

Time course of arousal response during periodic leg movements in patients with periodic leg movements and restless legs syndrome

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Accepted 5 March 2003

Abstract

Objective: The temporal evolution of periodic leg movements (PLM) and the relationship of their arousing effect on sleep episode has not been extensively investigated. We studied the nocturnal evolution of PLM associated or not with microarousal (MA) and associated with slow wave activity (PLM with slow wave activity) in 23 patients with PLM and/or restless legs syndrome (RLS).

Methods: All subjects had PLM associated with MA or with slow wave activity as well as without MA and all slept for 4 sleep cycles. Spectral electroencephalographic (EEG) analysis was done for the 4 sleep cycles to assess the nocturnal variation in slow wave activity (SWA).

Results: Sixty percent of PLM were associated with MA, 4% were associated with slow wave activity whereas 36% showed no EEG changes. There was a clear prevalence of PLM with MA in stages 1 and 2 while PLM without MA were prevalent in slow wave sleep. The night-time PLM index progressively declined from the first to the last sleep cycle ($P < 0.005$), without differences between PLM types, or between PLM and RLS patients. The decline of PLM duplicated the temporal trend in SWA over consecutive sleep cycles.

Conclusions: PLM showed a typical pattern of progressive decline throughout the night following the exponential decline in SWA. These over-time variations occurred independently of changes in the rate of PLM associated or not with MA or associated with slow wave activity, suggesting that variations in arousal threshold and sleep propensity did not affect the PLM arousing effect. The PLM-related arousal response might be affected by interaction of circadian and sleep stage influences with the addition of sleep oscillatory processes.

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Keywords: Periodic leg movements; Arousal threshold; Sleep homeostasis

1. Introduction

Periodic leg movements (PLM) is a laboratory finding present in 86% of patients with restless legs syndrome (RLS) or an associate finding in other sleep disorders such as narcolepsy and obstructive sleep apnea syndrome (Montplaisir et al., 1994). They consist of a rhythmic extension of the big toe and dorsiflexion of the foot, lasting 0.5–5 s and occurring at a frequency of approximately one every 20–40 s (Nicolas et al., 1999). An electrophysiological finding frequently associated with PLM is the presence of a microarousal (MA) detectable either simultaneously or before and after the onset of the motor phenomena (Karadeniz et al., 2000), and considered as a

factor contributing to unrestorative sleep and sleepiness commonly reported by patients with PLM or RLS syndrome.

Although several studies have described the nocturnal variation in PLM occurrence (Culpepper et al., 1992; Hening et al., 1999; Trenkwalder et al., 1999), no model has been put forward to explain why only some PLM showed typical MA. To date only a few studies have specifically investigated the factors implicated in the appearance of MA during PLM. In the first of these (Coleman et al., 1982), the authors found that while the amount of PLM is stable across 3 consecutive nights, the index of PLM associated with MA or awakening reveals a tendency towards night-to-night variability, the index of PLM associated with MA ranging from 22 to 13. Sleep stage and duration of the movement are assumed to be the most likely possibilities evoking arousal. Sixty-nine (Sforza et al., 1999a) to 89% (Pollmacher and Schulz, 1993) of PLM with MA are detected during stages 1

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and 2 of non-rapid eye movement (NREM) sleep, with the lower percentage of PLM with MA in slow wave sleep. Longer PLM duration was also seen as a primary factor inducing arousals, 79% of PLM lasting more than 3 s associated with MA (Pollmacher and Schulz, 1993). Thus, there is the possibility that changes in arousal threshold related to sleep stage and to intensity of the stimulus may be potentially mediating factors contributing to the appearance of MA during PLM. However, these studies have assumed that sleep stage effects are independent of sleep periods, and no data are available on how time of the night may interact to affect the arousal response to PLM. Moreover, no data are available on the density of PLM associated with slow wave activity, frequently present in patients with PLM and/or RLS (El-Ad and Chervin, 2000; Sforza et al., 2002).

Considering the typical circadian variation of arousal threshold and the homeostatic processes taking place during sleep, it is plausible that arousal response during PLM is subjected to significant modulation not only across sleep stage but also sleep cycle. If the occurrence of the PLM-related arousal is considered as a variation in arousal threshold (Broughton, 1975), the PLM with MA may be greater during stage 1 and during the latter part of the night when the arousal threshold progressively declines. Conversely, since sleep propensity is greater during the first part of the night, we can predict that PLM without MA would be greater during the first hours of the night when the sleep homeostatic process is higher (Borbely, 1982).

The first aim of our study was to investigate the nocturnal evolution of PLM and PLM-arousal response in order to characterize specific patterns of expression that may help to define the factors influencing the PLM occurrence and the associated arousal response. This was investigated by considering the difference in density of total PLM, PLM with and without MA, and PLM with slow wave activity between sleep stages and sleep cycles. Homeostatic sleep influences were studied by spectral analysis of slow-wave activity (SWA), a quantitative measure of slow-wave dynamics and a physiological marker of homeostatic regulation of sleep. In doing so, the present study will add more extensive understanding of the possible homeostatic and circadian influences on the nocturnal variation of PLM and the associated arousal response.

2. Methods

2.1. Patient population

Twenty-three patients (12 men and 11 women, mean age: 55.0 ± 2.4 years, range: 31–77), diagnosed with RLS ($n = 11$) or primary PLM syndrome ($n = 12$), were included in the study.

All patients fulfilled the clinical criteria for the diagnosis of RLS (Walters, 1995) or PLM (Coleman, 1982) syndrome according to standard criteria. Exclusion criteria were:

(1) presence of sleep disturbances such as sleep apnea and narcolepsy; (2) presence of central nervous system or psychiatric disorders; (3) intake of any drug such as a stimulant, sedative, hypnotic, neuroleptic, or antidepressant known to affect electroencephalographic (EEG) power, and (4) presence of at least 4 sleep cycles during the considered nocturnal sleep. Patients previously treated for PLM and/or RLS stopped their drug 3 weeks prior to polysomnography. Patients were informed that some of the collected data would be used for research purposes and they gave written informed consent.

2.2. Nocturnal sleep studies

All patients underwent a night of polysomnographic recording with time in bed scheduled from 22:00 hours to 07:00 hours, which represented their average daily sleep period. Polysomnography was performed using 3 EEG leads (C3–A2, C4–A1, O2–A1), right and left electro-oculogram, chin electromyogram and electrocardiogram (ECG). In order to assess apneas and hypopneas, nasal and oral airflow or nasal pressure were recorded with thermistors or a pressure transducer (Protech2, Minneapolis, MN), and thoracic and abdominal respiratory movements with strain gauges. Oxygen saturation (SaO_2) was measured continuously with a finger oxymeter. None of the patients showed an index of respiratory events (AHI) greater than 10 per hour of sleep. Tibialis electromyographic activity (EMG) was monitored using surface electrodes placed on the lower third of the right and left legs. EMG signal was recorded at a time constant of 0.3 s and a high band-pass filter setting of 90 Hz. A 50 μV sinusoidal calibration signal of approximately 1 min duration was obtained in all subjects at the start of monitoring. All patients showed a PLM index greater than 10 per hour of sleep.

Sleep was scored according to standard criteria using 20 s epochs (Rechtschaffen and Kales, 1968) and the following sleep parameters were defined: total sleep time (TTS), sleep efficiency (SE: total recording time/total sleep time $\times 100$), percentage of each sleep stage, wake after sleep onset (WASO) and sleep latency. MA was defined according to ASDA criteria (ASDA, 1992) as a return to alpha or fast frequency, well differentiated from the background EEG activity. The duration was, however, extended to include MA lasting ≥ 1.5 s and < 3 s (Martin et al., 1997). MA detection criteria for rapid-eye-movement (REM) sleep included an increase in submental EMG amplitude, in addition to a shift in EEG activity.

2.3. Arousal and PLM analysis

PLM were scored using Coleman's criteria (Coleman, 1982), i.e. movements lasting 0.5–5 s with inter-movement intervals of 4–90 s and occurring in series of at least 4 consecutive movements, and associated with the stage in which they occurred. PLM were categorized into 3 types as

previously reported (Sforza et al., 2002). Briefly, a PLM was considered to be associated with MA (PLM with MA) if the latter occurred simultaneously or within 1 s after the onset of tibialis muscle EMG activity. PLM not associated with any change in the EEG activity in all EEG leads was classified as PLM without MA (PLM without MA). A PLM was defined as being associated with synchronized EEG activity (PLM with slow wave activity) when a burst of delta activity or K-complexes occurred simultaneously or within 1 s of the onset of the PLM. For each type of PLM, the number, the index (number of periodic leg movements per hour of sleep), and the mean duration were computed for total sleep, for each sleep stage and each sleep cycle. To quantify the PLM temporal occurrence over the course of the night, arousal and PLM analyses were performed for the first 4 sleep cycles, recorded in all subjects.

The analysis was done for the whole group of patients, as well as for patients with primary PLM and RLS, in order to assess whether differences in the temporal evolution of PLM overall, and for the 3 types were present in the two groups.

2.4. EEG spectral analysis

The EEG signals were digitized at a sampling rate of 128 Hz with a low pass filter at 30 Hz. Power spectra were calculated with a commercial software package (ERA Phitools[®], Grenoble, France) which computes fast Fourier transform (FFT) on 4 s epochs with a Hanning window tapering. Artifacts were excluded on a 4 s basis by visual inspection on the derivation C3–A2 and analysis was performed on artifact-free epochs. Epochs with artifacts were considered as missing data in order to preserve sleep continuity. After spectra analysis, 5 4 s epochs were averaged to keep a correspondence with the 20 s sleep scoring windows. The absolute power values ($\mu\text{V}^2/\text{Hz}$) of 5 EEG components were defined: SWA (0.5–4.5 Hz), theta (4.5–7.5 Hz), alpha (8–12.5 Hz), sigma (12.5–15.5) and beta (15.5–35 Hz) power. To quantify the dynamics of the NREM sleep (stages 2–4) over the course of the night, spectral analysis was performed for the first 4 NREM sleep cycles on the C3–A2 derivation.

2.5. Statistical analyses

Wilcoxon signed-rank tests were used to calculate the differences between PLM types for their duration and index. Significant *F*-values were adjusted with Bonferroni correction for multiple comparison and significance was assumed at a *P* value less than or equal to 0.01.

A two-way repeated measures analysis of variance (ANOVA) was used to assess the effects of sleep stages on the presence and duration of MA associated with PLM. For a quantitative description of the temporal variation of PLM index over the course of the night, the analyses were performed on percent of the mean PLM for the entire night to normalize data distribution. A repeated measure ANOVA

was computed with PLM type as the between factor and sleep cycle (1st, 2nd, 3rd, 4th), in order to assess the hypothesis of an increase of PLM with MA across sleep cycles. To assess the dynamic of SWA over the course of the night, further analysis was performed on the percent of mean SWA during NREM sleep for the entire night.

All statistical analyses were performed with the SPSS statistical software package (SPSS for Windows, 9.0, SPSS Inc, Chicago, IL). Results in the text and in the tables are presented as mean \pm SEM.

3. Results

3.1. Polygraphic data

Details of sleep parameters and PLM visual arousal scoring are given in Tables 1 and 2.

Wake after sleep onset, sleep efficiency and percentage of sleep spent in different sleep stages indicated disturbed sleep, with a high number of awakenings and sleep stage transition, as well as low sleep efficiency. Duration of the first 4 cycles is also reported, and the comparison between sleep cycles showed a significant difference in length ($P = 0.005$), the last cycle being shorter than the others. Compared to PLM patients, RLS patients tended to have lower sleep efficiency (85.8 ± 1.9 vs $80.5 \pm 2.6\%$), increased wake after sleep onset (89.9 ± 11.5 vs 108.6 ± 15.1 min), and longer sleep latency (33.9 ± 9.5 vs 45.0 ± 8.9 min), but the differences did not reach statistical significance.

Seven thousand seven hundred and eighty-four PLM were scored with a mean duration of 2.7 ± 0.13 s and a

Table 1
Sleep and polygraphic parameters in the study group (mean \pm SEM)

	Mean	SEM
Total sleep time (min)	443.0	± 9.4
Sleep latency (min)	34.4	± 5.5
Sleep efficiency (%)	83.2	± 1.7
Wake after sleep onset (min)	98.9	± 9.4
Awakenings (n ^o)	94.9	± 10.1
Sleep stage transition (n ^o)	334.9	± 18.1
Stage 1 (%)	16.6	± 1.0
Stage 2 (%)	54.2	± 1.4
Stages 3–4 (%)	11.2	± 1.7
Stage REM (%)	19.4	± 1.0
1st cycle duration (min)	125.7	± 11.3
2nd cycle duration (min)	146.5	± 11.7
3rd cycle duration (min)	106.2	± 6.2
4th cycle duration (min)	88.0	± 8.1

PLM index, periodic leg movements index (number of periodic leg movements/hour of sleep); PLM with MA, PLM associated with microarousal; PLM with slow wave activity, PLM associated with a burst of delta waves or K-complexes; PLM without MA, PLM not associated with microarousal.

Table 2
Polygraphic characteristics of periodic leg movements during total sleep

	Mean	SEM	Range
Total PLM index (n/h)	47.0	5.2	16–120
Total PLM duration (s)	2.67	0.13	1.7–4.4
PLM with MA index (n/h)	30.1	3.8	12–81
PLM with MA duration (s)	2.8	0.14	2–4.6
PLM with slow wave activity index (n/h)	2.2	0.6	0.2–11
PLM with slow wave activity duration (s)	2.7	0.13	1.6–3.9
PLM without MA index (n/h)	14.7	2.2	2.1–41.4
PLM without MA duration (s)	2.5	0.13	1.7–3.9

PLM index, periodic leg movements index (number of periodic leg movements/hour of sleep); PLM with MA, PLM associated with microarousal; PLM without MA, PLM not associated with microarousal.

mean interval of 31.5 ± 1.3 s. The total number of PLM was highly variable among subjects with a mean average PLM number of 338.4 ± 36.1 , an average PLM index of 47.0 and an SEM of 5.2 (Table 2). Overall, 60% of movements were associated with MA, 4% with slow wave activity whereas 36% were characterized by no change in EEG activity. In terms of movement duration, there were no significant differences between types, although PLM with MA were longer than PLM without MA, or with slow wave activity.

Comparison between PLM and RLS patients showed significant differences between groups with higher values in RLS patients both for total PLM index during sleep (RLS patients: 60.0 ± 8.3 , PLM patients: 35.1 ± 4.1) ($P = 0.007$) and for PLM with MA index (RLS patients: 38.0 ± 6.1 , PLM patients: 22.9 ± 3.7) ($P = 0.01$). No significant differences between groups were seen for PLM with slow wave activity (RLS patients: 2.2 ± 0.9 , PLM patients: 2.0 ± 0.9) and PLM without MA (RLS patients: 19.7 ± 3.4 , PLM patients: 10.2 ± 2.1). No differences in PLM duration and interval for the 3 types of PLM were seen between the two groups.

3.2. Effect of stage of sleep

Since by definition, PLM with slow wave activity occurred in stage 2 and slow wave sleep, the effect of sleep stage was limited to PLM with and without MA. The distribution of total PLM and of PLM associated or not with MA varied across the different sleep stages (Fig. 1). Overall, PLM mostly occurred in stages 1 and 2 of NREM sleep, its index progressively declining in slow wave sleep and REM sleep. Comparison of PLM with and without MA (Fig. 1, Table 3) revealed that more PLM were associated with MA during stages 1 and 2 of NREM sleep and fewer during slow wave sleep and REM sleep. In slow wave sleep, PLM without MA were prevalent. The stage \times PLM type ANOVA showed a significant difference for stage ($F(3, 13) = 7.42$, $P < 0.001$) and a significant interaction ($F(3, 13) = 29.4$, $P < 0.0001$).

PLM with MA and without MA tended to be longer in stages 3–4 of NREM sleep than in light NREM sleep and REM sleep (Table 3), but the effect was small and not significant. There were no significant differences in PLM duration during other sleep stages for either PLM types.

3.3. Effect of cycle of sleep

The results of the nocturnal variation in PLM index for the total PLM and for the 3 PLM types during the first 4 sleep cycles are reported in Table 4 and the data are illustrated in Fig. 2. There was a trend for PLM activity to be higher at the beginning of the night, followed by a progressive decline over consecutive sleep cycles. As illustrated in Fig. 2, the PLM index peaked sharply during the first sleep cycle and then progressively declined from the initial value of 64.1 ± 10.0 to the final one at the fourth sleep cycle of 20.9 ± 5.8 ($F(3.13) = 11.2$, $P < 0.0001$). A similar declining profile over consecutive sleep cycles was present for all types of PLM, independently of the occurrence or not of MA. The PLM with MA index markedly decreased from a value of 42.6 ± 7.5 at the first sleep cycle to a final value of 13.5 ± 4.0 in the fourth sleep cycle. The PLM without MA fell from the initial value of 18.8 ± 3.9 to 7.2 ± 2.5 in the last sleep cycle. A similar trend was seen for PLM with slow wave activity markedly decreasing from a value of 3.0 ± 0.7 at the first sleep cycle to a final value of 0.3 ± 0.1 in the fourth sleep cycle. The two-way ANOVA with the factors time and PLM type revealed a significant main effect of time of the night ($F(3.13) = 11.2$, $P < 0.0001$) but not interaction ($F(3.13) = 1.61$, $P = \text{ns}$). The decrease in the PLM index during the night was not associated with significant changes in duration for the overall PLM, as well as for PLM with and without MA and slow wave activity (Table 4). As illustrated in Fig. 3, the PLM density for total PLM and for the 3 types of PLM progressively declined throughout the night with no differences between PLM and RLS patients.

The same ANOVA design was also performed on the PLM index of stage 2, in order to check whether the effect of the PLM index decrease across NREM sleep cycles was a consequence of higher values of stage 2 and lower slow wave sleep at the end of the night. The results of this ANOVA completely paralleled those of the ANOVA regarding the 4 sleep cycles overall. A significant main effect was found for the cycle factor ($F(3.13) = 10.8$, $P < 0.005$) without significant interaction cycle \times type of PLM.

To study the profile of dynamic change in SWA throughout the night, SWA was expressed as a percentage of the mean power during NREM sleep for the 4 sleep cycles. Data in Fig. 4 show the percentage of mean SWA power (upper panel) and PLM index (lower panel) across the first 4 sleep cycles. Close inspection of the figure reveals an initial and strong rise in SWA in the first sleep cycle and a progressive decline in consecutive cycles ($F = 17.5$, $P < 0.0001$). This

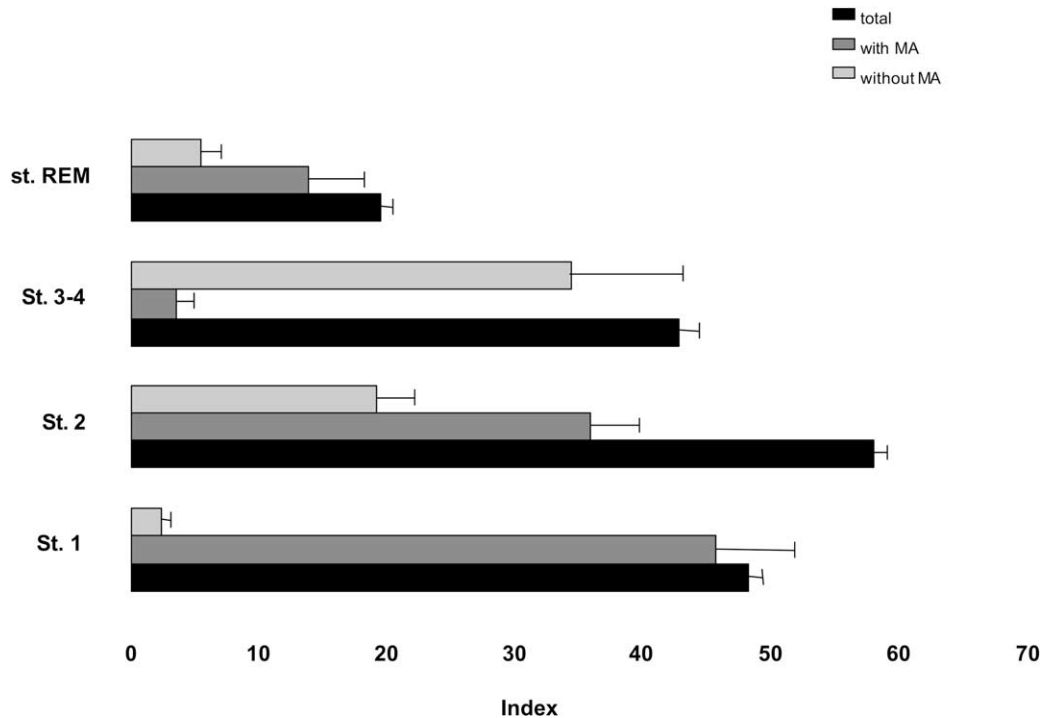


Fig. 1. Histograms showing the density of overall PLM and PLM associated or not with visually detected MA during each sleep stage. The greatest number of overall PLM and PLM with MA was scored during stages 1 and 2 of NREM sleep. During slow wave sleep and REM sleep, PLM occurred mostly without MA.

time-dependent trend in SWA was duplicated for the percentage changes in the PLM index, both in the total number and in the 3 types of PLM. The maximal rise in the number of PLM was present during the first sleep cycle when the SWA was greater. Thereafter, a progressive decline was present, for the PLM overall as well as for the PLM associated or not with MA or associated with slow wave activity, reaching the minimum at the fourth sleep cycle when the SWA was lower.

4. Discussion

To clarify the contribution of arousal threshold changes to the appearance of PLM with MA, we examined the nocturnal evolution of PLM associated or not with MA in a large group of patients with RLS and PLM syndrome. Our rationale was that if recurrence of MA requires variations in

arousal threshold, we should see PLM with MA mostly in the latter part of the night and, on the other hand, a greater number of PLM without MA and with slow wave activity in the first part of the night, when the individual sleep propensity is greater. The results of this study firstly indicate that the PLM density clearly decreased during the night with a profile paralleling the nocturnal exponential decay of SWA. Secondly, we demonstrate that the profile of declining PLM rate was similar for PLM associated or not with MA and with slow wave activity, suggesting that the occurrence of the PLM-related arousal response is independent of night-time changes in arousal threshold and in sleep propensity.

An important drawback in previous studies on arousal response during PLM is that the temporal variation throughout the night was not reported, giving little attention to the analysis of sleep cycle effect on the occurrence of an arousal response during PLM. One of the aims of the present study

Table 3

Polygraphic characteristics (mean \pm SEM) of periodic leg movements associated or not with microarousal during different sleep stages

	Stage 1	Stage 2	Stages 3–4	Stage REM
PLM with MA index (n/h)	45.6 (6.2)	35.8 (3.9)	3.5 (1.5)	13.9 (4.3)
PLM with MA duration (s)	2.7 (0.15)	2.8 (0.15)	3.3 (0.24)	2.4 (0.22)
PLM without MA index (n/h)	2.4 (0.7)	19.2 (2.9)	34.3 (8.7)	5.5 (1.6)
PLM without MA duration (s)	2.5 (0.24)	2.5 (0.12)	2.6 (0.22)	1.9 (0.21)

PLM index, periodic leg movements index (number of periodic leg movements/hour of sleep); PLM with MA, PLM associated with microarousal; PLM with slow wave activity, PLM associated with a burst of delta waves or K-complexes; PLM without MA, PLM not associated with microarousal.

Table 4
Polygraphic characteristics of periodic leg movements during the 4 sleep cycles

	Cycle 1	Cycle 2	Cycle 3	Cycle 4
PLM total index (n/h)	64.1 (10.0)	46.6 (7.3)	26.8 (6.8)	20.9 (5.8)
PLM with MA index (n/h)	42.6 (7.5)	29.7 (4.6)	15.8 (3.8)	13.5 (4.0)
PLM with MA duration (s)	2.8 (0.17)	2.7 (0.17)	2.6 (0.17)	3.0 (0.20)
PLM with slow wave activity index (n/h)	3.0 (0.7)	2.7 (1.2)	1.4 (0.8)	0.3 (0.1)
PLM with slow wave activity duration (s)	2.7 (0.19)	2.8 (0.20)	2.6 (0.18)	2.5 (0.20)
PLM without MA index (n/h)	18.8 (3.9)	14.2 (3.3)	9.7 (3.5)	7.2 (2.5)
PLM without MA duration (s)	2.4 (0.16)	2.6 (0.17)	2.3 (0.18)	2.1 (0.18)

was to investigate the effect of sleep episodes on the occurrence of PLM associated or not with MA. A first hypothesis was that if SWA represents a parameter of intensity of sleep process, a high arousal threshold would be expected when SWA is higher, progressively declining during the night and inducing a rise in PLM without MA and with slow wave activity in the first sleep cycle. In addition, since the arousal threshold progressively decreases across the night (Broughton, 1975; Lavie and Zomer, 1984; Sforza et al., 1999b), the number of PLM with MA would progressively increase during the night peaking just before the final awakening, in association with the lowering in arousal threshold. The most interesting finding of our study is that contrary to expectation, the overall occurrence of PLM and the arousal response associated with PLM show a trend in progressive decline throughout the night, indicating that nocturnal variation in arousal response to PLM is not strongly influenced by the depth of sleep and by the well-

known changes in arousal threshold. Close inspection of Fig. 4 reveals that the density of PLM overall, and of the 3 PLM types, peaked at the first sleep cycle and then progressively continued to fall throughout sleep episodes, reaching a plateau during the 3rd and 4th sleep cycles. This decreasing trend runs in a parallel direction as compared to the time course of SWA, the highest PLM index found when sleep is deeper and sleep propensity greater. Moreover, in contrast to the initial hypothesis, PLM with MA occur mostly in the first sleep cycle when the arousal threshold is higher, progressively declining over the night, following the decreasing trend in the occurrence of PLM overall. This time-of-night effect cannot be explained as a result of the increase in stage 2 and reduction of SWS in the last part of the night, since a separate analysis on stage 2 PLM index over the 4 consecutive sleep cycles confirmed the same pattern of variations during sleep episodes.

Whether or not PLM-related arousal response has an endogenous rhythm and which factors control its nocturnal trend is currently incompletely understood. This issue is controversial because variation in arousal occurrence can be influenced by many factors such as sleep stage, intensity and duration of the motor phenomenon, sleep instability and circadian changes in dopamine activity. Among them, the influence of sleep stage on arousal response to PLM has been well investigated. All of the previous investigations converged in indicating that consistent differences exist across NREM sleep stages and NREM and REM sleep (Nicolas et al., 1999), the higher threshold being found in slow wave and REM sleep and the lower in stages 1 and 2 (Williams et al., 1964; Rechtschaffen et al., 1966; Pollmacher and Schulz, 1993; Sforza et al., 1999a) and during unstable sleep (Parrino et al., 1996). Our data are broadly consistent with the above investigations, showing that the changes in arousal threshold during sleep have a reciprocal effect on the appearance of PLM with MA, which is attenuated in slow wave sleep compared to stage 1 and REM sleep (Pollmacher and Schulz, 1993; Sforza et al., 1999a). In contrast to previous data (Pollmacher and Schulz, 1993), an interesting observation is that there were no significant differences in duration between PLM with and without MA in our patients. We attributed the observed differences to the primary role of arousal responsiveness,

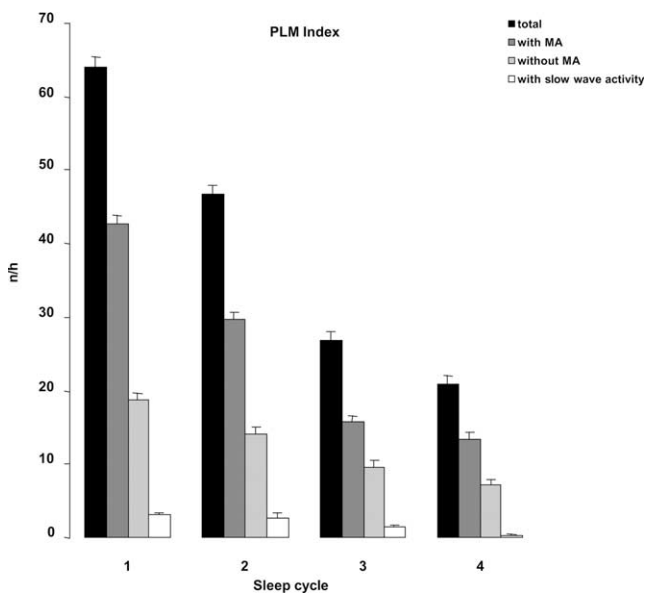


Fig. 2. Histograms of the PLM index for overall PLM, and PLM with and without MA and with slow wave activity during the first 4 sleep cycles. There was a trend for PLM activity to be higher at the beginning of the night, followed by a progressive decline over the consecutive sleep cycles affecting total PLM, PLM with and without MA and PLM with slow wave activity.

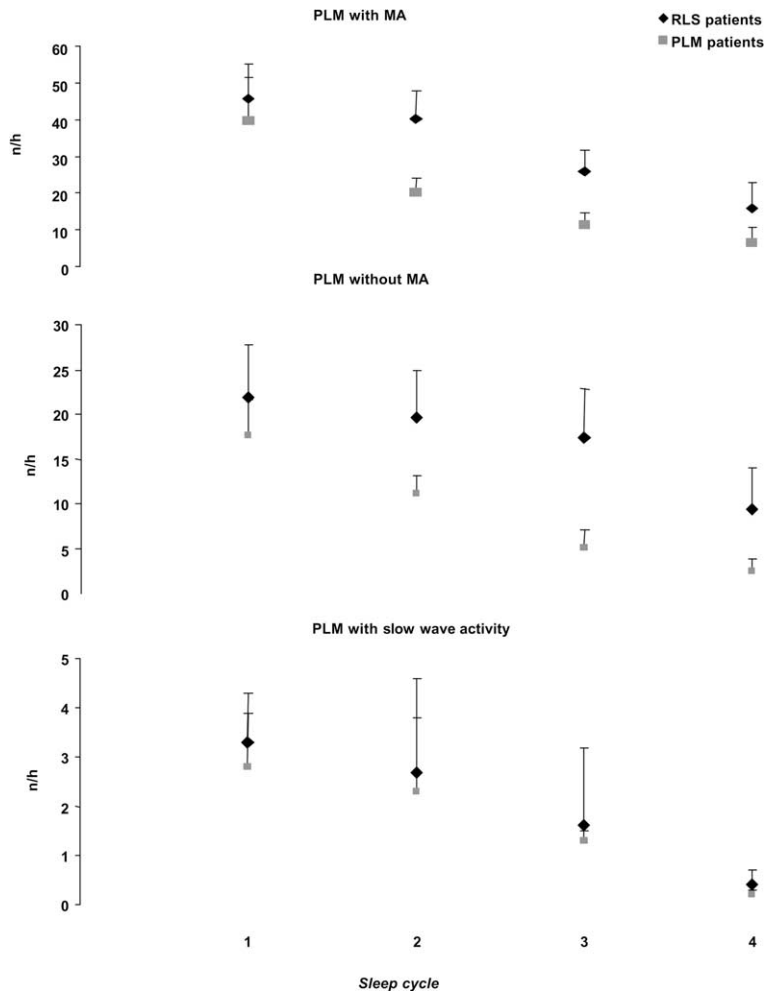


Fig. 3. Average (\pm SEM) index for PLM with and without MA and for PLM with slow wave activity in the first 4 sleep cycles in patients with RLS and PLM syndrome. The over-time evolution of PLM was not different between the two patient groups.

that is, variation in arousal threshold more than intensity of the stimulus influences the appearance of a MA during PLM. In favor of this hypothesis is the finding that PLM associated or not with MA were longer in SWS, indicating that during stable sleep, the upward resetting of the arousal threshold is accompanied by increased intensity of stimuli necessary to provoke arousal.

Although our data do not allow us to draw firm conclusions on the nocturnal PLM trend, two hypotheses might be proposed. The ‘sleep instability’ hypothesis (Terzano et al., 1985) explains the occurrence of PLM as well as other pathological sleep-related phenomena as the expression of a self-sustaining sleep oscillation process, allowing according to the time of the night, both sleep maintenance and sleep defense. The instability hypothesis has gained wider acceptance mainly because of its theoretical basis using analysis of the cyclic alternating pattern (CAP) consisting of phases of higher arousal, i.e. phases A, and phases with lower arousal, i.e. phases B, the first mostly associated with occurrence of PLM (Parrino et al., 1996) and epileptic spikes (Parrino

et al., 2000; Halasz et al., 2002). Despite the fact that in our patients PLM with slow wave activity and without MA occurred mainly in the first sleep cycle, their trend seems to follow more the nocturnal trend of overall PLM than the effect of sleep propensity on the arousal response.

An attractive alternative hypothesis is that the pattern of occurrence of PLM and PLM-related arousal response may reflect circadian influences acting on the motor pathways, irrespective of homeostatic effects and circadian variation in arousal threshold. In favor of this hypothesis are previous studies in RLS patients (Montplaisir et al., 1995; Hening et al., 1999; Trenkwalder et al., 1999; De La Llave et al., 2001; Duffy et al., 2001) suggesting that sensory and motor symptoms in patients with RLS showed a typical circadian rhythm affecting both wakefulness and sleep. The sensory symptoms and motor restlessness of RLS patients increased from a nadir in the morning to a maximum at night, with a peak occurring in the falling phase of core temperature (Boecker et al., 1995; Trenkwalder et al., 1999). The described peak in dysesthesia and restlessness in the hours

following midnight may reflect the peak in PLM density in the first sleep cycle found in our patients. Moreover, sensory symptoms fell during the night with a nadir between 6 and 8 AM when the occurrence of PLM density in our group is lower. Even though speculative, in the absence of analysis of circadian components, the results reported herein suggest that both the density of PLM and the appearance of the arousal response show variations throughout the night that may follow the circadian rhythm influences on sensory and motor patterns (Hening et al., 1999; Trenkwalder et al., 1999) and on dopamine receptor activity (Wilkes et al., 1981; Davila et al., 1989). Since the nocturnal variation in PLM density did not differ between PLM and RLS patients, the hypothesis of a common mechanism underlying the appearance of motor components of these sleep disorders may be postulated.

For discussion of our data, certain limitations, which could influence our results, should be considered. First, a limitation of our study is the variability of our analysis inherent to visual scoring, variability that may lead to

methodological bias in the detection of arousal response during PLM. However, our intrascorer reproducibility based on 20 repeated scores was good, ranging from 0.75 to 0.85, suggesting that this methodological bias would play a small role. Second, the lack of a control group and the small number of patients examined limits the accuracy of our results when analysis of SWA is considered. However, the main thrusts of the study were not to quantify differences in temporal evolution of SWA but to identify whether density of PLM followed a homeostatic rather than a circadian rhythm.

In conclusion, the present study demonstrates that PLM density progressively declines throughout the night following the physiological decay in sleep propensity. This trend was similar for PLM associated or not with MA, and for PLM with slow wave activity suggesting that the arousal response to PLM follows an inherent nocturnal pattern that seems to be independent of variation in arousal threshold and in sleep homeostatic processes. This nocturnal trend in PLM-related arousal response may suggest the interference of 3 factors, sleep instability process, sleep stage effect and circadian influences, all acting on neural and biochemical mechanisms implicated in the PLM. Further studies need to be performed to elucidate whether sleep independent activating effect or circadian factors have a greater influence on the nocturnal trend of PLM and the associated arousal response.

References

- American Sleep Disorders Association, EEG arousal: scoring rules and examples. *Sleep* 1992;15:174–84.
- Boecker MR, Badia P, Shaffer JI. The relationship between core temperature and time-of-the night patterns in PLMS activity. *Sleep Res* 1995;23:235.
- Borbely AA. A two process model of sleep regulation. *Hum Neurobiol* 1982;1:195–204.
- Broughton RJ. Biorhythmic variations in consciousness and physiological function. *Can Psychol Rev* 1975;16:217–30.
- Coleman RM. Periodic leg movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C, editor. *Sleeping and waking disorders*. Menlo Park, CA: Addison-Wesley; 1982. p. 265–95.
- Coleman RM, Bliwise DL, Sajben N, Boomkamp A, De Bruyn LM, Dement WC. Daytime sleepiness in patients with periodic movements in sleep. *Sleep* 1982;5(suppl. 2):S191–S202.
- Culpepper W, Badia P, Shaffer JI. Time-of-night patterns in PLMS activity. *Sleep* 1992;15:306–11.
- Davila R, Zummarraga M, Andia I, Friedhoff AJ. Persistence of cyclicity of the plasma dopamine metabolite, homovanillic acid, in neuroleptic treated schizophrenic patients. *Life Sci* 1989;44:1117–21.
- De La Llave Y, Garcia-Borreguero D, Barrio S, Larrosa O, Granizo JJ, Allen R. Severity of disease and circadian patterns of periodic leg movement activity in restless legs syndrome: preliminary report. *Sleep* 2001;24(suppl):A101.
- Duffy JF, Winkelman JW, Dijk DJ, Czeisler CA. Circadian modulation of PLMS. *Sleep* 2001;24(suppl):A100.
- El-Ad B, Chervin RD. The case of a missing PLM. *Sleep* 2000;23:450–1.
- Halasz P, Terzano MG, Parrino L. Spike-wake discharge and the micro-

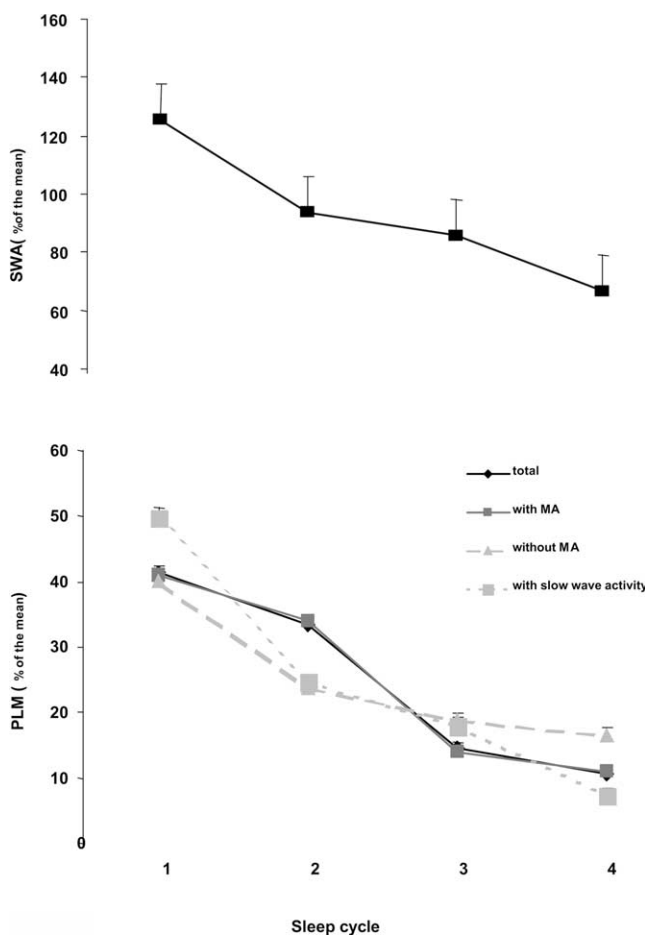


Fig. 4. Percentage of mean for SWA (upper panel) and for total PLM, PLM with MA, PLM without MA and PLM with slow wave activity (lower panel) for the entire night throughout 4 sleep cycles. Inspection of the figure reveals a similar trend in the evolution for PLM and SWS, with a progressive decline throughout the night, not different for the 3 PLM types.

- structure of sleep–wake continuum in idiopathic generalised epilepsy. *Neurophysiol Clin* 2002;32:38–53.
- Hening WA, Walters AS, Wagner M, Rosen R, Chen V, Kim S, Shah M, Thai O. Circadian rhythm of motor restlessness and sensory symptoms in the idiopathic restless legs syndrome. *Sleep* 1999;22:901–12.
- Karadeniz D, Ondze B, Besset A, Billiard M. EEG arousals and awakenings in relation with periodic leg movements during sleep. *J Sleep Res* 2000;9:273–7.
- Lavie P, Zomer J. Ultrashort sleep-waking schedule. II. Relationship between ultradian rhythms in sleep ability and the REM–NREM cycles and effects of the circadian phase. *Electroenceph clin Neurophysiol* 1984;57:35–42.
- Martin SE, Engleman HM, Kingshott RN, Douglas NJ. Microarousals in patients with sleep apnoea/hypopnoea syndrome. *J Sleep Res* 1997;6:276–80.
- Montplaisir J, Godbout R, Pelletier G, Warnes H. Restless legs syndrome and periodic limb movements during sleep. In: Kryger M, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. Philadelphia, PA: Saunders; 1994. p. 589–97.
- Montplaisir J, Boucher S, Gosselin A, Poirier G, Lavigne G. The restless legs syndrome: evening vs. morning restlessness. *Sleep Res* 1995;24:302.
- Nicolas A, Michaud M, Lavigne G, Montplaisir J. The influence of sex, age and sleep/wake state on characteristics of periodic leg movements in restless legs syndrome patients. *Clin Neurophysiol* 1999;110:1168–74.
- Parrino L, Boselli M, Buccino GP, Spaggiari MC, Di Giovanni G, Terzano MG. The cyclic alternating pattern plays a gate-control on periodic limb movements during non-rapid-eye movement sleep. *J Clin Neurophysiol* 1996;13:314–23.
- Parrino L, Smerieri A, Spaggiari MC, Terzano MG. Cyclic alternating pattern (CAP) and epilepsy: how a physiological rhythm modulates a pathological event. *Clin Neurophysiol* 2000;111:S39–S46.
- Pollmacher T, Schultz H. Periodic leg movements (PLM): their relationship to sleep stages. *Sleep* 1993;16:572–7.
- Rechtschaffen A, Kales A. *A manual of standardized terminology, technique and scoring system for sleep stages of human sleep*. Los Angeles, CA: Los Angeles Brain Information Service, Brain Information Institute, UCLA; 1968.
- Rechtschaffen A, Hauri P, Zeitlin M. Auditory awakening threshold in REM and NREM sleep stages. *Percept Mot Skills* 1966;22:927–42.
- Sforza E, Nicolas A, Lavigne G, Gosselin A, Petit D, Montplaisir J. EEG and cardiac activation during periodic leg movements in sleep. Support for a hierarchy of arousal responses. *Neurology* 1999a;52:786–91.
- Sforza E, Krieger J, Petiau C. Arousal threshold to respiratory stimuli in OSA patients: evidence for a sleep-dependent temporal rhythm. *Sleep* 1999b;22:69–75.
- Sforza E, Jouny C, Ibanez V. Time-dependent variation in cerebral and autonomic activity during periodic leg movements in sleep: implications for arousal mechanisms. *Clin Neurophysiol* 2002;111:1611–9.
- Terzano MG, Mancina D, Salati MR, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiological component of normal NREM sleep. *Sleep* 1985;8:137–45.
- Trenkwalder C, Hening WA, Walters AS, Campbell SS, Rahman K, Chokroverty S. Circadian rhythm of periodic limb movements and sensory symptoms of restless legs syndrome. *Mov Disord* 1999;14:102–10.
- Walters AS. Toward a better definition of the restless legs syndrome. The international restless legs syndrome study group. *Mov Disord* 1995;10:634–42.
- Williams HL, Hammack JT, Daly RL, Dement WC, Lubin A. Responses to auditory stimulation, sleep loss and the EEG stages of sleep. *Electroenceph clin Neurophysiol* 1964;16:269–79.
- Wilkes MM, Babaknia A, Hoff JD, Quigley ME, Kraus PF, Yen SS. Circadian rhythm in circulating concentration of dihydroxyphenylacetic acid in normal women. *J Clin Endocrinol Metab* 1981;52:608–11.