

Effect of Periodic limb Movement on polysomnographic data of OSA patients on CPAP with residual sleepiness**Eptehal M. Dongol^a , Hazem Mo. Abdelkhalek^b , Ahmed Y. Badawy^c , Islam El Malky^{d*}**^aPulmonology and Sleep Medicine, Department of Chest Diseases and Tuberculosis, Faculty of Medicine, South Valley University, Qena, Egypt.^bNeurology Department, Faculty of Medicine Tanta University, Tanta, Egypt.^c Pulmonology and Sleep Medicine, Department of Chest Diseases and Tuberculosis Faculty of Medicine, Mansoura University, Mansoura, Egypt.^dDepartment of Neurology, Faculty of Medicine, South Valley University, Qena, Egypt.**Abstract****Background:** Many patients with obstructive sleep apnea (OSA) report no improvement in the excessive daytime sleepiness, despite compliant CPAP treatment. Associated periodic limb movements (PLMs) with OSA might be a cause of failure.**Objectives:** Our study aimed to assess the increased periodic limb movements index (PLMI) in patients with residual excessive sleepiness (RES) on CPAP and polysomnographic changes caused by the occurrence of PLMs in this group of patients, and predictors of PLMS's presence.**Patients and methods:** We searched the electronic medical records of the OSA patients who were followed up in the CPAP outpatient clinic between 2010-2015. Patients who had completed at least one year of treatment were assessed. We included only patients with OSA and RES due to only PLMs (45 patients) (group one) against patients with OSAS, RES and with no definite cause (11 patients) (group two).**Results:** There was significant difference between both groups (more in group one) in the age and waist circumference (p value 0.04 and 0.017, respectively). There was significantly longer sleep onset latency (28.01 vs. 9.29), lower total sleep time (5.5 vs. 6.6 hours) and lower sleep efficiency percentage (72.44% vs. 87.1 %) in group one than in group two (P-value of 0.042, 0.019 and 0.011, respectively). Also, there were significantly higher means of wake after sleep onset (WASO) and total arousal index in group one than in group two. Waist circumference was the only predictor for increased PLMs index in this population study, by logistic regression with OR (95%CI) 0.168 (0.011-0.324).**Conclusion:** Increased PLMI during sleep significantly impact the polysomnographic variables. The waist circumference might be the only predictor of increased PLMs index.**Keywords:** OSA (obstructive sleep apnea); PLMs (periodic limb movements); excessive daytime sleepiness; excessive residual sleepiness (RES)**DOI:** 10.21608/svuijm.2022.169296.1433***Correspondence:** islam.elmalky@yahoo.com**Received:** 21 October, 2022.**Revised:** 30 October, 2022.**Accepted:** 31 October, 2022.**Cite this article as:** Eptehal M. Dongol , Hazem Mo. Abdelkhalek , Ahmed Y. Badawy, Islam El Malky. (2022). Effect of Periodic limb Movement on polysomnographic data of OSA patients on CPAP with residual sleepiness. *SVU-International Journal of Medical Sciences*. Vol.5, Issue 2, pp: 553-563.**Copyright:** © Dongol et al (2022) Immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge. Users have the right to Read, download, copy, distribute, print or share link to the full texts under a [Creative Commons BY-NC-SA 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/)

Introduction

Periodic limb movements during sleep (PLMs) is a motor sleep-related disorder characterized by periodic episodes of repetitive and stereotypical movements of lower limbs (Al-Alawi et al. 2006) which may cause frequent arousal and sleep inefficiency (Walters and Rye, 2009). These movements are in the form of ankle dorsiflexion, toe dorsiflexion, and partial knee flexion (Walters and Rye, 2009). PLMs consist of a sequence of four or more consecutive movements occurring with the interval of 5 to 90 s, lasting for at least 0.5 s and up to a maximum of 10 s (Berry, Bro et al., 2012)(AASM scoring criteria). PLMs were reported in patients with different sleep disorders such as obstructive sleep apnea syndrome (OSAS) (Chervin, 2001).

Many patients with obstructive sleep apnea report non-improvement in daytime sleepiness, despite compliant CPAP treatment and reduction of the apnoea-hypopnea index (AHI) (Budhiraja et al., 2020). Associated PLMs with OSAS might be a cause of improvement failure.

Our study aimed to assess the presence of increased PLMs index in patients with residual excessive sleepiness (RES) on CPAP and possible sleep changes caused by the occurrence of PLMs in this group of patients, and factors predicting PLMs's presence.

Patients and methods

This study had a retrospective design. Approval of the hospital ethical committee was obtained to collect the data of the patients. We searched the electronic medical records of the OSAS patients who were followed up in the CPAP outpatient follow-up clinic between 2010-2015 in a previous publication (Dongol et al., 2021). Patients who had completed at least one year of treatment were followed and assessed. Using the ESS (Epworth

Sleep Scale), patients who complained of Excessive Daytime Sleepiness (EDS) with the CPAP were included. Firstly, the annual report was reviewed to calculate the patient's compliance with CPAP using the recorded nightly hours and percent of nights when they used the CPAP.

Usage of CPAP, 70 % or more of nights for more than 4 hours per night, is mandatory to be considered compliant with CPAP. We excluded the incompliant patients who had troubles with the CPAP application.

The patient evaluation was performed for any possible condition that may cause EDS. After CPAP-related and possibly other causes of EDS were excluded, the patient was referred for overnight PSG with CPAP in situ to assess the breathing and motor sleep-related conditions objectively.

We have excluded other causes of RES such as depression, other sleep disorders causing hypersomnolence, restless leg syndrome (RLS), combined RLS with PLMs, and drug-induced hypersomnolence (figure 1). We included only patients with OSAS and RES due to only PLMs (45 patients) (group one) against patients with OSAS, RES and without definite cause (11 patients) (group two). The sleep disorders were diagnosed according to the international classification of sleep disorders –II(American Academy of Sleep 2005)

All night Polysomnographic (PSG) recordings were performed with Polysomnographic devices Embla N7000. For electroencephalographic (EEG) recording, five silver plate surface electrodes in F4, C4, O2, Cz, and A1 were used according to the international 10–20 System. Electromyographic (EMG) recordings were obtained through skin plate electrodes located on the chin and over the tibialis muscles of both legs. Electrooculographic (EOG) recordings

were obtained from skin electrodes placed 1 cm above and 1 cm lateral to the right and 1 cm below and 1 cm lateral to the left lateral canthi of each eye. For Electrocardiogram (ECG) recordings, disposable surface electrodes were placed below the right clavicle and over the seventh intercostal space and mid-clavicular line (modified lead 11). The respiratory flow was measured through a thermistor in the nostrils. Oxygen saturation was measured with a pulse oximeter Nonin technology. A well-trained technician manually scored PLM. They were considered the repetition of four 0.5 to 10-second limb movements (from 8 microvolts above resting EMG to 0.5 second less than 2 microvolts above resting EMG) in a regular interval between 5 and 90 seconds. The diagnosis of PLM

disorder was performed visually during the review of the recording, and the calculation of the PLM index confirmed the severity. PLM disorder was diagnosed if the PLM index was higher than 15. The apnea-hypopnoea index (AHI) was calculated. The sleep architecture was manually scored following the standard criteria of the American Academy of Sleep Medicine (AASM) scoring manual 2005. For data analysis, patients with increased PLMs index (more than 15/hour) and no RLS (group one), and patients with no known other causes of sleepiness (group two) were included. The clinical data, including demographic and clinical data (age, sex, body mass index, and vascular risk factors) and the CPAP usage data, including the nightly use and percent of nights used, were included. (Fig.1).

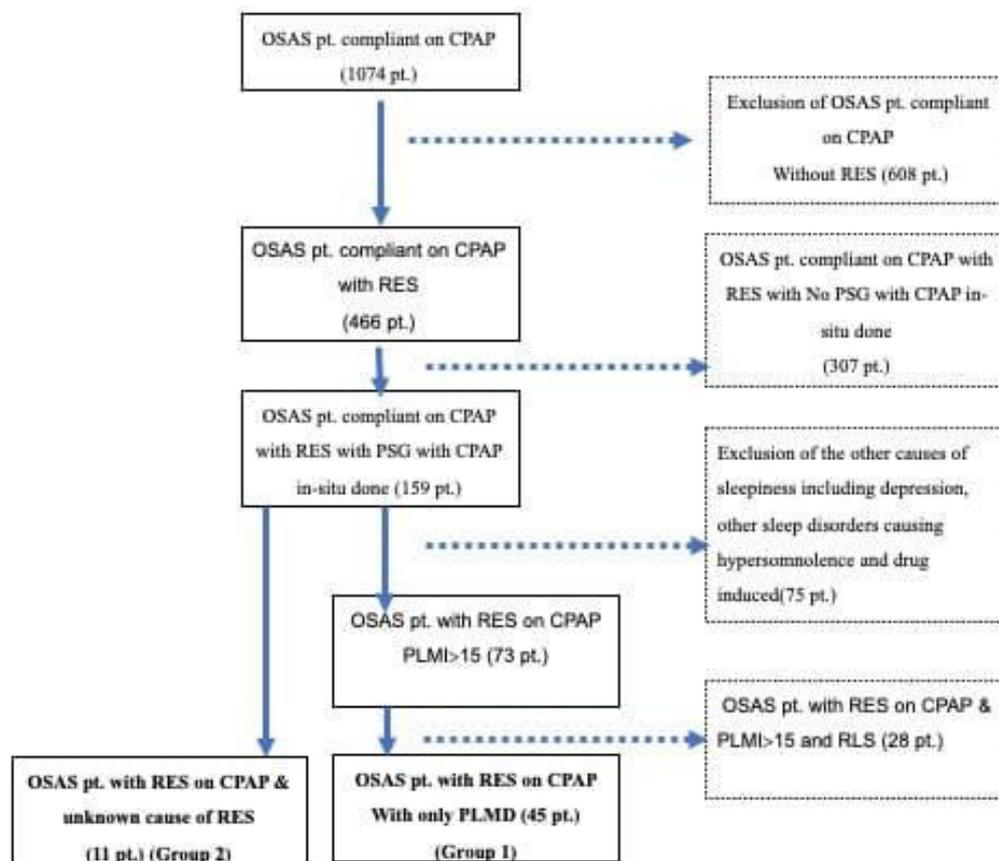


Fig.1. Flow chart of study population
The polysomnographic data included the Sleep efficiency parameters such as

sleep period, wake after sleep onset (WASO), Total sleep time, sleep onset

latency, sleep efficiency, REM Latency, Apnea/Hypopnea index (AHI), oxygen desaturation index (ODI), Percentages of different sleep stages of the total sleep time including N1, N2, N3, REM percentage and REM Latency, total arousal index., mean and lowest oxygen saturation during the night, and periodic limb movement of sleep index.

Statistical Analysis

The collected data were gathered and revised, and statistical analysis was done using the program SPSS version 23. Descriptive analysis was expressed in frequency for qualitative data and mean \pm standard deviation for the quantitative data. The normality of the distribution of the data was checked. Comparison between both groups was made by parametric and non-parametric measures according to normality tests. Multivariate regression analysis was performed to discover the predictive factors for the presence of PLMs.

Results

Demographic data

The current retrospective study aimed to evaluate the patients with obstructive sleep apnea syndrome (OSAS) who had residual excessive sleepiness (RES) despite adequate CPAP treatment. It was conducted in our sleep disorders tertiary centre.

Table (1) shows the main demographic data, pre-CPAP data, and CPAP usage data. The age of the patients with increased PLMs index (group one) was significantly older than the patients with unknown cause of RES (group 2) 54.69 ± 7.92 vs. 49.27 ± 8.577 years (P-value = 0.041). There was no significant difference in the gender distribution between both groups (P-value = 0.966). The mean waist circumference was significantly higher in group one than in group two (45.9 ± 7.29 vs. 39.7 ± 8.15 inches, P-value = 0.017), while there was no significant difference in the neck circumference (P-value=0.188). All the diabetic patients had increased PLMs index with no diabetic patient in the other group.

Table 1. Demographic, pre-CPAP and CPAP usage data between patients with PLMS versus patients with unidentified cause of RES

Demographic variables	Group one with PLMS (N=45)	Group two with unknown cause for RES (N=11)	p-value
Age (years) (mean \pm SD)	54.69 \pm 7.92	49.27 \pm 8.577	0.041*
Gender (Male N/%)	34(75.6)	9(81.8)	0.966
Neck Circumference(inch) (mean \pm SD)	17.48 \pm 1.4	16.82 \pm 1.49	0.188
Waist Circumference(inch)(mean \pm SD)	45.9 \pm 7.29	39.7 \pm 8.15	0.017*
Pre-CPAP ESS (/24)	15.82 \pm 4.33	17.2 \pm 4.5	0.529
Pre-CPAP AHI(/hr)	35.59 \pm 30.23	40.28 \pm 27.09	0.752
ESS on CPAP (/24)	15.11 \pm 2.9	16.9 \pm 2.46	0.053
Prescribed CPAP pressure(cmH2O)	12.79 \pm 2.3	13.8 \pm 1.35	0.189
Nightly hours of CPAP usage	6.4 \pm 1.5	6.6 \pm 1.36	0.791

(hrs)			
Percentage of CPAP usage (%)	89.44±11.5	92.10±9.7	0.483
Hypertension (N%)	11(24.4)	4(36.4)	0.461
Diabetes mellitus (N%)	5(11.1)	0	--
Ischaemic Heart Disease (N%)	8(17.8)	2(18.2)	1

PLMS: Periodic limb Movements, RES: Residual Excessive Sleepiness. (*) means statistically significant

No significant differences were found regarding the pre-CPAP variables, including the pre-CPAP ESS and AHI, between both groups (P-value = 0.529 and 0.752 respectively). There were no significant differences regarding the post-CPAP ESS, prescribed CPAP pressure, nightly hours of CPAP usage, and percent of CPAP usage in both groups (P-values= 0.053, 0.189, 0.791, and 0.483, respectively).

Sleep Structure

Table (2) shows the comparison of both groups; there was significantly lower total sleep time (5.5 vs. 6.6 hours) and sleep efficiency percentage (72.44% vs. 87.1 %) in group one than in group two (P-value = 0.019 and 0.011, respectively). Also, there were significantly higher means

of WASO (97.44 vs. 52.69), sleep onset latency (28.01 vs. 9.29), PLMS index (50.6 vs. 2.77), and total arousal index (26.34 vs. 14.11) in group one than in group two with a P-value of 0.042, 0.007, 0.0001 and 0.007, respectively. At the same time, there were no significant differences regarding the total sleep period, REM latency, AHI, and ODI, with a P-value of more than 0.05 for all. The percentages of sleep stages on all the compliant OSAS with RES who had PSG with CPAP in situ were within the normal range. There were no significant differences in sleep stages between both groups, with P-values of 0.530, 0.262, 0.53, and 0.685 for stages N1, N2, N3, and REM, respectively.

Table 2 . Polysomnographic variables between patients with PLMS versus patients with unidentified cause of RES

Polysomnographic variables	Group one with PLMD (N=45) (mean±SD)	Group two with unknown cause for RES (N=11) (mean±SD)	p-value
Sleep period (min.)	427.16±65.2	449.9±56.11	0.291
Total sleep time (hour)	5.5±1.46	6.6±0.75	0.019*
WASO (min.)	97.44±67.9	52.69±40.56	0.042*
Sleep onset latency (min.)	28.01±40.8	9.29±9.0	0.007*
Sleep efficiency (%)	72.44±17.7	87.1±8.6	0.011*
REM latency (min.)	146.57±103.8	118.5±85.67	0.411
AHI/hr	2.7±4.1	0.54±0.32	0.087
ODI /hr	4.0±5.6	1.17±1.4	0.106
PLMS index/hr	50.6±38.03	2.77±6.5	0.0001*
Total arousal index /hr	26.34±14.1	14.11±6.27	0.007*
N1% of TST	9.67±5.81	6.7±1.77	0.530
N2% of TST	41.07±9.77	45.15±14.11	0.262
N3% TST	29.76±9.9	27.5±12.88	0.530
REM% of TST	19.47±8.44	20.6±6.9	0.685

PLMS: Periodic limb Movements, RES: Residual Excessive Sleepiness, WASO: wake after sleep onset

AHI: Apnea Hypopnea index, ODI: oxygen desaturation index REM: Rapid Eye Movements
(*) means statistically significant

Multivariate logistic regression was performed on the statistically significantly different variables between both groups in the **table (3)**. Waist circumference was the only

predictor of PMLD in this population study with OR (95%CI) 0.168 (0.011-0.324). All other factors showed no significance including the age and sleep efficiency related parameters.

Table 3. Regression analysis of various variables for the presence of increased PLM index

Variables	Uni-variate analysis			Multi-variate analysis		
	P value	Wald statistic	OR (95% CI)	P-value	Wald statistic	OR (95% CI)
Age	0.032	4.574	0.113 (0.009-0.217)	0.645	0.002	0.041 (-0.135-0.218)
Waist Circum.	0.029	4.78	0.191 (0.020-0.362)	0.036*	0.212	0.168 (0.011-0.324)
Total sleep time	0.039	4.25	-0.016 (-0.031--0.001)	0.420	4.407	0.013 (-0.045-0.019)
WASO	0.025	5.045	0.0036 (0.005-0.067)	0.803	0.650	0.011 (-0.077-0.100)
Sleep efficiency	0.017	5.691	-0.146 (-0.267—0.026)	0.790	0.062	0.060 (-0.502-0.381)

PLM: Periodic limb Movement, WASO: wake after sleep onset. (*) means statistically significant

Discussion

In this study, we compared patients with increased PLMI of sleep and patients with unknown causes of RES after exclusion of other possible causes of RES. The increased PLMI has not affected significantly the daytime symptoms but it has affected many polysomnographic variables.

The presence of increased PLMI did not significantly affect the CPAP use where there was no significant difference between the two groups regarding the CPAP usage percent and nightly usage. This result differed from those of Budhiraja et al., who reported a high PLMI during sleep that negatively affects the CPAP

compliance in the long term (Budhiraja et al., 2020).

The mean age of the patients with high PLMI (group one) was significantly higher than the other group (54.69 ± 7.92 vs. 49.27 ± 8.577 years, P-value = 0.041), which is in accordance with many studies (Haba-Rubio et al., 2005, Haba-Rubio et al., 2016) (58.8 ± 11.3 vs. 52 ± 10.5 yr; P=0.03) and (64 ± 11 vs. 57 ± 11 , P-value <0.001) respectively. Recently, in a relatively large OSAS population (more than 800 OSAS patients), both patient groups of emergent and persistent increased PLMs index were older (Lee et al., 2022).

In this study, there was no significant difference between the two groups

regarding the gender, where most of the patients in the two groups were males, which can be explained by that OSAS is more prevalent in males (Fietze et al., 2019) which in accordance to other studies which reported male predominance (Haba-Rubio, Marti-Soler et al. 2016). On the other hand, a study found higher prevalence of increased PLMs index in women but this was in patients less than 55 years old (Ren et al., 2016).

We found that patients in group one with PLMD had a significantly higher waist circumference (45.9 ± 7.29 vs. 39.7 ± 8.15 inches), which was the only predictor of PLM for that group. Habu et al. reported that patients with PLMI of more than 15/hr had significantly higher body mass index (Haba-Rubio et al., 2005).

It is noticed that all the diabetic patients in this study had a higher PLMs index. Many studies reported an established link between diabetes, metabolic syndrome, and truncal obesity with PLM (Haba-Rubio et al., 2005).

The assessment of daytime sleepiness was done subjectively using the ESS. When comparing both groups, there was no significant difference in the ESS before or after CPAP treatment. Although there was no statistically significant difference, the patients with increased PLMI had lower mean ESS than the other group (15.11 vs. 16.9). Heba et al. reported a considerable difference with lower ESS in the patients with PLMI of more than 15/hr (Haba-Rubio et al., 2005). In addition, even in OSAS patients, there was no significant correlation between the increased PLMs index and excessive daytime sleepiness in recent research (Zhou et al., 2021) and even in earlier studies which included a large number of population as in the HypnoLaus study (Haba-Rubio, Marti-

Soler et al. 2018) and the Wisconsin Sleep Cohort (Leary et al., 2018).

In our study, there was no significant difference between the two groups regarding AHI or ODI, ensuring controlled sleep apnoea in both groups for assessment of RES while using the CPAP. The added effect of PLMS was reflected negatively on the polysomnographic parameters. Few studies evaluated the impact of increased PLMI on sleep parameters (Haba-Rubio et al., 2016, Hardy De Buisseret et al., 2017). Haba-Rubio et al., who conducted the population-based HypnoLaus study, assessed the clinical significance of periodic limb movement during sleep. The study included 2162 who clinically evaluated by a sleep study at home (Haba-Rubio et al., 2016). Another recent study evaluated the difference between the subjects with high PLMI combined high PLMI and RLS vs. normal subjects. They conducted a comparison between the patients with isolated PLMS vs. the controls (Hardy De Buisseret et al., 2017).

In Our study, there was a significantly lower sleep efficiency in the patients with PLMS (group one) than in group two (72.44% vs. 87.1%) in similarity to Haba-Rubio et al., where there was a significant difference between the subjects with PLMI of more than 15 and those with PLMI less than 15 (82.6% vs. 85.4% (Haba-Rubio et al., 2016). In our study, there was a significantly more delayed sleep latency in group one vs. group two (28.1 vs. 9.29 minutes and a P-value = 0.007) which was in accordance to Haba-Rubio (Haba-Rubio, Marti-Soler et al. 2016). In our study, there was a significantly higher WASO time in the patients with PLMS vs. the patients with unknown cause of RES. This finding is comparable to the results of Haba-Rubio (Haba-Rubio et al., 2018).

There was a highly significant difference between the patients with PLMS vs. patients with an unknown cause of RES regarding the arousal index. The mean arousal index was 26.34/hour for the patients with PLMS vs. 14.11/hour for the patients with an unknown cause of RES, which agrees with Haba-Rubio, who stated a highly significant difference in the arousal index between the patients with high PLMI vs. low PLMI. Recent research showed a low respiratory arousal threshold in patients with OSAS and increased PLMs index, (Wang et al., 2021) which may persist even after efficient CPAP therapy. Moreover, many studies illustrated increased arousal index in patients with combined OSAS and increased PLMs index (Zhou et al., 2021). These polysomnographic changes may signify the importance of PLM treatment in those OSA patients with RES in spite of adequate CPAP usage. Indifference to our study, Lin et al. reported that the sleep onset, efficiency, and WASO were not significantly different. However, they worked with patients who had increased PLM index and healthy controls, contrary to our study (Lin et al., 2020).

There was no significant difference in the percentages of the different sleep stages between the patients with PLMS vs. patients with unknown cause of RES, which is in accordance with a study that evaluated the sleep stages percentages in patients with combined OSAS and increased PLMs index (Zhou et al. 2021). This previous indifference to other studies which found a significant difference between the patients with high and low PLMI with an increased percentage of N1 and decreased N3 percentage. This conflict can be explained by their choice of patients from the community, not patients who had obstructive sleep

apnoea who complained of RES while using the CPAP to be in their study (Haba-Rubio et al., 2016, Hardy De Buisseret et al., 2017).

One of the limitations of this study is that it is a retrospective study, so it was not possible to treat those patients with increased PLMs and follow them up to see changes in daytime sleepiness and polysomnographic data. The number of the cases is considered relatively low, so the study of a larger cohort of patients is warranted for better evaluation.

Conclusion

Increased periodic limb movements index during sleep significantly impact the polysomnographic variables, “mainly sleep efficiency-related variables” and whether it is the cause of RES in OSA patients treated efficiently by CPAP is still unclear. The waist circumference is the only predictor factor for the increased PLMs index in this population study. The decision to treat those patients for the increased PLMs index necessities further evaluation.

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