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Sleep Medicine 5 (2004) 407–412

SLEEP MEDICINE

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Udine Special Section

# Changes in cerebral and autonomic activity heralding periodic limb movements in sleep

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Received 1 December 2002; accepted 15 October 2003

**Abstract**

**Background and purpose**: Periodic limb movement disorder (PLMD) is frequently accompanied by awakenings or signs of EEG arousal. However, it is matter of debate whether EEG arousals trigger leg movements or both EEG arousal and leg movements are separate expressions of a common pathophysiological mechanism. Previous studies showed that cardiac and cerebral changes occur in association with periodic limb movements (PLMs), and that a combining increase in delta activity and in heart rate (HR) occurs before the onset of PLMs.

**Patients and methods**: This paper presents some preliminary data, obtained from a sample of 5 subjects with PLMD not associated to restless legs syndrome. To describe the temporal pattern of cardiac and EEG activities changes concomitant with PLMs in NREM sleep we used time frequency analysis technique.

**Results**: PLM onset is heralded by a significant activation of HR and delta activity power, beginning 4.25 and 3 s respectively before PLMs onset, with PLMs onset and arousal onset falling together.

**Discussion**: Delta and HR variations herald PLMs and activation of fast EEG frequencies. Such a stereotyped pattern is common in PLMs and in spontaneous or stimuli-induced arousals. Moreover a similar pattern seems to encompass the CAP phenomenon. The whole of these phenomena can be linked to the activity of a common brainstem system, which receives peripheral inputs, regulating the vascular, cardiac and respiratory activities and synchronizing them to cortical oscillations of EEG.


*Keywords:* Periodic limb movements; Arousal; Heart rate activity; EEG; Delta; NREM sleep; Cyclic alternating pattern; Common brainstem system

## 1. Introduction

Periodic limb movements disorder (PLMD), a frequent finding in polysomnograms, is characterized by stereotyped, repetitive, non-epileptic movements of the limbs, more frequently of the legs. Besides restless legs syndrome (RLS), PLMD co-occurs with a wide range of sleep related pathologies, especially in patients with difficulties in starting and maintaining sleep and in patients with excessive daytime sleepiness [1–3]. They also occur in a wide variety of sleep disorders including obstructive sleep apnea syndrome, narcolepsy and neurological pathologies associated with REM behavior disorder [1–7]. The pathogenesis of PLMD is unknown; dysfunction of several different areas of the nervous system, including brain, spinal chord and peripheral nerves, has been suggested [8–16]. PLMD is frequently accompanied by awakenings or signs of EEG arousal that are thought to disrupt sleep continuity, thus causing a feeling of non-restorative sleep and daytime sleepiness [3,17]. It is not clear whether EEG arousals trigger leg movements or whether EEG arousal and leg movements are separate expressions of a common pathophysiological mechanism. This problem has been recently addressed [18] using inspective EEG techniques. Findings of a significantly higher number of arousals prior to leg

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1389-9457/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.sleep.2004.01.008

movements suggest that arousals are not simply the consequence of PLMD but that, on the contrary, both EEG arousals and PLMD are manifestations of a common underlying arousal disorder. However, time relationships detectable by such inspective techniques are far from precise. Recent use of more sophisticated EEG spectral and automatic analysis techniques has found that cardiac and cerebral changes occur in association with periodic limb movements (PLMs), even when EEG signs of arousal cannot be detected, and that a combined increase in delta activity and HR occurs before the onset of PLMs [19]. However, EEG spectral analysis has the same theoretical limitations when applied to very short time windows, implying a low-resolution power. Other quantitative EEG analysis techniques, such as the wavelet transform, seem to be more useful when studying short, transient events [20]; moreover, these techniques allow time and frequency domain analysis. The aim of this paper is to present some preliminary data obtained with wavelet transform technique, together with a critical review of available literature, in order to elucidate time relationships between cerebral, autonomic and motor activities and to draw up a working hypothesis to link all these changes with arousal mechanisms.

## 2. Patients and methods

### 2.1. Study samples

Five patients (2 M and 3 F, mean age 56 ± 14 years, range: 41–72 years), diagnosed with PLMD, with insomnia and without any other sleep disorder, were studied. On the basis of a clinical interview and laboratory findings, conditions known to be associated with PLMD were excluded. No patient had been taking medication that might affect the central nervous system or the cardiovascular system, and none had been treated for cardiopathy, RLS or PLMD.

The mean Epworth sleepiness scale was 11 ± 3 (range: 8–16) and each patient had more than 10 PLMs per hour of sleep. All patients underwent two nights of polysomnographic (PSG) recording, the first an adaptation night used to rule out the concomitance of other sleep disorders and the second a proper PSG. Recording started at 23:00 and ended at 7:00. Informed consent was obtained from all patients.

### 2.2. Nocturnal sleep studies

Nocturnal sleep was monitored by means of a digital polygraph (GalNT, EBNeuro). Each PSG included electroencephalogram, electro-oculograms, submental and anterior tibial electromyograms, measurements of oro-nasal airflow, chest and abdominal excursions, oxyhemoglobin saturation (finger pulse oxymetry) and single-lead electrocardiogram from a standard (V5) precordial lead.

EEG was acquired from 3 electrodes (F4, C4, O2), positioned according to the 10–20 International Electrodes Placement System, in physical reference with successive reconstruction of bipolar derivations. The low-pass filter was set at 70 Hz, the time constant at 0.1, and the notch filter was switched on; sensitivity was 10 μV/mm. The EMG signal was recorded with a time constant set at 0.01 s and a low-pass filter setting of 70 Hz. A 50 μV sinusoidal calibration signal of approximately 1 min duration was obtained for all subjects at the start of monitoring. The quality of the EMG recording was ascertained by asking the patient to flex his knees and feet. All signals were sampled at a 512 Hz frequency by an analog-digital converter with 16 bit resolution. Each record was visually scored according to the standard criteria [21], and the hypnograms were stored as digital data with a link to the recording.

### 2.3. Including and excluding criteria for event selection

PLMs occurring during stages 2, 3 and 4 of NREM sleep were automatically detected [22], and onset and offset of the events were checked by one of the authors. PLMs were included if the movements lasted 0.5–5 s, with a between-movement interval of 20–90 s, and occurred in series of at least 4 consecutive movements [17] and were excluded if EEG channels revealed artifacts from 10 s before to 20 s after PLM onset.

Movement onset was detected when the amplitude of EMG activity increased more than 60% above the preceding background, as evaluated by an exponential weighted moving average, mainly influenced by the 10 s preceding the event. PLM offset was detected when EMG activity steadily lowered to a level corresponding to one half of the mean event amplitude. Every event was then stored and linked to the stage during which it occurred in NREM sleep. The overall number of included PLMs was 512.

### 2.4. Data analysis

Data from bipolar EEG channel C4–O2 were analyzed by means of the wavelet transform—a technique that enables the representation of a signal in the time frequency domain-from 10 s before to 20 s after a PLM, analyzing the time course of the signal in different frequency bands, with variable frequency and time resolution. The transformed data were then processed to evaluate the signal power, with a time resolution of 0.125 s, for 5 frequency bands: 0.5–4 (*delta*), 4–8 (*theta*), 8–12 (*alpha*), 12–16 (*sigma*), and 16–32 (*beta*).

Heart rate was evaluated by measuring the interval between consecutive *R*-waves of the QRS complexes in the electrocardiogram. The QRS complexes were automatically detected by searching for quasi-periodic sequences of waveforms made up by 2 or 3 close peaks clearly emerging from the background. The waveforms detected in this first step were then compared to a model of QRS complexes to

select valid *R*-waves by combining information concerning time distribution and correlation to the model. The model itself was progressively adapted to each recording by averaging the selected waveforms.

The tibial EMG activity was quantified by evaluating its power as the average of its square values. This mean value was computed for each time point by an exponential weighted moving average in which the greatest weight was relative to the current value, while past values contributed with fast decreasing weights (70% of the total share coming from the last 0.625 s).

Data from the wavelet analysis (5 EEG power bands), heart rate and tibial EMG activity were stored and averaged for the time interval associated to every event (30 s), with a time resolution of 0.125 s. The baseline values, mean and standard deviation, were computed for each parameter and event, with reference to a time interval from 10–5 s before PLM onset.

The series of values for each parameter with a 0.125 s resolution was then transformed into variations with respect to the baseline values set at 100.

### 2.5. Statistical analysis

The statistical analysis was exploratory and did not include any confirmatory test at this stage. In order to detect time periods with major variations, with respect to the baseline values, a confidence interval was defined for each event and parameter. This interval included values within three standard deviations from the baseline mean value, corresponding to a nominal significance of $P < 0.01$. Differences from baseline were considered significant when time periods in which a parameter exceeded this confidence interval were longer than 1 s. A baricentric point was computed for the time intervals with significant increased values of the averaged wavelet power, indicating the mean position of the segment involved in the parameter variation.

## 3. Results

Fig. 1 shows the profiles of averaged wavelet power for delta [0.5–4 Hz] (A), theta [4–8 Hz] (B), alpha [8–12 Hz] (C), sigma [12–16 Hz] (D), and beta [16–32 Hz] (E) band activities, the averaged HR variation (F), and the averaged tibial EMG activity (G) 10 s before and 20 s after the PLM onset expressed as variations from the baseline.

All profiles of averaged EEG frequency bands show a significant upward deflection corresponding to the PLM phenomenon. The profile of the delta band power shows that this rise begins to be significant 3 s before PLM onset. For the other bands, the rise begins to be significant ($P < 0.01$) within the last second before PLM onset (theta at −0.625 s, alpha at −1 s, sigma at −0.75 s, beta at −1 s).

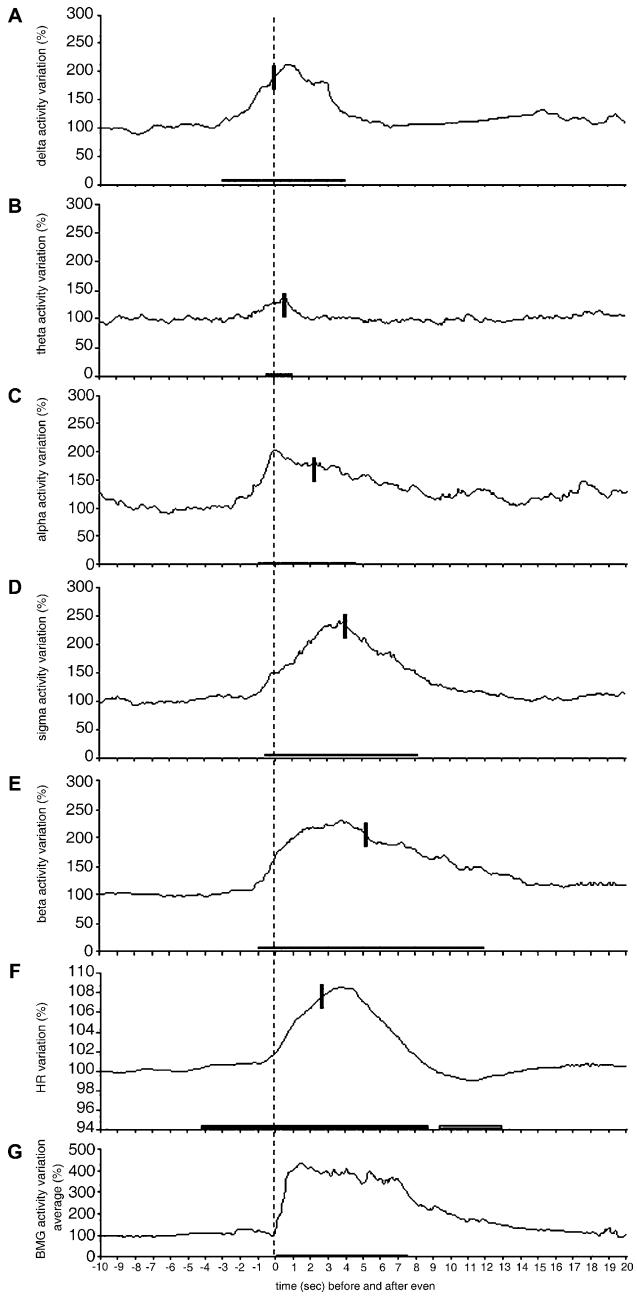


Fig. 1. Profiles of averaged wavelet power for delta [0.5–4 Hz] (A), theta [4–8 Hz] (B), alpha [8–12 Hz] (C), sigma [12–16 Hz] (D), and beta [16–32 Hz] (E) activities, the averaged HR variation (F) and averaged tibial EMG activity (G) for a time window of 30 s (from 10 s before to 20 s after the PLM onset). The series of values for each parameter has a 0.125 s time resolution and is expressed as variations with respect to the baselines, which were set at 100. Baselines were computed for every profile as mean values from 10 to 5 s before the PLM onset.

The length of the upward deflection of averaged power values shows a progressive trend from lower to higher frequency bands. The baricentric point of delta deflection is temporally coincident with the PLM onset. Theta, alpha, sigma and beta frequencies show a progressively increasing length of significant upward deflection and a progressive shift toward the right of their baricentric points.

A significant downward deflection was never reached with respect to the baseline values. The averaged HR profile shows a significant upward deflection, beginning to be significant 4.25 s before PLM onset and lasting for 8.625 s. A significant downward deflection, lasting 3.625 s, precedes the full recovery to baseline values. No significant variations of tibial EMG activity were detected before the PLM onset.

## 4. Discussion

Our study aimed to describe the temporal pattern of changes in cardiac and EEG activities concomitant with PLMs in NREM sleep. It seems evident that PLM onset is heralded by a significant activation of HR and delta activity power, beginning, respectively 4.25 and 3 s before the leg movement takes place. Faster EEG frequency bands showed an activation starting immediately before the PLM onset. In averaged variations of tibial EMG, there was no presence of muscular activity able to induce the initial changes in EEG and ECG signals before PLM onset. The time evolution of alpha, sigma and beta frequency variations shows that their activation largely develops after the PLM onset. Moreover, there is a trend toward a progressive increase in the importance of activation from lower to faster frequencies, evidenced by the progressive increase in duration of the significant upward deflection and by the progressive shift to the right of the baricentric point.

Our data highlight that impressive cardiac and EEG changes take place before the onset of the motor phenomenon. The temporal relationship between delta activity, cardiac activation and PLM onset lead us to consider these phenomena as a preparatory condition, involving both central and autonomic nervous systems, exerting a permissive function on the activity of spinal motoneurons. According to Sforza et al. [19], the rise of delta waves and HR could be considered as the first level of a transient activation from sleep. PLMs, and the subsequent progressive activation of the faster EEG frequencies, should be considered as the second phase in the continuum of the arousal response associated with these movements. Our data, obtained by means of time-frequency analysis techniques (which allow more sound temporal resolution), strongly confirm the data obtained by Sforza et al. by means of spectral analysis techniques. These authors reported that, irrespective of the importance of EEG changes linked to PLMs, the pattern of arousal response (consistently similar to ours) consisted of an abrupt increase in delta activity and HR a few seconds before the onset of the PLM, followed by a progressive rise in fast EEG frequencies and tachycardia, peaking from 1 to 3 s after the PLM onset [19].

On the whole, these data give strong evidence that PLMs are not the trigger phenomenon of cardiac and EEG activation, but on the contrary seem ruled by a central oscillatory mechanism regulating both EEG and autonomic functions.

A continuum in arousal response, with the same temporal characteristics highlighted by the use of spectral analysis technique, has been described for EEG and HR changes associated with spontaneous arousal [23]. This study showed a stereotyped pattern of cerebral and autonomic variation. Irrespective of the strength of the arousal considered, EEG and autonomic responses were present, consisting of a rise in HR and slow EEG frequencies starting 1 s before the arousal onset. Similar results have been described in NREM sleep by De Carli et al. [24], reporting an increase in delta activity in the 3.5 s epoch preceding the arousal.

Besides a cardiac activation, other autonomic functions have been shown to be involved in the arousal phenomena. In fact, increases in mean arterial blood pressure, HR and delta activity precede the occurrence of EEG arousal events, whether the arousal is elicited by an external stimulus or arises spontaneously [25]. Similar changes in HR and respiratory-acts rate, which precede the arousal-related EEG changes, have been reported in feline NREM sleep [26], the working hypothesis being that microarousals may serve as part of an activated central nervous mechanism for homeostatic regulation in response to autonomic and respiratory irregularities during sleep.

Delta burst has been described in upper airway resistance syndrome (UARS) and OSAS as an arousal response to airflow limitation [27,28]. In apneic patients, at least in NREM sleep, delta amplitude progressively increases during apneas, reaching highest levels just before the beginning of the postapneic hyperventilation when alpha and fast EEG activities appear [27].

In UARS frequent brief arousals, associated with progressive increases of esophageal pressure (PES), characterize the sleep EEG of these patients. The spectral picture of these phenomena [29,30] is characterized by an increase of HR and of averaged delta band power values beginning several seconds before and accompanying the PES reversal, regardless either of the presence of a visually detectable EEG arousal or of an increased EMG activity. In the period after the PES reversal, faster frequencies (alpha, sigma and beta activities) show a progressively delayed increase whose importance was greater in arousal-related events. This pattern has been interpreted [29] as indicative of a compensatory central nervous system mechanism promoting the continuation of sleep.

On the whole, our data and that from the current literature we reviewed indicate that a stereotyped pattern of cerebral and autonomic variations characterizes the microstructural fluctuations of the arousal level during NREM sleep. Either spontaneous arousals or those related to motor phenomena, blood pressure variations or cardiac activations show a qualitatively common EEG spectral pattern, irrespective of the presence of a detectable arousing stimulus, its type or its strength. Since a stereotyped pattern

of variations in HR and EEG spectral composition is present before and during spontaneous arousal, PLM, respiratory efforts and cardiovascular variations, it is tempting to suggest, according to Sforza et al. [19], that oscillatory processes in autonomic and EEG activities might adjust in anticipation to the motor phenomenon.

Spectral analysis at the microstructural level depicts sleep as a continuous oscillatory process [31,32]. Homeostasis during sleep is maintained by continuous reactive adjustments in response to changes in vigilance and cardiorespiratory functions [33]. Coherent oscillations of EEG, level of consciousness, systemic arterial pressure, cardiac rate arteriolar tone, breathing and peripheral motoneurons excitability during human sleep were described by Lugaresi et al. as early as 1972 [34]. The occurrence of periodic EEG sequences emerging from the tonic background suggests a possible role of these phasic, repetitive and stereotyped patterns in the formation and maintenance of sleep architecture [35–38]. These homeostatic reactions, expressed polygraphically by transient arousal-related phasic events during NREM sleep, were categorized by Terzano and co-workers as cyclic alternating pattern (CAP) [39,40]. CAP consists of two alternating EEG patterns: aggregates of arousal related phasic events (A Phase) separated by intervals of EEG background activities (B phase). A phases are closely related to a transient modification of the arousal level and have immediate repercussions on EEG synchrony. Moreover, during the A phase, changes in the autonomic correlates of arousal are often present. The spectral profile of CAP sequences [32] consists of periodic gatherings of EEG total power crossing the zero line, in correspondence to visually scored A phases, whereas the troughs of total power were closely related to the visual identification of the B phases. The representation of A phases by means of spectral descriptors [41,42] highlighted a rather constant and stereotyped temporal pattern of the phenomenon: an early increase of low frequencies power is followed by an increase in faster frequencies with a progressively increasing delay. This pattern appears to be strictly similar and somehow superimposable to the one we describe herein, related to the occurrence of PLM. Similarities are enhanced by the findings of an oscillatory pattern in HR variations encompassing CAP [43,44]. According to preliminary data from our lab (De Carli et al. unpublished data), HR would show a typical pattern of tachycardia–bradycardia starting 1–3 s before the A phase onset, indicating an activation heralding the EEG phenomena, reaching its maximum across it and followed by an inhibitory effect. Some other studies have shown a close link between PLM and CAP. PLM occurs most often during A phases of CAP [45]. Periodic EEG oscillations, very similar to the ones defined as CAP, are also present in the case of a missing PLM [46]. A significant increase of synchronization between EEG, HR and breathing signals was found in the passage between non-CAP sleep and CAP sleep, suggesting the possibility of a common central oscillator triggering the different system evaluated [47].

Since all phenomena we have taken into consideration (CAP, PLM, spontaneous arousals or arousals related by detectable stimuli) are always characterized by an initial increase in delta power and HR, followed by an inhibition and by a progressive activation of faster EEG frequencies, we are in favor of the working hypothesis of a neural oscillatory network regulating the cyclic arousability of the sleeping brain. This hypothesis could unify CAP, other sleep oscillatory microstructural processes outside the CAP framework and the hierarchy of the arousal response. Accordingly, the delta power and HR increase may be considered as the early sleep-maintaining response of the brain arousability to low intensity stimuli, implicating the activation of the brainstem.

According to the common brainstem system (CBS) theory [48,49], CBS activity is modulated by numerous afferent inflows. The most important influences come from baroreceptor afferents, which are integrated with other information from pulmonary receptors and arterial chemoreceptors in the relay station of the nucleus tracti solitarii. CBS exerts regulatory influences on the activities of peripheral visceral and somatomotor systems, synchronizing them to the activities of higher brain structures. However the neurons of the CBS also present an oscillatory rhythmic activity that is able to adjust the vascular, cardiac, respiratory and EEG delta–theta rhythms in case of altered internal or external situations [48,50]. Internal or external stimuli could be processed by the CBS, inducing the initial part of the arousal response, aimed at maintaining sleep, and mainly characterized by mild HR and EEG delta waves activation. Further activation of the CBS could induce an increase in the firing rate of this system, yielding major changes in autonomic and cerebral activities, as a survival defensive response.

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