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Research Article

Clinical Characteristics of Patients with Periodic Limb Movement in Sleep Who Showed Excessive Daytime Sleepiness

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ABSTRACT

Background: Some patients with periodic limb movement in sleep (PLMS) have disrupted sleep and excessive daytime sleepiness (EDS). The clinical characteristics of patients with PLMS and EDS remain to be elucidated.

Objective: To address the clinical characteristics of patients with PLMS affected by EDS, we assessed the clinical variables in patients with and without EDS and determined the influencing factors using polysomnography (PSG).

Methods: This retrospective study included 306 patients with PLMS who did not take drugs. They visited our clinic between March 2015 and February 2021. Their sleep was recorded using PSG. PLMS was defined as having brief (0.5-5 seconds) repetitive limb movements, with a frequency of 15 or more times per hour. The Epworth Sleepiness Scale (ESS) was used as a subjective sleepiness indicator. Using the ESS, EDS was defined as a score ≥ 11. Multivariable logistic regression analysis was performed to determine the factors influencing EDS in patients with PLMS.

Results: Of the 306 patients, 43 had PLMS. EDS was detected in 23 patients with PLMS. Logistic regression analyses revealed lower odds of EDS in men (odds ratio [OR] 0.187, 95% confidence interval [CI] 0.041-0.856, P = 0.0307) and older individuals (OR 0.92, 95% CI 0.862-0.982, P = 0.0119) among patients with PLMS.

Conclusions: Older male patients with PLMS were less likely to have EDS. To our knowledge, this is the first study to demonstrate that men and older individuals had a lower likelihood of experiencing EDS among patients with PLMS.

Keywords: Excessive daytime sleepiness (EDS);Epworth sleepiness scale (ESS);Periodic limb movement in sleep (PLMS)

INTRODUCTION

Periodic limb movement in sleep (PLMS) is an independent disorder of repetitive, highly stereotyped limb movements that occur during sleep. This movement comprises dorsiflexion of the toes and ankles, accompanied by flexion of the knees, and sometimes of the hips. It is frequently observed in patients with restless legs syndrome (RLS), narcolepsy, rapid eye movement sleep behavior disorder (RBD), and obstructive sleep apnea (OSA) [1]. It is also observed in several other medical conditions and patients taking hypnotics, antidepressants, and antipsychotics [2]. PLMS can also occur in generally healthy people, especially those over 40 years of age [3,4].

In this study, the PLMS-I score was determined using polysomnography (PSG). When PLMS was accompanied by arousal, the PLMS with arousal index was used. Periodic limb movement disorder (PLMD) was defined as the presence of PLMS equal to or greater than 15 times per hour in adults or PLMS equal to or greater than five times per hour in children, with a complaint of insomnia and/or excessive daytime sleepiness (EDS) that cannot otherwise be explained [5]. In adults, PLMS is relatively common, but PLMD is rare.

Recently, many studies have investigated associations between PLMS and sympathetic nervous system activation [6-8]. Furthermore, cardiovascular risk in patients with PLMS has been reported [9].

PLMS is considered a disorder that induces EDS. However, previous studies have shown conflicting results regarding EDS in patients with PLMS [10]. Hyo et al. reported that PLMS may reduce EDS in men with OSA patients [11]. It is important to clarify the presence of EDS in patients with PLMD. However, there are even more limited data regarding the clinical characteristics of EDS in patients with PLMS.

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This study aimed to determine the factors influencing EDS in patients with PLMS. We also evaluated sleep quality in patients with PLMS with or without EDS.

MATERIALS AND METHODS

Patients: A flowchart of the study is shown in Fig. 1. In total, 3792 patients who visited the Fukuoka Urasoe Clinic, between March 2015 and February 2021, and underwent PSG were included in the study. Their chief complaints were daytime sleepiness and/or loud snoring. We excluded 323 patients whose ESS data were not available, 325 patients under 16 years of age, and 2259 patients who scored ≧ 5 on the apnea-hypopnea index. We also excluded patients who had diseases or drugs affecting sleepiness and PLMS. In detail, 30 patients with RBD, 26 patients with RLS including 3 patients with PLMD, 132 patients with narcolepsy, 179 patients with idiopathic hypersomnia, and 15 patients with neurodevelopmental disorders were excluded. Further, ten patients with allergic rhinitis taking histamine-2 receptor blocker, one patient with urticaria taking a histamine-2 receptor blocker, and one patient with atopic dermatitis taking a histamine-2 receptor blocker were excluded. In addition, 97 patients with insomnia taking hypnotics, 54 patients with depressive disorders, 12 patients with anxiety disorders, 2 patients with panic disorder, 9 patients with bipolar disorders, 4 patients with schizophrenia, 3 patients with adjustment disorders, and 7 patients with epilepsy were also excluded. Consequently, 306 patients were finally enrolled in this study. One patient had a history of bipolar disorder, one patient had an adjustment disorder, and six patients had depressive disorders. In these 8 patients, these disorders were well controlled without the need for medications.

Periodic leg movements were scored according to the American Academy of Sleep Medicine criteria (2015) [12]. The patients with PLMS of ≧ 15 times per hour were defined as having PLMS.

Patients with RLS, narcolepsy, idiopathic hypersomnia, and RBD were defined as per the diagnostic criteria of the International Classification of Sleep Disorders, version 3 [5]. A diagnosis of mental disorders was made by psychiatry specialists before visiting our clinic. A diagnosis of type 2 diabetes mellitus (T2DM) was made in four patients before visiting our clinic. Two of these patients were receiving diet therapy as part of the treatment for T2DM, and two were taking oral hypoglycemic agents. The mean disease duration of T2DM in these patients was 5.8 years. There were no self-reported diabetic complications as diagnosed by a physician.

Patients with hypertension were defined as those for whom a diagnosis of hypertension had been made previously, those being treated with antihypertensive drugs, and those who had a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg. Seven patients had hypertension, of whom two had been treated with calcium-channel blockers and angiotensin II receptor blockers, and one had been treated with only β-blocker.

Informed consent was obtained from all patients before enrollment in this study. The study was conducted according to the principles of the Declaration of Helsinki and its later amendments. The study protocol was approved by the Institutional Ethics Committee of the Nakamura Clinic, Urasoe, Okinawa, Japan.

Sleepiness: Subjective sleepiness was assessed using the Epworth Sleepiness Scale (ESS), which is an extensively used self-administered, eight-question survey [13]. We evaluated the ESS using the Japanese version of the ESS [14]. The survey was completed on the first visit. We used the standard cut-off score of ≥11 points to indicate EDS.

Measurement: All patients enrolled in this study underwent blood chemistry measurements, electrocardiography (ECG), and a pulmonary function test as a regular examination for first-time patients on the day of the first visit to our clinic.We also measured blood pressure twice in the office after 5 min of resting in a chair and the average measurement was recorded. Subsequently, we measured the patients' blood pressure at follow-up in the same way and averaged the two measurements.

PSG: As described in our previous study [15], standard overnight PSG included continuous monitoring using central electroencephalography (EEG), electrooculography, submental and anterior tibial electromyography, and ECG using conventional leads. Airflow was monitored with oral and nasal thermistors, and respiratory effort was measured by respiratory inductance plethysmography with transducers placed around the chest and abdomen. Oxyhemoglobin saturation was continuously recorded using a pulse oximeter (3900P, Datex-Ohmeda Co., Louisville, CO, USA). All variables were continuously recorded using REMbrandt™ version 8.0 (EMbla, Broomfield, CO, USA) and RemLogic™ version 3.2 (EMbla, Thornton, CO, USA). All recordings were scored directly on the screen by a polysomnographer certified by the Japanese Society of Sleep Research using the standard criteria of Rechtschaffen and Kales. Apnea, hypopnea, and periodic leg movements were scored according to the newest (2015) American Academy of Sleep Medicine criteria [12].

Statistical analyses: All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics [16]. The Mann-Whitney U test was used to compare continuous variables between patients with PLMS with or without EDS to identify significant variables. It was also used to compare the sleep parameters. Fisher's exact test was used to compare the ratio of variables between PLMS patients with and without EDS. Logistic regression analysis was used to assess the odds of EDS in patients with PLMS. All continuous values were expressed as the mean ± standard deviation (SD).

To calculate the sample size, we assumed: α= 0.05, β = 0.2, and the expected difference of male patient ratio in PLMS patients between with EDS and without EDS to be 0.35. As a result, the sample size was 36, indicating that the study's sample size was sufficient for the analysis.

RESULTS

Comparison of clinical variables between PLMS patients with and without EDS

Of the 306 patients, 43 (14%) had PLMS. EDS was detected in 23 (53%) out of 43 patients with PLMS. Table 1 Shows the results of a comparison of clinical variables between PLMS patients with and without EDS. No significant difference was observed in the ratio of hypertension and T2DM between PLMS patients with and without EDS. The ratio of men and age value was decreased in PLMS patients with EDS as compared with those without EDS (male: 39.1% vs.73.7%, P = 0.0332; age value: 41.4 ±14.5 vs. 54.2 ± 11.8, P = 0.00792).

Table 1: Comparison of clinical variables between PLMS patients with and without EDS (N=43).

	PLMS (+) (N = 43)		
Variables	**EDS(+) (N = 23)**	**EDS(-) (N = 19)**	**P-value**
Male n, (%)	9 (39. 1%)	14 (73.7%)	0.0332
Age (years)	41.4 ± 14.5	54.2 ± 11.8	0.00792
Body weight (Kg)	56.1 ± 8.94	61.7 ± 10.4	0.0516
Hypertension n, (%)	2 (8.70%)	5 (26.3%)	0.214
T2DM n. (%)	1 (4.34%)	3 (15.8%)	0.313

EDS: Excessive Daytime Sleepiness, PLMS: Periodic Limb Movement in Sleep, T2DM: Type 2 Diabetes Mellitus; Data are expressed as mean ± standard deviation, or number (percentage).

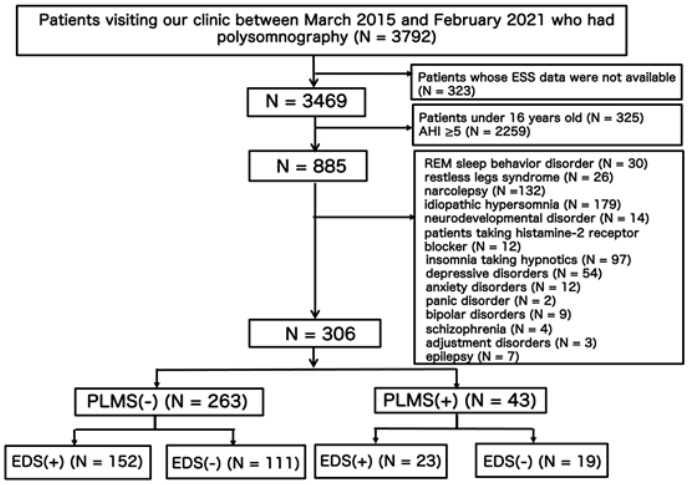

Figure 1: Study flow - chart. Among 3792 patients who underwent PSG, 306 were enrolled in the study. We excluded 266 patients without PLMS, and 43 patients with PLMS were included in this analysis.

Multivariate analysis of the clinical factors and EDS in patients with PLMS

Logistic regression analyses were carried out, including body weight, sex, and age. Male sex (odds ratio [OR] 0.187, 95% confidence interval [CI] 0.041-0.856, *P* = 0.0307) and older age (OR 0.92, 95% CI 0.862-0.982, *P* = 0.0119) were independent influencing factors of EDS in PLMS patients (Table 2).

Comparison of sleep parameters between PLMS patients with and without EDS

As shown in Table 3, the percentage of wake after sleep onset (WASO) and Stage N1 showed a significant decrease in PLMS patients with EDS as compared to those without EDS (WASO: 15.6% ± 12.3% vs. 29.3% ± 22.7%, *P* = 0.00588; Stage N1: 14.6% ± 6.80% vs. 29.0% ± 21.1%, *P* = 0.00165). In contrast, the percentage of Stage N3 showed a significant increase in PLMS patients with EDS as compared to those without EDS (12.0% ± 10.2% vs. 5.27% ± 6.96%, *P* = 0.00914).

DISCUSSION

The results of the present study revealed that older male patients with PLMS were associated with a lower prevalence of EDS. However, as shown in Table 3, the results of PSG suggested that the quality of sleep was decreased in the patients with PLMS without EDS as compared to those with EDS, in which a decreased WASO ratio, a small ratio of Stage N1, and an increase in Stage N3 were observed. PSG should be performed to correctly diagnose PLMS. To our knowledge, this is the first study to demonstrate the lower likelihood of EDS in older male patients with PLMS.

Table 2: Multivariate analysis of the clinical factors and EDS in patients with PLMS (N=43).

Variables	OR	95% CI	P-value
Male	0.187	0.041-0.856	0.0307
Age	0.92	0.862-0.982	0.01 19

EDS: Excessive Daytime Sleepiness, PLMS: Periodic Limb Movement in Sleep, OR: Odds Ratio, CL: Confidence Interval.

Table 3: Comparison of sleep parameters between PLMS patients with and without EDS (N=43).

	PLMS (+) (N = 43)		
Parameters	EDS (+) (N = 23)	EOS (-) (N = 19)	P-value
AHI	1.88 ± 1.21	2.79 ± 1.59	0.053
Sleep time with Sp02 < 90 %	0.0939 ± 0.359	0.0474± 0.206	0.692
Lowest Sp02 (%)	90.9 ± 8.45	92.1 ± 1.81	0.335
Arousal index (/h)	20.6 ± 11.7	27.6 ± 18.6	0.0904
PLMS-1 (/h)	31.2 ± 16.0	43.3 ± 25.5	0.129
PLMSA-1 (/h)	7.68 ± 11.3	11.2 ± 18.6	0.3
TST (min)	366 ± 59.2	316 ± 110	0.0532
Sleep latency (min)	12.8 ±12.3	18.0 ± 26.5	0.714
Sleep efficiency (%)	83.3 ± 13.3	70.2 ± 22.6	0.0924
WASO (SP,%)	15.6 ± 12.3	29.3 ± 22.7	0.00588
Stage N1 (TST,%)	14.6 ± 6.80	29.0 ± 21.1	0.00165
Stage N2 (TST, %)	54.9 ± 8.32	49.8 ± 14.8	0.312
Stage N3 (TST, %)	12.0 ± 10.2	5.27 ± 6.96	0.00914
Stage REM (TST,%)	18.5 ± 4.38	15.9 ± 7.86	0.206

PLMS: Periodic Limb Movement in Sleep, EDS: Excessive Daytime Sleepiness, AHI: Apnea-hypopnea Index, PLMS-1: Periodic Limb Movement in Sleep Index, PLMSA-1: Periodic Limb Movement in Sleep with Arousal Index, WASO: Wake After Sleep Onset. SP: Sleep Period, TST: Total Sleep Time, REM: Rapid Eye Movement; Data are expressed as mean ± standard deviation.

Gender differences and the influence of age on EDS have been reported in patients with OSA [17]. Honig et al. reported that EDS was different between men and women with OSA. Moreover, they showed that sleepiness in men was more significantly influenced by OSA and sleep variables than women. In addition, younger women were more frequently affected by EDS than older women among patients with OSA. They reported that sleep parameters did not correlate with EDS in patients with OSA. It has been suggested that in young female patients, there may be other reasons causing EDS. Moreover, the manifestation and pathogenesis of PLMS symptoms may be different in young women versus older men.

Gender differences were also reported in the prevalence of PLMS in patients with OSA [18]. Young women had a significantly higher prevalence of PLMS than young men with OSA. It was presumed that the gender difference in the prevalence of PLMS among patients with OSA may be due to a decreased ferritin level.

EDS in patients with PLMS is controversial. No obvious association was observed between the PLMS category among patients with sleepiness in the general population study [10] or patients with OSA [19]. Haba-Rubio et al. reported that PLMS may be present without any complaints of disturbed sleep or daytime sleepiness, especially in the elderly [20].

Sleep parameters in patients with PLMS and without EDS indicate a reduction in sleep quality. One reason for this finding may be related to the age of patients with PLMS and without EDS was higher than that of those with EDS.

It has also been reported that older age, PLMS, and hypertension were protective factors for incidences of EDS in the general population [20]. After adjustment for age, PLMS was shown to reduce EDS in male patients with OSA [11]. Allen et al. surmised that patients with PLMS had an overactive hypocretin system maintaining a high level of alertness throughout the day [21]. In our study, hypertension was not correlated with EDS in patients with PLMS. However, Martynowicz et al. reported that the ESS score was lower in hypertensive patients than in normotensive subjects with OSA [22]. They inferred that this evidence may be due to the higher activity of the sympathetic nervous system in hypertensive patients [23]. As sympathetic activation is reported in patients with PLMS, it may result in increased blood pressure [8] and decreased EDS.

Study limitations: The present study had several limitations. The present data were from a single center, and consequently, the present evidence may not be generalized. We could not assess the effects of alcohol consumption, smoking, and caffeine intake, which may affect EDS. We did not perform multiple sleep latency tests, therefore, we could not objectively evaluate sleepiness. We could not explain the reasons for poor sleep quality and the absence of EDS in patients with PLMS. As this was a case-control study, we were not able to determine the cause-effect among EDS, PLMS, and other consequences. The mechanism underlying age and sex differences in EDS among patients with PLMS could not be investigated in this study.

CONCLUSIONS

The results of the present study revealed that older male patients with PLMS had a lower prevalence of EDS. From the PSG study, sleep quality deteriorated in patients with PLMS and without EDS as compared to those with EDS. EDS is not a predictive symptom of PLMS. The prevalence of PLMS may be underdiagnosed in older male patients. PSG should be performed to accurately diagnose PLMS. To the best of our knowledge, this is the first study to demonstrate a lower likelihood of EDS among older men with PLMS.

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CONFLICT OF INTEREST

This study was performed without financial support and there are no conflicts of interest to declare.

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