Original Research

Periodic Limb Movements of Sleep: A Survey on Polysomnographic Characteristics of Patients with Obstructive Sleep Apnea

Morteza Saeidi[1], Fariborz Rezaeitalab[2*], Saeed Akhlaghi[3], Farnaz Kharaghani[4], Hussein Sharar[1], Mina Abbasi[5], Mahshid Mahyad[1]

[1.] *Department of Neurology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2.] *Division of Sleep Medicine, Psychiatry and Behavioral Sciences Research Center, Neuroscience Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[3.] *Department of Biostatistics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran*
[4.] *Department of Radiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[5.] *Student Research Committee, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

Received: 03 Dec. 2021 Accepted: 02 Feb. 2022

Abstract

Background and Objective: Periodic limb movements of sleep (PLMS) and obstructive sleep apnea (OSA) are two common sleep disorders that frequently co-occur in one subject. In this study, we evaluated the polysomnographic (PSG) features of patients with OSA with and without PLMS.

Materials and Methods: Patients with OSA diagnosed by PSG who referred to our sleep clinic over 2 years were studied for PLMS during a standard diagnostic sleep study. PSG features including apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and sleep quality were evaluated and compared between patients with OSA with and without PLMS.

Results: We evaluated 122 patients with OSA, of whom 17 had comorbid PLMS. Mean sleep quality was significantly lower in patients with PLMS compared to those without PLMS ($P < 0.05$). There was no significant difference in terms of mean age, gender, arousal index (AI), ODI, and apnea/hypopnea between the two groups.

Conclusion: Patients with OSA with PLMS comorbidity have remarkably lower sleep quality and this finding is independent of the severity of arousals or respiratory events. Proper evaluation, diagnosis, and treatment of PLMS comorbidity in patients with OSA might improve treatment response.

Keywords: Periodic limb movement disorder; Obstructive sleep apnea; Polysomnography; Sleep quality

Citation: Saeidi M, Rezaeitalab F, Akhlaghi S, Kharaghani F, Sharar H, Abbasi M, et al. **Periodic Limb Movements of Sleep: A Survey on Polysomnographic Characteristics of Patients with Obstructive Sleep Apnea.** J Sleep Sci 2022; 7(1-2): 16-21.

Introduction

Periodic limb movement of sleep (PLMS) is a common sleep disorder with a prevalence of about 25% in adults which significantly increases with age (1). PLMS is defined as at least four consecutive episodes of stereotypic movements of one or both limbs, predominantly legs. These movements which include toe extension, ankle dorsiflexion, and occasionally knee or hip flexion should occur with an interval of 5-90 seconds during any stage of sleep and last 0.5-10 seconds (when unilateral) or 0.5-15 seconds (when bilateral) (2). Movements could be accompanied by various levels of arousal or awakening; however, the patient is usually unaware of both movements and arousals. PLMS could be seen in healthy populations and usually bears no clinical significance unless accompanied by otherwise unexplained disturbances in sleep and/or daytime sleepiness, with an index

*** *Corresponding author***: *F. Rezaeitalab, Division of Sleep Medicine, Psychiatry and Behavioral Sciences Research Center, Neuroscience Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
Tel: +98 51 38429828, Fax: +98 51 38429828
Email: rezaeitalabf@mums.ac.ir

of > 15 PLMS per hour [periodic limb movement index (PLMI)] (3); hence, it is named periodic limb movement disorder (PLMD).

PLMS coexists frequently with other types of sleep disorders including restless leg syndrome (RLS) (4), rapid eye movement (REM) sleep behavior disorder (RBD) (5), narcolepsy (6), and obstructive sleep apnea (OSA) (7, 8); therefore, a diagnosis of PLMD cannot be established before these conditions are treated appropriately (3, 9).

OSA is another common adult sleep disorder with an estimated global prevalence of approximately 50% (10). About 24% to 50% of patients with OSA have PLMS (7, 11). OSA-PLMS coexistence raises several issues. First, OSA is frequently accompanied by limb movements (LM) before, during, or after an apnea/hypopnea event this might interfere with the correct diagnosis of PLMS in these patients. To address this issue, it has been suggested that only LM events > 0.5 seconds apart from an apnea/hypopnea event be counted as PLMS (2). However, there is compelling evidence that respiratory-related LMs (RRLMs) occur at a different timespan, mostly near the end of the respiratory events (12-14), which might probably cause an underestimation of PLMS events in the presence of apnea/hypopnea events. This evidence has been used as an explanation for the observed aggravation or "unmasking" of PLMS after OSA treatment using continuous positive airway pressure (CPAP) devices (15-20).

Second, while OSA is a known risk factor for the development of hypertension (HTN) and cardiovascular and cerebrovascular events (18), a growing body of evidence indicates that PLMS might independently be associated with sympathetic hyperactivity (19), HTN (20, 21), and a greater risk of cerebrovascular (22), cardiovascular (23-25), and cognitive disorders (26), although this evidence has been inconsistent (23, 27-29). There is an open question that OSA-PLMS comorbidity might further increase the risk of vascular disease.

Third, it is not yet known how PLMS coexistence would affect treatment compliance and success in patients with OSA and whether concurrent PLMS treatment would increase this rate and decrease the cardiovascular consequences of OSA (18, 20).

In this study, our objective is to evaluate the polysomnographic (PSG) features of OSA with and without PLMS to better understand the effects of PLMS-coexistence on PSG features of patients with OSA. This would serve as a first step to the assessment of the significance of this coexistence in treatment and then prognosis.

Materials and Methods

Participants: Patients referred to our university sleep clinic for the diagnosis of sleep apnea from 2017 to 2020 were studied. Pregnant participants and patients with a history of parasomnias, coexisting neurological disorders affecting RLS such as Parkinson's disease or neuropathies, heart failure, chronic kidney disease, and those who had been on medication with effect on RLS (such as antidepressants, antihistamines, or opiates) were excluded. All patients underwent a standard diagnostic PSG study. A total of 225 patients, who were diagnosed with OSA based on the American Academy of Sleep Medicine (AASM) criteria (3), were included. Besides, the diagnosis of PLMS was made based on the criteria of AASM (3).

According to that, RRLMs, which are defined as LMs that occur during a period from 0.5 seconds preceding a respiratory event to 0.5 seconds following that, were excluded. The International Restless Legs Syndrome Study Group (IRLSSG) criteria were used for the diagnosis of RLS in all patients (30, 31).

Protocol of this study was approved by our institutional research ethics board (code: IR.MUMS.fm.REC.1395.390). All participants signed a written consent form and the study was conducted following the Declaration of Helsinki.

PSG study: Overnight PSG was performed using Harmonie Software 7.0 (Stellate Systems, Montreal, Canada). Electroencephalograms (EEGs) (6 channels), bilateral anterior tibial muscle electromyograms (EMG), arterial oxygen saturation, chest and abdominal movements, and nasal airflow were recorded. Scoring of apnea/hypopnea events and determination of sleep stages were performed based on AASM recommendations (32).

In this regard, an apnea event was defined as a ≥ 90% decrease in airflow for at least 10 seconds. A hypopnea event was defined as a ≥ 30% decrease in airflow lasting for ≥ 10 seconds accompanied by at least 3% oxygen desaturation or arousal. Likewise, respiratory effort-related arousals (RERAs) were defined as flattening ≥ f the inspiratory portion of the nasal airflow pres-

sure for at least 10 seconds leading to arousal which does not fulfill the criteria for an apnea or hypopnea event and is not accompanied by oxygen desaturation. Accordingly, the apnea-hypopnea index (AHI) is calculated as the number of apnea and hypopnea events per hour of sleep. Arousal index (AI) and oxygen desaturation index (ODI) were defined as the number of arousal events and the number of ≥ 3% arterial oxygen desaturation events per hour of sleep, respectively.

PLMS was assessed using AASM diagnostic criteria (3) based on a PLMI ≥ 15 during a standard diagnostic PSG study (33).

Statistical analysis: Descriptive statistics including frequency and percentage and mean ± standard deviation (SD) were used to describe appropriate data. Normally-distributed variables were compared by independent samples *t*-test, and non-normally-distributed variables were compared by Mann-Whitney U test between the two groups. The relationship between categorical variables was analyzed using the chi-square test. Statistical analyses were performed using the SPSS software (version 20, IBM Corporation, Armonk, NY, USA). P-values less than 5% were considered statistically significant.

Results

After the exclusion of patients meeting the aforementioned exclusion criteria, 122 patients who fulfilled AASM criteria for OSA (3) including 100 (82%) men and 22 (18%) women were included in this study. The mean age of participants was 45.1 ± 12.6 years (18-68 years). Of all patients, 18 (13.5%) were diagnosed with PLMS, 17 (94.4%) of them being men. The mean AHI was 26.5 ± 24.8 (range: 5-136), of which 43 (35.25%) cases were mild (AHI: 5-15), 50 (40.98%) were moderate (AHI: 15-40), and 29 (23.77%) cases were severe (AHI > 40). Characteristics of the patients with and without PLMS and their PSG features are presented in table 1.

There was no significant difference between the two groups (with vs. without PLMS) in terms of age (P = 0.17), gender (P = 0.64), Epworth Sleepiness Scale (ESS) score (P = 0.68), and past medical and drug history.

Table 1. Characteristics of patients with obstructive sleep apnea (OSA) with and without periodic limb movements of sleep (PLMS)

Characteristic	OSA without PLMS (n = 105)	OSA with PLMS (n = 17)	P-value
Gender			0.300
Men	84 (68.90)	16 (13.10)	
Women	21 (17.20)	1 (0.80)	
Age (year)	45.51 ± 12.84	45.65 ± 11.00	0.880
ESS score	9.15 ± 5.99	10.06 ± 7.19	0.680
Wakefulness after sleep onset (minute)	81.67 ± 54.80	136.12 ± 62.59	0.001*
Sleep latency (minute)	28.78 ± 43.49	19.24 ± 26.47	0.760
Number of awakenings	26.04 ± 14.93	31.65 ± 17.92	0.130
Sleep to N3 latency (minute)	81.80 ± 72.50	205.90 ± 165.49	0.006*
Sleep to REM latency (minute)	149.53 ± 112.23	231.65 ± 126.03	0.008*
Duration of N1 stage (minute)	20.38 ± 14.38	25.94 ± 14.81	0.070
Duration of N2 stage (minute)	48.79 ± 10.48	48.47 ± 11.35	0.910
Duration of N3 stage (minute)	16.78 ± 9.12	12.94 ± 7.62	0.100
Duration of REM stage (minute)	13.72 ± 7.78	13.00 ± 9.25	0.590
AI	23.21 ± 14.43	30.18 ± 21.31	0.180
Desaturation index	15.64 ± 9.93	32.07 ± 19.82	0.850
AHI			
Total	27.88 ± 22.79	34.75 ± 33.94	0.940
Mild (≤ 15)	36 (29.51)	7 (5.74)	0.840
Moderate (15-30)	44 (36.07)	6 (4.92)	
Severe (> 30)	25 (20.49)	4 (3.28)	
RLS	46 (43.81)	9 (52.94)	0.480
Sleep quality index	77.41 ± 14.23	65.53 ± 19.70	0.010*

According to these findings, latencies to N3 and also rapid eye movement (REM) sleep were significantly higher when periodic limb movements (PLM) accompanied obstructive sleep apnea **(**OSA).

Data are presented as mean ± standard deviation (SD) or number and percentage. All comparisons were performed using Mann-Withney U test, except N2 and N3, for which *t*-test was performed.

*Significant value

OSA: Obstructive sleep apnea; PLMS: Periodic limb movements of sleep; ESS: Epworth Sleepiness Scale; AHI: Apnea-hypopnea index; REM: Rapid eye movement; AI: Arousal index; RLS: Restless leg syndrome

Among PSG indices, AI (P = 0.18), ODI (P = 0.85), and AHI (P = 0.94) were not significantly different between the two groups. Sleep latency, defined as the time from lights off to the first epoch of sleep, was similar in the two groups (P = 0.38). Mean sleep quality, defined as the percentage of total sleep time to the total time spent in bed, was significantly lower in patients with PLMS compared to those without PLMS (65.53 ± 19.70% vs. 77.41 ± 14.23%, P = 0.01). This result remained significant after adjustment for the degree of apnea/hypopnea, entering AHI, and desaturation into the multivariate analysis (Table 2). We also found a significantly longer total duration of wakefulness after sleep onset in the PLMS group (136.12 ± 62.59 vs. 81.67 ± 54.80, P = 0.001); however, the number of awakening episodes was not significantly different between the two groups (31.65 ± 17.92 vs. 26.04 ± 14.93, P = 0.13).

Table 2. Comparison of sleep quality after adjustment for apnea-hypopnea index (AHI) and desaturation index

	Beta	95% CI	P-value
PLMS category	-11.168	-19.141 to -3.194	0.006
AHI	-0.048	-0.222 to 0.127	0.591
Desaturation	-0.043	-0.274 to 0.188	0.714
Further adjustment for history of mood disorders			
PLMS category	-11.232	-19.318 to -3.146	0.007
AHI	-0.039	-0.215 to 0.137	0.661
Desaturation	-0.054	-0.286 to 0.179	0.649

CI: Confidence interval; PLMS: Periodic limb movements of sleep; AHI: Apnea-hypopnea index

Discussion

In this study, we evaluated the effect of PLMS on the PSG features of patients with OSA. Our findings show that patients with OSA with or without PLMS experienced similar frequency of arousal, oxygen desaturation, and apnea/hypopnea events during sleep. Nonetheless, sleep quality was worse in those who had PLMS in addition to OSA. This implies that PLMS might independently decrease sleep quality and this effect is not mediated by the severity of sleep apnea/hypopnea. Iriarte et al. compared 4 groups including pure PLMS, pure OSA, OSA plus PLMS, and healthy controls, and found that compared to healthy controls, sleep quality was worse among patients with pure PLMS accompanied by more episodes of arousal; however, they could not find any difference between pure versus PLMS-associated OSA patients in terms of sleep quality (34). Haba-Rubio et al. evaluated 618 subjects with PLMS in their cohort study (29) and found that sleep architecture was altered significantly in patients with PLMS presenting with increased N2 but decreased N3 and REM stages. This was accompanied, and probably explained by an increase in sleep latency and arousal in these patients. Similar sleep structure abnormalities occur in patients with OSA (35).

In our study, although not statistically significant, we found that N1 duration was higher and N3 duration was lower in OSA patients with PLMS compared to those without PLMS and these were accompanied by longer duration of wakefulness after sleep onset. As a significant statistical finding, latencies to N3 and also REM sleep were higher when PLMS accompanied OSA. This further emphasizes that patients with PLMS-comorbid OSA might suffer from more severe sleep architecture abnormalities.

Baran et al. found that PLMI significantly increased after CPAP titration in patients with moderate and severe OSA (AHI: 15-30 and > 30, respectively) compared to those with mild OSA (15). Although they did not report sleep quality in their sample, they found that OSA severity determined the CPAP effect on PLMS and that "unmasking" of a previously unrevealed PLMS occurred mainly in the moderate and severe OSA cohorts. Repetitive RRLMs which occur in severe OSA may mask coexisting PLMS in these patients. Treatment with CPAP improves RRLMs, thereby allowing for better identification of a preexisting PLMS. Our study showed that in pre-titration assessment, the presence of PLMS was not associated with OSA severity. Hence, it is important to assess patients with OSA precisely for coexistent PLMS and its severity. This will allow us to better counsel patients about the expected treatment effects and their course.

Altogether, we conclude that PLMS in association with OSA might have additional independent effects on sleep architecture and quality, which based on current literature, may not improve or even become worse by OSA treatment. Hence, clinicians might consider that residual sleep inefficiency due to PLMS might contribute to poor clinical response. Therefore, a careful search for PLMS while performing PSG in patients with OSA before and after CPAP treatment and addressing this condition is highly recommended.

It should be noted that the cross-sectional nature of this study is an important limitation and

further generalization of our results should appreciate this fact. Moreover, we did not evaluate the effect of OSA treatment on PSG parameters and the quality of life of the patients. Future studies assessing detailed PSG data in a longitudinal design both before and after treatment will provide a better understanding of the therapeutic implications of PLMS and the effect of specific PLMS treatment on adherence and response to OSA treatment and the resulting cardiovascular risk.

Conclusion

PLMS is prevalent among patients with OSA. In addition, this comorbidity can result in lower sleep quality, independent of the severity of arousals or respiratory events. Appropriate evaluation, diagnosis and treatment of PLMS comorbidity in patients with OSA might contribute in improving the efficiency of treatment of OSA.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

We thank the Research Vice-Chancellor of Mashhad University of Medical Sciences, Mashhad, Iran, for funding this study (grant number: 990246) and wish to acknowledge all patients who participated in this study.

References

1. Leary EB, Moore HE, Schneider LD, et al. Periodic limb movements in sleep: Prevalence and associated sleepiness in the Wisconsin Sleep Cohort. Clin Neurophysiol 2018; 129: 2306-14.
2. Ferri R, Fulda S, Allen RP, et al. World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint task force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). Sleep Med 2016; 26: 86-95.
3. American Sleep Disorders Association (AASM). The International Classification of Sleep Disorders (ICSD-3). Darien, IL: AASM; 2014.
4. Montplaisir J, Boucher S, Poirier G, et al. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: A study of 133 patients diagnosed with new standard criteria. Mov Disord 1997; 12: 61-5.
5. Fantini ML, Michaud M, Gosselin N, et al. Periodic leg movements in REM sleep behavior disorder and related autonomic and EEG activation. Neurology 2002; 59: 1889-94.
6. Dauvilliers Y, Pennestri MH, Petit D, et al. Periodic leg movements during sleep and wakefulness in narcolepsy. J Sleep Res 2007; 16: 333-9.
7. Al-Alawi A, Mulgrew A, Tench E, et al. 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.
8. Ferri R, Koo BB, Picchietti DL, et al. Periodic leg movements during sleep: Phenotype, neurophysiology, and clinical significance. Sleep Med 2017; 31: 29-38.
9. Sateia MJ. International classification of sleep disorders-third edition: Highlights and modifications. Chest 2014; 146: 1387-94.
10. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: A literature-based analysis. Lancet Respir Med 2019; 7: 687-98.
11. Chervin RD. Periodic leg movements and sleepiness in patients evaluated for sleep-disordered breathing. Am J Respir Crit Care Med 2001; 164: 1454-8.
12. Fulda S, Heinzer R, Haba-Rubio J. Characteristics and determinants of respiratory event-associated leg movements. Sleep 2018; 41: zsx206.
13. Huang CY, Yu CC. Different diagnostic criteria for periodic leg movements in patients with obstructive sleep apnea after continuous positive airway pressure titration. Neuropsychiatr Dis Treat 2019; 15: 2129-36.
14. Manconi M, Zavalko I, Fanfulla F, et al. An evidence-based recommendation for a new definition of respiratory-related leg movements. Sleep 2015; 38: 295-304.
15. Baran AS, Richert AC, Douglass AB, et al. Change in periodic limb movement index during treatment of obstructive sleep apnea with continuous positive airway pressure. Sleep 2003; 26: 717-20.
16. Hedli LC, Christos P, Krieger AC. Unmasking of periodic limb movements with the resolution of obstructive sleep apnea during continuous positive airway pressure application. J Clin Neurophysiol 2012; 29: 339-44.
17. Yamashiro Y, Kryger MH. Acute effect of nasal CPAP on periodic limb movements associated with breathing disorders during sleep. Sleep 1994; 17: 172-5.
18. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet 2009; 373: 82-93.
19. Wu MN, Lai CL, Liu CK, et al. Basal sympathetic predominance in periodic limb movements in sleep with obstructive sleep apnea. J Sleep Res 2015; 24: 722-9.
20. Koo BB, Sillau S, Dean DA, et al. Periodic limb movements during sleep and prevalent hypertension in the multi-ethnic study of atherosclerosis. Hypertension 2015; 65: 70-7.
21. Lombardi C, Parati G, Soranna D, et al. Periodic limb movements during sleep and blood pressure

changes in sleep apnoea: Data from the European Sleep Apnoea Database. Respirology 2020; 25: 872-9.
22. Lin TC, Zeng BY, Chen YW, et al. Cerebrovascular accident risk in a population with periodic limb movements of sleep: A preliminary meta-analysis. Cerebrovasc Dis 2018; 46: 1-9.
23. Kendzerska T, Kamra M, Murray BJ, et al. Incident cardiovascular events and death in individuals with restless legs syndrome or periodic limb movements in sleep: A Systematic Review. Sleep 2017; 40: zsx013.
24. Koo BB, Mehra R, Blackwell T, et al. Periodic limb movements during sleep and cardiac arrhythmia in older men (MrOS sleep). J Clin Sleep Med 2014; 10: 7-11.
25. Yumino D, Wang H, Floras JS, et al. Relation of periodic leg movements during sleep and mortality in patients with systolic heart failure. Am J Cardiol 2011; 107: 447-51.
26. Lin CC, Chou CH, Fan YM, et al. Increased risk of dementia among sleep-related movement disorders: A population-based longitudinal study in Taiwan. Medicine (Baltimore) 2015; 94: e2331.
27. Alessandria M, Provini F. Periodic Limb movements during sleep: A new sleep-related cardiovascular risk factor? Front Neurol 2013; 4: 116.
28. Chiaro G, Manconi M. Restless legs syndrome, periodic limb movements during sleep and cardiovascular risk. Auton Neurosci 2019; 220: 102554.
29. Haba-Rubio J, Marti-Soler H, Tobback N, et al. Clinical significance of periodic limb movements during sleep: The HypnoLaus study. Sleep Med 2018; 41: 45-50.
30. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord 1995; 10: 634-42.
31. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003; 4: 121-32.
32. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012; 8: 597-619.
33. Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med 2008; 4: 157-71.
34. Iriarte J, Murie-Fernandez M, Toledo E, et al. Sleep structure in patients with periodic limb movements and obstructive sleep apnea syndrome. J Clin Neurophysiol 2009; 26: 267-71.
35. Shahveisi K, Jalali A, Moloudi MR, et al. Sleep architecture in patients with primary snoring and obstructive sleep apnea. Basic Clin Neurosci 2018; 9: 147-56.