxygen saturation, *SPT* sleep period time, *T-arousal index*, total-arousal index, *TST* total sleep time

* Mann–Whitney *U* test

Table 4 Matched pair comparison of JESS between PLMS and non-PLMS groups stratified by AHI

Stratum with AHI <15	JESS		
	PLMS group ($n = 6$)	Non-PLMS group ($n = 12$)	P value*
Crude mean (95 % CI)	9.7 (5.5–13.9)	7.3 (4.4–10.3)	0.341
AHI-adjusted mean (95 % CI)	9.2 (5.9–12.5)	7.6 (5.2–9.9)	0.388
Stratum with AHI ≥15	JESS		
	PLMS group ($n = 11$)	Non-PLMS group ($n = 22$)	P value*
Crude mean (95 % CI)	13.4 (10.8–15.9)	7.9 (6.1–9.7)	<0.001
AHI-adjusted mean (95 % CI)	13.1 (10.7–15.5)	8.0 (6.3–9.7)	0.002

AHI apnea hypopnea index, *CI* confidence interval, *JESS* Japanese version of the Epworth Sleepiness Scale, *PLMS* periodic limb movements during sleep

* Analysis of covariance (ANCOVA)

laboratory caused a disruption in sleep or a delay in sleep onset, [18] resulting in fewer PLMS than otherwise might have been detected. The use of bed partner interviews may be helpful for the evaluation of PLM in longer term.

Second, the number of participants with PLMS was small. In patients with AHI <15/h, the difference of JESS score between PLMS and non-PLMS groups was not statistically significant. This may be due to low statistical power. Indeed, the standardized effect size [19] in those with AHI <15/h was calculated to be 0.54, which would have required larger sample sizes than in this study to be detected. Further studies are needed to study the association in healthier individuals with AHI <15/h.

Third, cross-sectional design of the present study prevents us from inferring any causal relationship. Intervention studies may be warranted to investigate causality. Finally, in the present study, we did not study elderly patients who are known to have higher PLM activity. Future studies should include older individuals since there may be differences in the relationship. Nevertheless, we believe that this study contributes to add information, to some extent, for the role of PLMS on the genesis of daytime sleepiness in patients with OSAS. We construe we have focused on a point that should be considered during treatment of OSAS and other sleep-related disorders.

Conclusion

In conclusion, the relationship between PLMS and JESS was independent of AHI, and clear on stratum of AHI ≥15/h, which may indicate the influence of PLMS on JESS.

Compliance with ethical standards

Conflict of interest All the authors have no conflicts of interests to declare.

References

1. Iber C, American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications. Westchester: American Academy of Sleep Medicine; 2007.
2. American Academy of Sleep Medicine. International classification of sleep disorders. Diagnostic and coding manual. American Academy of Sleep Medicine: Darian; 2014.
3. Natarajan R. Review of periodic limb movement and restless leg syndrome. J Postgrad Med. 2010;56:157–62.
4. Bixler EO, Kales A, Vela-Bueno A, Jacoby JA, Scarone S, Soldatos CR. Nocturnal myoclonus and nocturnal myoclonic activity in the normal population. Res Commun Chem Pathol Pharmacol. 1982;36:129–40.
5. Coleman RM, Bliwise DL, Sajben N, Boomkamp A, de Bruyn LM, Dement WC. Daytime sleepiness in patients with periodic movements in sleep. Sleep. 1982;5(Suppl 2):S191–202.
6. Mendelson WB. Are periodic leg movements associated with clinical sleep disturbance? Sleep. 1996;19:219–23.
7. Chervin RD. Periodic leg movements and sleepiness in patients evaluated for sleep-disturbed breathing. Am J Respir Crit Care Med. 2001;164:1454–8.
8. Montplaisir J, Michaud M, Denesle R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. Sleep Med. 2000;1:163–7.
9. Takegami M, Suzukamo Y, Wakita T, et al. Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. Sleep Med. 2009;10:556–65.
10. Doi Y, Minowa M, Uchiyama M, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. Psychiatry Res. 2000;97:165–72.
11. Al-Alawi A, Mulgrew A, Tench E, Ryan CF. Prevalence, risk factors and impact on daytime sleepiness and hypertension of periodic leg movements with arousals in patients with obstructive sleep apnea. J Clin Sleep Med. 2006;2:281–7.
12. Kapur VK, Baldwin CM, Resnick HE, Gottlieb DJ, Nieto FJ. Sleepiness in patients with moderate to severe sleep-disordered breathing. Sleep. 2005;28:472–7.
13. Vernet C, Redolfi S, Attali V, et al. Residual sleepiness in obstructive sleep apnoea: phenotype and related symptoms. Eur Respir J. 2011;38:98–105.
14. Scofield H, Roth T, Drake C. Periodic limb movements during sleep: population prevalence, clinical correlates, and racial differences. Sleep. 2008;31:1221–7.

15. Aritake-Okada S, Namba K, Hidano N, et al. Change in frequency of periodic limb movements during sleep with usage of continuous positive airway pressure in obstructive sleep apnea syndrome. J Neurol Sci. 2012;317:13–6.
16. Ferri R, Fulda S, Manconi M, et al. Night-to-night variability of periodic leg movements during sleep in restless legs syndrome and periodic limb movement disorder: comparison between the periodicity index and the PLMS index. Sleep Med. 2013;14:293–6.
17. Trotti LM, Bliwise DL, Greer SA, et al. Correlates of PLMs variability over multiple nights and impact upon RLS diagnosis. Sleep Med. 2009;10:668–71.
18. Agnew HW Jr, Webb WB, Williams RL. The first night effect: an EEG study of sleep. Psychophysiology. 1966;2:263–6.
19. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: Lawrence Erlbaum Publishers; 1988.