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Are Periodic Leg Movements Associated With Clinical Sleep Disturbance?

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Summary: We examined 67 patients with periodic leg movement (PLM) disorder who were seen in a university-based sleep center. The most common reasons for coming to the sleep center were insomnia, sleepiness and a request for an evaluation for possible sleep apnea. There was a significant positive correlation between PLM arousal index and age but no association with gender. Approximately one-quarter of patients were under age 30. The multiple sleep latency test (MSLT) revealed borderline normal wakefulness in the group as a whole (sleep latency of 10.2 ± 0.9 minutes), and there was no significant correlation between the PLM arousal index and either the MSLT mean sleep latency or a measure of subjective sleepiness. Similarly, the PLM arousal index did not differentiate those who entered with chief complaints of insomnia or sleepiness. There was no significant difference in the PLM arousal index in those who reported that they did or did not awaken refreshed in the morning. In summary, in this clinical population we found no significant association between the PLM arousal index and the subjective complaint of disturbed sleep, an objective measure of daytime sleepiness or a sense of awakening refreshed in the morning. Other interesting observations included the relatively high frequency of a PLM index >5 in patients under 30 years old and a relatively high rate of past treatment for depression. **Key Words:** Periodic leg movement disorder—Nocturnal myoclonus—Myoclonus—Insomnia—Sleepiness.

Periodic leg movement (PLM) disorder (formerly known as nocturnal myoclonus) occurs in 13% of patients complaining of insomnia and 6% of those being evaluated for excessive sleepiness (1). Many features of the disorder remain unclear, including why it manifests as either insomnia or sleepiness, whether the insomnia takes the form of difficulty falling asleep or sleep maintenance difficulty (2), its possible association with some medications and indeed whether it causes sleep disturbance at all (3). Also puzzling is the frequent appearance of PLMs in other disorders, including narcolepsy (4) and obstructive sleep apnea (OSA) (5). In order to explore some of these issues, we are reporting our experience with all patients with PLM disorder taken from a large case series from our program. The central question we wished to test was whether polygraphic measures of PLMs could be associated with clinical complaints of insomnia or sleepiness, an objective measure of sleepiness [the multiple sleep latency test (MSLT)] or a sense of awakening unrefreshed in the morning.

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METHODS

The patients presented here come from a sample of 1,692 patients seen at a university-based sleep disorders center between September 1987 and September 1993 (1). Of these, 1,515 were 18 years or older, and 1,171 had polysomnograms. Among these 1,171 patients, 67 were found to have PLM disorder. This group included 40 males and 27 females aged 50.5 ± 2.0 (SEM) years. Details of polysomnographic recording are found in Mendelson (6). The polygraphic criteria of PLMs were that they be movements in the anterior tibialis channel of 0.5 to 5 seconds of duration, in trains of at least three movements with intermovement intervals of 4 to 90 seconds, and that they be accompanied by electroencephalographic (EEG) signs of arousal. The latter included either a K complex, alpha activity of at least 2 seconds duration or a change to a lighter sleep stage for at least 6 seconds. Such EEG changes were counted if they occurred simultaneously or within 1 second following a leg movement, but not if they preceded the movement. Inclusion criteria were that patients have a PLM arousal index (frequency of such PLMs per hour) of at least 5. Inclusion also required that no other medical disorder could account for the patient's primary complaint. Five were receiving medications thought to be

Table 1. *Reported sleep characteristics*[a] (n = 67)

Difficulty sleeping	73.1%
No. of nights per week with sleep difficulty	3.9 ± 0.4
Difficulty falling asleep[b]	2.2 ± 0.2
Awakenings during the night[b]	2.5 ± 0.2
Early morning awakening[b]	1.9 ± 0.2
Daytime sleepiness[b]	2.3 ± 0.2

[a] All values are expressed as mean ± SEM.
[b] Response on a scale of 1 to 5 in which 1 = "not really a problem" and 5 = "a very major difficulty". These responses refer only to the 73.1% of PLM disorder patients who responded that they had disturbed sleep.

associated with PLM disorder: one each was receiving imipramine, amitriptyline and nortriptyline, and two were taking lithium. Because the data analysis was not altered by their presence or absence, we included them in this presentation. In this main study group, any patient with other major pathophysiologies of sleep, such as OSA, was also excluded. In the entire series of 1,171 patients, four had restless legs syndrome and are not included in this analysis. In addition to the main cohort of 67 patients, we also report on 518 OSA and 21 narcolepsy patients who had PLM arousal indices of at least 5 [for diagnostic criteria, see Mendelson (6)].

Statistical analysis of quantitative data was performed by analyses of variance (ANOVAs); when significant differences were found, posthoc least-significant-difference tests were performed. The relation of two quantitative measures was assessed by two-tailed Pearson *r* product–moment correlations. Categorical data were examined by two-tailed Chi-square tests.

RESULTS

Symptomatology

The three most common reasons patients with PLM disorder came to the sleep center were a specific request to be evaluated for possible sleep apnea (34.2%), insomnia (29.8%) and excessive daytime sleepiness (26.9%). The patients described disturbed sleep 3.9 ± 0.4 nights per week for a duration of 6.9 ± 1.4 years. The specific types of difficulties described by patients who reported that they had disturbed sleep is presented in Table 1. Daytime sleepiness was reported in a categorical question by 59.7%. Difficulty with memory was described by 32.8%. A history of past treatment for depression was found in 29.8%.

Polygraphic sleep measures

Sleep characteristics are found in Table 2. It can be seen that there was a relatively long sleep latency and poor sleep efficiency. The mean sleep latency on the MSLT was 10.2 ± 0.9 minutes, which in this laboratory is considered to be borderline normal wakefulness.

Table 2. *Polygraphic sleep characteristics*[a]

Total sleep (minutes)	292.6 ± 10.5
Sleep latency (minutes)	28.1 ± 5.1
Sleep efficiency (%)	53.1 ± 4.2
PLM arousal index (no. per hour)	31.3 ± 3.2
Stage 1 (minutes)	28.3 ± 3.5
Stage 2 (minutes)	205.2 ± 8.4
Stage 3 (minutes)	11.4 ± 1.6
Stage 4 (minutes)	2.8 ± 1.0
REM (minutes)	48.0 ± 4.3
REM latency (minutes)	142.9 ± 10.7
Awakenings, total	26.3 ± 2.1
Awakenings >3 minutes	5.6 ± 0.6
Wake time after sleep onset (minutes)	94.3 ± 7.6
MSLT mean sleep latency (minutes)	10.2 ± 0.9

[a] All values represent mean ± SEM.

Association of PLM arousal index with gender and age

There was a significant positive correlation (r = 0.35, $p < 0.05$) between PLM arousal index and age (Fig. 1). Although the clinical impression has often been that PLM disorder is rare in young adults, 28.3% of these patients were under 30 years old. There was no significant association between PLM arousal index and gender.

Association of PLM arousal index with objective or subjective sleepiness

There was no significant correlation between the PLM arousal index and the mean sleep latency on the

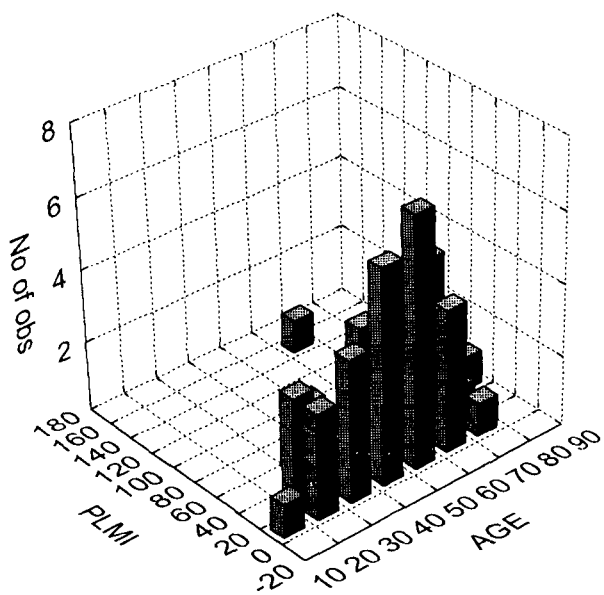

FIG. 1. Correlation of PLM arousal index (PLMI) and age in 67 patients with a PLMI of at least 5 per hour (r = 0.35, $p < 0.05$).

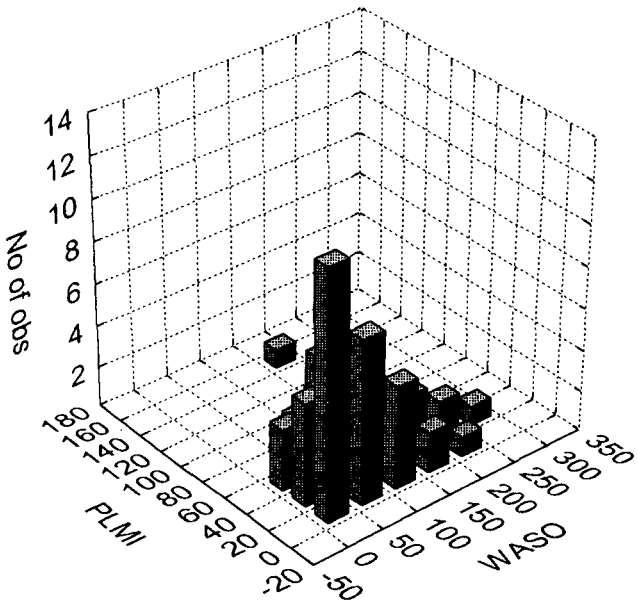

FIG. 2. Correlation of PLM arousal index (PLMI) and wake time after initial sleep onset in 67 patients with a PLMI of at least 5 per hour ($r = 0.31693$, $p < 0.05$).

MSLT, a subjective measure of sleepiness on a scale of 1 to 5 (see Table 1), sleep efficiency, number of awakenings lasting more than 3 minutes or the apnea/hypopnea index. An ANOVA found no significant association of the PLM arousal index to a chief complaint of either insomnia or sleepiness. There was, however, a significant positive association between the PLM arousal index and the amount of wake time after sleep onset ($r = 0.31693$; see Fig. 2).

Association of nocturnal sleep disruption with daytime sleepiness

There was no significant correlation between the number of awakenings (either the total number or those lasting longer than 3 minutes) or wake time after sleep onset and either the MSLT sleep latencies or subjective sleepiness. The nocturnal sleep latency was negatively associated with the MSLT sleep latency ($r = -0.01$, $p < 0.05$).

Association of PLM arousal index and a sense of awakening refreshed in the morning

Among the entire group, nine reported that they generally awakened refreshed in the morning, and 58 reported that they did not. There was no significant difference in the PLM arousal indices (28.6 ± 6.2 and 31.8 ± 3.6, respectively) between these two groups.

PLMs in patients with OSA and narcolepsy

In addition to the analysis we just presented, we also examined PLMs in patients with a primary diagnosis of OSA ($n = 518$) and narcolepsy ($n = 21$). The OSA patients had a mean age of 48.4 ± 12.2 years, and 83.0% were males. Their mean apnea/hypopnea index was 53.5 ± 37.6 per hour, and the mean minimum arterial oxygen saturations in nonrapid eye movement (NREM) and REM sleep were 83.2 ± 7.3% and 76.2 ± 13.1%, respectively. The narcolepsy patients all had a history of excessive sleepiness, which is characteristic of narcolepsy, as well as histories of cataplexy. They had a mean sleep latency on the MSLT of 3.0 ± 0.6 minutes and a mean of 2.7 ± 0.2 REM onset sleep episodes on the MSLT.

The mean PLM indices in the OSA and narcolepsy patients were 2.3 ± 0.4 and 3.9 ± 1.7 per hour, respectively. Ten percent and 19.0% of these two groups, respectively, had PLM arousal indices of at least 5 per hour. For these patients, the PLM arousal indices were 17.0 ± 2.0 and 17.2 ± 4.1 per hour, respectively. Among the entire population of OSA patients, there was a significant positive correlation between the PLM arousal index and age ($r = 0.13$; $p < 0.05$); among OSA patients with a PLM arousal index of at least 5 per hour, there was no significant relationship between the two. Among the OSA, but not the narcoleptic, patients, those with PLM indices of at least 5 were less sleepy than those with lower indices, as assessed by the MSLT, with values of 7.8 ± 0.6 and 6.4 ± 0.2 minutes, respectively [$F(1,470) = 3.949598$, $p < 0.05$]. Similarly, among the OSA patients there was a trend ($p < 0.06$) for those with PLM indices of at least 5 per hour to report less subjective sleepiness (2.2 ± 0.3 vs. 2.7 ± 0.1 on a scale of 1 to 5, as used in Table 1). In the entire OSA group, there was a statistically significant but quantitatively small positive correlation between the PLM arousal index and the mean sleep latency on the MSLT ($r = 0.10$, $p < 0.05$). There was no significant association of the PLM arousal index and the apnea/hypopnea index. On the other hand, there were significant positive correlations between PLM arousal index and the mean minimum arterial oxygen saturations in NREM ($r = 0.15$, $p < 0.05$), mean minimum saturation in REM ($r = 0.18$, $p < 0.05$), absolute minimum saturation in NREM ($r = 0.17$, $p < 0.05$) and absolute minimum saturation in REM ($r = 0.18$, $p < 0.05$) sleep.

DISCUSSION

Several aspects of the demographics of our sample are of interest. Approximately one-quarter of the patients were under age 30, a finding in contrast to some

clinical reports (e.g. 7) and a frequent clinical impression (14). As in a study of 100 patients evaluated at a sleep center (8), there was no significant difference in the sex ratio between the PLM patients and other patients, and the PLM patients were slightly older (50.5 ± 2.0 years vs. 45.6 ± 0.4 years). Also, as in a study of community-dwelling elderly subjects (9), there was a positive association of frequency of PLMs with age, but unlike that study we found no association with gender. The difference in whether there was an association in gender may result from the different age groups, types of population (patients vs. nonpatients) and methods of scoring PLMs, which are discussed later.

The study of PLMs in community-dwelling elderly subjects also found minimal association of PLMs with complaints about sleep and no association with reported sleep time or sleep latency (9). Others have suggested that patients with insomnia are no more likely to have PLMs than matched controls (7). Our data do not directly address this issue, as all the subjects presented to the sleep center for an evaluation of sleep difficulty. On the other hand, the finding that there was no association of the PLM arousal index with a presenting complaint of insomnia compared to sleepiness suggests that the relation of PLMs to a subjective complaint of sleep disturbance is neither obvious nor simple. In the PLM disorder patients we also found no clear association between PLM arousal index and various measures of daytime sleepiness or nocturnal sleep disturbance, with the exception of wake time after sleep onset. The latter may be at least partially an artifact, insofar as our criteria for scoring a PLM required that it be associated with some evidence of EEG arousal.

A previous report found that PLM disorder patients who complained of insomnia had more PLMs than those who complained of daytime sleepiness (10). We did not find a specific relationship between chief complaint and PLM arousal index. The reason for the difference between these results is not clear, aside from the much larger sample size in the present study (67 vs. 11), which may have led to a regression toward the mean.

One striking finding was the relatively high rate (29.8%) of a past treatment for depression among the PLM disorder patients. As a comparison, we determined the frequency of such a history in all other patients in the database, excluding those whose diagnosis implied psychiatric disorder (sleep disturbance associated with major depression, sleep disturbance associated with psychosis, insomnia secondary to generalized anxiety disorder). It was found that the rate of past treatment for depression in these remaining patients was 18.8% (Chi-square = 5.04, df = 1, $p < 0.02$). The meaning of this higher rate of past treatment for depression among PLM disorder patients is not clear; hypotheses which might be explored in future studies include the possibilities that these patients, who often complain of poor sleep and other symptomatology, might have been mistakenly considered to be depressed or that the disturbed sleep in these patients is in some, more fundamental, way associated with the genesis or expression of depressive symptomatology.

Our analysis of PLMs in OSA patients also revealed several interesting results. In the OSA patients, we found no correlation between the PLM arousal index and the apnea/hypopnea index. A weak relationship between the two (r_s = 0.05) was found in a study of community-dwelling elderly (9). Besides the differences in the populations studied, another cause of this discrepancy may be differences in scoring methods: we did not count PLMs associated with apneas whereas the other study did.

Among OSA patients, the finding that those with greater PLM arousal indices were *less* sleepy on the MSLT and had somewhat less severe arterial oxygen desaturations was somewhat surprising. It should be noted, however, that this association, although statistically significant, is quantitatively very small. Indeed, the coefficient of determination (r^2) of the correlation between the PLM arousal index and MSLT sleep latency indicated that the proportion of common variance of the two variables is very small, only 1.0%. This observation and the lack of an association of PLMs and the apnea/hypopnea index are significant in that they are not consistent with models which suggest that the PLMs are a nonspecific response to disturbed sleep. The possibility has been raised by some groups (e.g. 11) that the high incidence of PLMs in obstructive sleep apnea may be less associated with the illness per se than with age; our finding of a positive correlation of PLM arousal index and age in the entire group of OSA patients would be consistent with this notion.

Stepanski et al. (12), in a study which divided arousals into four categories, found that among OSA and PLM disorder patients, the total number of arousals was positively correlated with propensity to fall asleep on the MSLT, and this was particularly true for the lower level arousals (increases of EEG frequency accompanied by an increase in electromyogram amplitude and brief alpha bursts). We did not find significant correlations between the number of arousals (either those lasting longer than 3 minutes or all arousals) with either the MSLT mean sleep latency or a measure of subjective sleepiness. One possible difference between the studies is a larger "*n*" in the present work, which may have resulted in a regression toward the mean. Another difference lies in the much more so-

phisticated categorization of types of arousals in the Stepanski study, and it remains possible that if we had used such a system the results might have been more similar. Like them, however, we did find a negative association between nocturnal sleep latency and the MSLT mean sleep latency.

The usual description of PLMs indicates that EEG signs of arousals or awakenings may accompany the leg movement, and this approach is codified in the International Classification of Sleep Disorders (13). Some investigators also include EEG signs of arousal which immediately precede the leg movement (2). In this study we used a very specific definition of PLMs, i.e. they were counted only if they were accompanied by EEG arousals. Thus, we refer to our measure of the rate of PLMs as a "PLM arousal index" (13). We also specified that EEG arousals were to be counted only when they occurred simultaneously with or within 1 second following a leg movement; those which preceded a leg movement were not included. In addition, only those PLMs which were not associated with apneas were counted. We chose these criteria for several reasons. First, insofar as a number of studies have found minimal association of PLMs with clinical symptomatology (e.g. 7,9), it seemed to us that any positive associations with symptomatology would be more likely in patients whose PLMs were associated with arousals. Second, we did not include leg movements which were preceded by EEG arousals in order to avoid the possibility that the PLMs might be interpreted as resulting from the arousals. Third, we excluded leg movements associated with apneas in order to eliminate the possibility that any of the PLMs might be nonspecific movements caused by the apneas. Even with these strict criteria, there was no clear association between the PLM arousal index and measures of sleepiness or subjective sleep complaint in a patient population. Similarly, we found no association of the PLM arousal index with a sense of awakening unrefreshed in the morning. In the past we examined another patient group with a high rate of PLMs, patients with chronic renal failure and end stage renal disease (15). In that group there was no statistically significant difference in the number of PLMs in those who complained of poor sleep and daytime fatigue compared to those who did not. Taken together these data suggest to us that in the population studied here there is little or no demonstrable relationship between PLMs as defined here and subjective reports of sleep disturbance or sleepiness.

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