

Comparison of motor pattern of periodic limb movements in patients with restless legs syndrome and obstructive sleep apnea syndrome

Murat GÜLTEKİN*, Sevda İSMAİLOĞULLARI, Murat AKSU
Department of Neurology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

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Background/aim: Periodic limb movements (PLMs) are repetitive and stereotypical movements of the lower extremities that occur during sleep. The purpose of this study was to analyze the leg muscle activity patterns in PLMs seen in restless legs syndrome (RLS) and obstructive sleep apnea syndrome (OSAS).

Materials and methods: In this study, 1260 PLMs from 4 patients with RLS and 4 patients with OSAS were analyzed. The spreading and frequency characteristics of the gastrocnemius, medial hamstring, and vastus muscles were examined separately for each muscle in addition to the tibialis anterior muscle already included in the standard polysomnography recording.

Results: A greater number of PLMs (57.34%) were observed in patients with RLS. A greater number of apnea-related PLMs (59.83%) were observed in patients with OSAS. The number of PLMs with spreading characteristics was higher in both patient groups. In both groups, the first muscle to contract was most frequently the tibialis anterior. Analysis of the subsequent contraction patterns showed no regular course in RLS and OSAS patients.

Conclusion: PLMs may occur with a nonstereotypical muscle spreading pattern generated by different, independent, and, most frequently, unsynchronized spinal generators.

Key words: Periodic limb movement, spreading pattern, restless legs syndrome, obstructive sleep apnea syndrome

1. Introduction

Periodic limb movements (PLMs) during sleep are sleep-related events seen as periodic episodes of repetitive and stereotypical movements of lower extremities. These movements are in the form of ankle dorsiflexion, toe dorsiflexion, and partial knee flexion (1,2). PLMs consist of a sequence of 4 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 (3). PLMs were reported in patients with different sleep disorders (4–8). PLMs were determined in 80%–90% of patients with restless legs syndrome (RLS) (9). PLMs are also a frequent symptom in obstructive sleep apnea syndrome (OSAS). PLMs may have a temporal association with respiratory events or may occur independently from respiratory events. PLMs may increase or decrease depending on the severity of OSAS (10). In addition to these disorders, PLMs may also be seen in narcolepsy and REM sleep behavior disorder (11–13). To date, the etiology of PLMs has not been fully explained. There are various hypotheses regarding their pathophysiology. The purpose of this study is to compare

the activity patterns of leg muscles in PLMs seen in 2 distinct diseases, RLS and OSAS.

2. Materials and methods

Four patients diagnosed with RLS and 4 patients diagnosed with OSAS, all of whom had concomitant PLMs and polysomnography (PSG) recordings performed in the sleep laboratory of the Erciyes University Medical Faculty Neurology Department from 30 November 2006 to 30 November 2007, were included in the study. Patients were included in the study according to the following criteria:

1. For RLS patients, RLS diagnosis based on the international RLS study group diagnostic criteria accompanied by PLMs (14).
2. For the OSAS patients, apnea-hypopnea index (AHI) of >15 accompanied by PLMs.
3. Periodic leg movement index (PLMI) of >30 in both patient groups (RLS and OSAS).
4. For RLS patients receiving treatment, discontinuation of treatment at least 7 days prior to the PSG recording.

* Correspondence: gultekin@erciyes.edu.tr

5. For OSAS patients receiving treatment (continuous positive airway pressure), discontinuation of treatment at least 7 days prior to the PSG recording.

Patients who received surgical treatment and patients with RLS or OSAS who refused to discontinue treatment were excluded from the study.

2.1. Polysomnography

Polysomnography was performed according to the Comet sleep recording system. For the first recording, standard PSG was performed in all patients. These standard recordings included 6 EEG channels (C4-M1, C3-M2, F4-M1, F3-M2, O2-M1, O1-M2; based on the 10–20 electrode placement system), 2 EOG channels, 1 submental muscle EMG channel, 1 nasal airflow channel, EMG channels for right and left legs, and oximetry channels. EMG recording was performed with superficial electrodes for the submental muscle and both tibialis anterior muscles.

For the second PSG recording, 2 EEG channels (C3-M2, C4-M1), 2 EOG channels, 1 submental muscle EMG channel, 1 nasal airflow channel, 1 chest movement channel, 1 abdominal movement channel, 1 microphone channel, 1 ECG channel, and 8 EMG channels for the tibialis anterior, gastrocnemius, medial hamstring, and medial vastus muscles of the right and left legs were used. Data were obtained by numbering the muscles from 1 to 8: 1 = right tibialis anterior, 2 = right gastrocnemius, 3 = right medial hamstring, 4 = right medial vastus, 5 = left tibialis anterior, 6 = left gastrocnemius, 7 = left medial hamstring, 8 = left medial vastus.

Scoring of sleep staging was performed manually by a specialized physician in the sleep laboratory. PLMs were defined according to the scoring criteria for sleep and related events published by the American Academy of Sleep Medicine (3). A PLM occurring in a single muscle was specified as a nonspreading PLM. PLMs occurring in more than one muscle were specified as spreading PLMs. Each of the spreading PLMs was determined by taking into account the spread over time. In conclusion, PSG recordings of approximately 6720 min for 8 patients and 1260 PLMs were investigated and included in the study.

2.2. Statistics

SPSS 15.0 for Windows and MINITAB 14 were used for the evaluation of PLM data in this study. The 2-proportion Z-test was used for the comparison of intergroup rates. Comparison of the groups according to the muscle movements was performed with the exact test or chi-square test. Muscle movements were distributed across the groups based on the one-sample Kolmogorov–Smirnov test (uniform). $P < 0.05$ was considered statistically significant.

3. Results

While 919 PLMs were detected in the RLS group, 341 PLMs were detected in the OSAS group. PLM data from the patients were divided into 6 groups for statistical comparison:

Spreading PLMs:

Group 1: Spreading PLMs in patients with RLS.

Group 2: Apnea-related and spreading PLMs in patients with OSAS.

Group 3: Nonapneic and spreading PLMs unrelated to apnea in patients with OSAS.

Nonspreading PLMs:

Group 4: Nonspreading PLMs in patients with RLS.

Group 5: Apnea-related and nonspreading PLMs patients with OSAS.

Group 6: Nonapneic and nonspreading PLMs in patients with OSAS.

The calculation of spreading rates across the groups revealed a statistically significant difference ($P = 0.009$) between Group 1 ($n = 392$) and Group 2 ($n = 43$). There was no statistically significant difference ($P = 0.057$) between Groups 1 and 3 ($n = 102$). However, there was a statistically significant difference ($P = 0.001$) between Groups 2 and 3.

There was statistical significance in all 3 groups in the evaluation of nonspreading PLMs. The intragroup comparisons revealed a statistically significant difference ($P = 0.001$) between Groups 4 and 6. However, there was no statistically significant difference ($P = 0.058$) between Groups 4 and 5. There was also no statistically significant difference ($P = 0.050$) between Groups 5 and 6.

When the spreading PLMs were investigated according to occurrence in one or both legs, a statistically significant difference ($P = 0.007$) was found between Groups 1 and 2. However, there was no statistically significant difference between Groups 1 and 3 or between Groups 2 and 3 (Table 1).

PLMs occurred more frequently in the left leg in the RLS group while they occurred more frequently in the right leg in the OSAS group. The 2-proportion Z test was used to evaluate the spreading PLMs in a single leg according to their occurrence in the right or left leg. A statistically significant difference ($P = 0.001$) was found between Groups 1 and 2. Similarly, there was a statistically significant difference ($P = 0.001$) between Groups 1 and 3 and between Groups 2 and 3 (Table 2).

Spreading PLMs were evaluated within the groups according to the first 3 muscles according to the spreading pattern and according to the frequency and number of spreading in different patterns. Tables 3, 4, and 5 are based on these evaluations.

Investigation of the muscle spreading patterns of PLMs based on these findings revealed individual differences in muscle spreading patterns of the patients. Different

Table 1. The rates of occurrence in one or both legs and statistical comparison for spreading PLMs.

	One-leg PLMs, n (%)	Both-leg PLMs, n (%)	P
Group 1	86 (16.3)	441 (83.7)	0.007
Group 2	28 (29.8)	66 (70.2)	0.007
Group 3	22 (21.6)	80 (78.4)	0.09

Group 1: PLMs with spreading in RLS patients.

Group 2: PLMs with spreading and related to apnea in OSAS patients.

Group 3: PLMs with spreading and not related to apnea in OSAS patients.

Table 2. Occurrence rates and statistical comparison of PLMs spreading in a single leg.

	Group 1 PLMs (%)	Group 2 PLMs (%)	Group 3 PLMs (%)
Right leg	4.7%	92.9%	40.9%
Left leg	95.4%	7.2%	59.1%

Group 1: PLMs with spreading in RLS patients.

Group 2: PLMs with spreading and related to apnea in OSAS patients.

Group 3: PLMs with spreading and not related to apnea in OSAS patients.

Table 3. PLM muscle spreading patterns in patients with RLS.

Number	PLM spreading %	First frequency pattern	%	Second frequency pattern	%	Third frequency pattern	%	Different spreading numbers
Patient 1	6.52	5 - 7 - 8	16.6	1 - 3 - 5	16.6	5 - 6 - 1	8.3	10
Patient 2	77.92	7 - 8 - 3	31.7	5 - 7 - 8	14.6	1 - 3 - 7	8.3	24
Patient 3	59.57	5 - 6 - 7	41.1	1 - 6 - 7	7.1	1 - 7 - 8	7.1	11
Patient 4	69.60	1 - 5 - 6	25.1	5 - 6 - 8	22.4	5 - 6 - 1	18.9	22

Numbers of muscles: 1 = right tibialis anterior, 2 = right gastrocnemius, 3 = right medial hamstring, 4 = right medial vastus, 5 = left tibialis anterior, 6 = left gastrocnemius, 7 = left medial hamstring, 8 = left medial vastus.

Table 4. Muscle spreading patterns of apnea-related PLMs in patients with OSAS.

Number	PLM spreading %	First frequency pattern	%	Second frequency pattern	%	Third frequency pattern	%	Different spreading numbers
Patient 1	61.76	5 - 6 - 8	42.85	5 - 6 - 7	14.28	5 - 2 - 7	9.52	8
Patient 2	30.92	1 - 2 - 3	28.33	1 - 3	18.33	1 - 3 - 2	11.66	15
Patient 3	10.71	5 - 3 - 4	16.66	1 - 4 - 5	16.66	5 - 1 - 3	16.66	6
Patient 4	12.28	5 - 6 - 1	28.57	5 - 6	14.28	6 - 5 - 7	14.28	6

Numbers of muscles: 1 = right tibialis anterior, 2 = right gastrocnemius, 3 = right medial hamstring, 4 = right medial vastus, 5 = left tibialis anterior, 6 = left gastrocnemius, 7 = left medial hamstring, 8 = left medial vastus.

Table 5. Muscle spreading patterns of nonapneic PLMs in patients with OSAS.

Number	PLM spreading %	First frequency pattern	%	Second frequency pattern	%	Third frequency pattern	%	Different spreading numbers
Patient 1	38.24	5 - 8 - 7	25	5 - 6 - 2	12.5	5 - 7 - 8	12.5	7
Patient 2	69.08	1 - 2 - 3	7.40	1 - 6 - 8	7.40	1 - 3 - 6	5.55	42
Patient 3	89.29	5 - 1 - 3	16.66	5 - 1 - 2	11.11	5 - 4 - 2	5.55	14
Patient 4	87.72	5 - 6	40.90	5 - 6 - 2	13.63	2 - 6 - 3	9.09	12

Numbers of muscles: 1 = right tibialis anterior, 2 = right gastrocnemius, 3 = right medial hamstring, 4 = right medial vastus, 5 = left tibialis anterior, 6 = left gastrocnemius, 7 = left medial hamstring, 8 = left medial vastus.

spreading patterns were detected even in the PLMs of the same patient. The first muscle to contract was the tibialis anterior in 835 of the 919 PLMs (90.85%) in the RLS group. The first muscle to contract was the tibialis anterior in 311 of the 341 PLMs (91.12%) in the OSAS group.

4. Discussion

Both periodic limb movement disorder (PLMD) and RLS respond well to dopaminergic treatment, suggesting a common pathophysiological mechanism. PLMs are assumed to result from the sleep-related dysfunction of inhibitory pathways causing 'downregulation' on inhibition at the spinal level. Among PLMs detected in the RLS group in our study, 57.34% were spreading PLMs while 392 (42.66%) were nonspreading PLMs. This is the result of the evaluation of total PLMs observed in 4 patients with RLS included in this study. There were more spreading PLMs compared to nonspreading PLMs in 3 of the 4 patients with RLS.

PLMs occurring in both legs were most commonly seen in patients with RLS among the groups. PLM spreading is usually bilateral in patients with RLS. This finding indicates that neural pathways at the spinal level are activated bilaterally or that there is usually bilateral activation in the potential generator in the brain stem.

While 137 of the 341 PLMs (40.17%) obtained in the OSAS group in this study were apnea-related, 204 were not apnea-related (59.83%). When these 2 subgroups were evaluated regarding PLM spreading, all of the patients in the apnea-related group were observed to develop predominantly spreading PLMs. This finding demonstrates that a greater number of nonapneic PLMs develop in patients with OSAS. Furthermore, it indicates the presence of a generator causing PLMs independent from apnea in these patients.

It was seen that 95.35% of the PLMs spreading to a single leg in patients with RLS were detected in the right leg. Meanwhile, 92.85% of the apnea-related PLMs in the OSAS group occurred in the right leg and 59.1% of the

nonapneic PLMs were observed in the left leg. According to these findings, nonspreading PLMs localized in a single leg occurred predominantly in the left extremity in patients with RLS. This indicates that left neural pathways at the spinal level may have more excitability. An interesting finding was seen in patients with OSAS. Apnea-related PLMs were more frequently seen in the right leg and these patients may have more excitability in their right neural pathways, similar to the situation seen in RLS patients regarding the left leg. Nonapneic PLMs were predominantly localized in the left leg. This finding indicates that left neural pathways are more excitable. Taken together, these findings indicate the presence of a potential generator activated on the right side at the supraspinal level particularly in nonspreading PLMs in patients with RLS and a similar outcome for the nonapneic PLMs in patients with OSAS. On the contrary, these findings support the presence of a generator activating on the left side for the apnea-related PLMs.

When a comparison was made only between the different patient groups, it was observed that 70% of all PLMs were in the OSAS group, regardless of the association with apnea. A reverse outcome was seen particularly in patients with OSAS compared to those with RLS. Therefore, it may be concluded that the generators causing PLMs in 2 distinct disorders, namely RLS and OSAS, may be localized differently.

Upon the evaluation of the 1260 PLMs obtained in our study, we found that the muscle contraction patterns of PLMs occurring in the legs of patients with RLS as well as the patients with OSAS consisted of different combinations. In both groups, the first muscle to contract was most frequently the tibialis anterior. This finding was consistent in 90.95% of all PLMs. These findings demonstrate the presence of a potential PLM generator in the spinal region L4-5, which is the innervation zone for the tibialis anterior muscle. The fact that the tibialis anterior is the first muscle to contract particularly suggests an origin causing PLMs at this spinal level.

The analysis of the subsequent contraction patterns showed no regular course in RLS and OSAS patients. However, the second to contract after the tibialis anterior was most frequently the gastrocnemius in RLS patients with spreading PLMs (44.40%). This pattern was found in 44.89% of the patients with OSAS. Surprisingly, contractions were detected in agonist and antagonist muscles in the beginning of PLMs and commonly following the onset. This finding was consistent with the available literature information.

Weerd et al. (15) analyzed PLMs using superficial EMG electrodes in a study. The first muscle to contract was most commonly the tibialis anterior (32% of all PLMs). All other combinations were seen less frequently. Thus, various combinations were demonstrated regarding the muscle spreading patterns in PLMs. The consecutive contractions of agonist and antagonist muscles were observed in 16% of the PLMs in this study.

Plazzi et al. (16) examined the first 100 consecutive PLMs of each patient included in their study. The most frequently contracted muscle was the tibialis anterior (right: 74%, left: 76%), followed by the gastrocnemius (right: 66%, left: 54%) and then the rectus femoris (right: 36%, left: 49%). This study also demonstrated that antagonist muscles are activated simultaneously. Based on these findings, it was shown that PLMs had no stereotypical pattern, even in the same patient. It was also demonstrated that EMG activity had no caudal or rostral onset according to the spinal spread.

Our findings regarding the spreading pattern of PLMs in patients with RLS are consistent with the literature. Predominantly, more than one muscle is activated during PLMs. We showed that there were no regular patterns regarding the muscle spread in PLMs. While PLMs muscle

patterns varied among the patients with RLS, we observed at least 10 combinations and up to a maximum of 24 different combinations. There were at least 6 combinations and up to a maximum of 42 different combinations among the patterns observed in the OSAS group. In light of these findings, it can be concluded that the neural mechanisms leading to PLMs are not limited to a single pathway.

The polysynaptic reflex hyperexcitability in RLS was demonstrated by Bara-Jimenez et al. (17). They showed higher excitability in the spinal cord for the patients with PLMs and RLS by demonstrating the high spinal cord special spreading value and the low threshold in flexor reflexes. These findings may explain the origin differences regarding the spreading hyperexcitability of the spinal cord in the consecutive PLMs observed in the same patient. Rijsman et al. (18) investigated H reflexes in 9 patients with PLMD and a control group of 11 subjects. No difference was found in H/M rates regarding the excitation of the motor neuron pool at the same level in the patient group and the control group. These data demonstrate the presence of decreased inhibition resulting from the alterations in interneuronal circulation through the descending spinal pathways in patients with PLMD.

Evaluation of our data, along with the findings of previous studies, may provide outcomes regarding the motor pattern of PLMs. Based on this evaluation, PLMs may occur with a nonstereotypical muscle spreading pattern generated by different, independent, and, most frequently, unsynchronized spinal generators. Our study includes analysis performed with the largest number of PLMs in the available literature. It provides a significant contribution to the understanding of the pathophysiology of PLMs, seen in 5%–30% of the general population.

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