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Motor pattern of periodic limb movements in sleep in idiopathic RLS patients

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Abstract

Objective: Periodic limb movements in sleep (PLMS) are recurrent sleep-related movements that often occur in association with restless legs syndrome (RLS). The purpose of the present study was to examine the pathophysiology of PLMS in patients with idiopathic RLS.

Methods: Ten patients with idiopathic RLS who were medication-free or who had withdrawn from medication at least 2 weeks prior to the study underwent an extensive neurophysiological investigation that included nocturnal video-polysomnographic recording (VPSG), EMG recording, and the Multiple Sleep Latency Test (MSLT). Sleep efficiency and PLMS index were calculated during VPSG.

Results: All patients had an increased PLMS index, decreased sleep efficiency, and a pathological MSLT score. Leg muscles were the first to be activated, often with alternation of side, and no constant recruitment pattern could be found from one episode of PLMS to another, even in the same patient. No ordinate caudal or rostral spread of the EMG activity was observed.

Conclusions: The results suggest that there are different, independent, and unsynchronized generators for PLMS. The direct participation of the cerebral cortex in the origin of PLMS is unlikely, suggesting that abnormal spinal cord hyperexcitability may act as the primary cause of PLMS, triggered by unidentified sleep-related factors.

Keywords: Restless legs syndrome; Motor pattern

1. Introduction

Periodic limb movements in sleep (PLMS) are recurrent sleep-related movements characterized by rapid flexion of the foot at the ankle and partial flexion of the knee, typically associated with a slower extension of the big toe. Similar movements may involve the upper limbs. PLMS often occur associated with the restless legs syndrome (RLS). PLMS last 0.5–5 s [1], appear especially during light sleep (stages 1–2) and relaxed wakefulness, and recur quasi-periodically every 20–40 s [2,3].

Several models have been suggested to explain the pathophysiology underlying PLMS. Though reduced cortical inhibition [4,5] or an impairment of cortical-subcortical motor structures, particularly of motor inhibitory pathways [6], has been reported in RLS, the absence of any cortical potentials preceding the PLMS confirms our own [7] and Trenkwalder et al.'s [8] findings and seems to exclude a direct participation of the cerebral cortex in the origin of the PLMS. Furthermore, PLMS periodic synchronicity with other oscillations that simultaneously involve EEG activity, autonomic functions, and muscle tone suggest a subcortical, probably reticular, site of origin of PLMS [9,10]. Neurophysiological studies are consistent with a mechanism active at the pontine level or rostral to it [11], and high-resolution functional magnetic resonance imaging in patients with PLMS and RLS confirms a significant activation of the red nucleus and the brainstem [12]. Nevertheless, studies also suggest that PLMS can be directly generated in the spinal cord. In fact, patients undergoing spinal cord anesthesia or with progressive paraparesis due to a thoracic spinal cord lesion may present with PLMS, and a propriospinal pattern of PLMS has been suggested recently [13]. Finally, other studies find electrophysiologic and pathologic signs of peripheral axonal neuropathy in RLS patients, suggesting a role of the peripheral nervous system in the pathogenesis of PLMS [7,14–17].

We recently investigated the EMG propagation pattern of PLMS in patients with idiopathic RLS and found that in PLMS, leg muscles were those more frequently involved, often with alternation of side, and that there was no constant recruitment pattern from one PLMS episode to another, even in the same patient. There was no ordinate caudal or rostral spread of the EMG activity, indicating the engagement of different, independent and sometimes unsynchronized generators for each PLMS. The abnormal spinal cord

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hyperexcitability may act as the primary cause of PLMS, triggered by unidentified sleep-related factors [18].

2. Methods

We studied ten patients with idiopathic RLS [19] (familial in two cases): six men, four women, aged from 50 to 71 years (mean 60 years), with a mean disease duration of 13 years. All patients reported PLMS during the pre-dormitum and five also during relaxed wakefulness.

Neurophysiological investigation included somatosensory evoked potentials (SEPs) [20], transcranial magnetic stimulation (TMS) [21], electromyography with nerve conduction velocity (EMG-CV) [22], back-averaging of the EEG preceding the PLMS (at least 50 PLMS) [23], nocturnal video-polysomnographic recording (VPSG), and Multiple Sleep Latency Test (MSLT) the day after. All patients were drug-free or had withdrawn from medications at least 2 weeks prior to VPSG.

The VPSG recording montage included EEG (Cz–O2); surface EMG of the right and left biceps brachii, triceps brachii, rectus abdominis, thoracolumbar paraspinales (levels T10–L2), rectus femoris, biceps femoris, tibialis anterior, and gastrocnemius muscles; and electrocardiogram and abdominal respirogram. The data were stored in a computerized system at 1024 sampling frequency for off-line motor pattern analysis. Sleep was scored according to standard criteria [24], and PLMS index (number of PLMS per hour of total sleep time) and sleep efficiency (percentage of time spent asleep over time from 'lights off' to 'lights on') were calculated. The first 100 consecutive PLMS [1,25] of each patient were analyzed in order to establish how frequently each muscle was involved in the PLMS, how frequently the EMG activity started in a particular muscle, and the time delay between the first activated muscle and each of the other muscles.

3. Results

SEPs, TMS, and EMG-CV were normal in all patients. No cortical potentials preceding the PLMS were found on back-averaging of EEG in any of the patients.

All patients had an increased PLMS index (37–166, mean 107) and decreased sleep efficiency (25–80%, mean 56%) [26], and five had a pathological MSLT [27]. In particular, patients with PLMS index greater than 100 showed a lower total sleep time, decreased sleep efficiency, and pathological MSLT.

EMG pattern analysis showed that the muscles most frequently involved were in the order tibialis anterior (right 74%, left 76%), gastrocnemius (right 66%, left 54%), biceps femoris (right 55%, left 57%) and rectus femoris (right 36%, left 49%), triceps brachii (right 14%, left 10%), biceps brachii (right 8%, left 13%), rectus abdominis (right 6%, left 3%) and thoracolumbar paraspinales (right 4%, left 5%). Antagonist muscles could be activated at the same time and with an alternation of side.

The first activated muscles were in the order tibialis anterior (in 53% of the PLMS), gastrocnemius (18%) and biceps (13%), and rectus femoris (7%). Only occasionally did PLMS start in the upper limb muscles (biceps brachii in 3% and triceps brachii in 5% of the PLMS) and rarely in axial muscles (rectus abdominis 0.3%, thoracolumbar paraspinales 0.8%).

The pattern of activation analysis showed no stereotypic recruitment pattern from one to another PLMS, even in the same patient. In particular, there was no ordinate caudal or rostral propagation of the EMG activity according to a metameric spinal propagation. Furthermore, the time delays between the first and subsequently activated muscles, particularly between the first and the last activated muscles (duration), were extremely variable and long, ranging from a few milliseconds to 2 s.

4. Discussion

Our data offer a contribution to the understanding of the pathophysiology of PLMS by focusing the study on the motor pattern of PLMS, which we disclosed through evidence of independent and often unsynchronized spinal generators and of a bizarre, nonstereotypic pattern of recruitment and muscle propagation. Moreover, ancillary data, especially the absence of any cortical potentials preceding the PLMS, confirm previous findings [7,8] and exclude a direct participation of the cerebral cortex in the origin of the PLMS. In addition, we did not detect any abnormality in the peripheral nervous system or in the sensory and pyramidal tracts in our patients.

In summary, we collected evidence indicating the following.

(1) The lower limb muscles, particularly the tibialis anterior, gastrocnemius, and biceps femoris, were those most frequently involved in PLMS. PLMS activity also started more often in the tibialis anterior. In 90% of our patients there was additional involvement of the muscles of the upper limbs, although PLMS can actually begin in the biceps brachii or triceps brachii. Therefore, our findings suggest activation (or disinhibition) of muscles innervated at the lumbosacral L4–S1 levels, and, to a lesser extent, at the cervical C6–C7 segments, placing the site of origin of the PLMS recorded at least at a middle cervical level.

(2) The finding that PLMS can be generated below cervical spinal level, even in RLS, is not in disagreement with PLMS appearing after spinal lesion (of the a thoracic tract) [28–31], or in syringomyelia with preservation of lumbosacral enlargement [32], suggesting disinhibition of a lumbosacral generator (only the lower limbs were involved in these patients) [29].

(3) The pattern of muscular recruitment found in the recorded PLMS was extremely inconstant, and the delay

between the first and the last – and indeed every other subsequent – muscle activated was variable and long, up to 2 s. The initiating muscles could differ even in the same patient, from one PLMS to another. The pattern above does not fit with a propriospinal pattern of propagation typical of propriospinal myoclonus [33,34]. In fact, propriospinal myoclonus is characterized by rostral and caudal diffusion of the jerks to involve multiple spinal segments, their origin in axial muscles, a long duration of the EMG bursts (100–300 ms, sometimes with polymyoclonic shape), marked jitter in intermuscle latencies, and low spinal conduction velocity. Moreover, propriospinal myoclonus displays a strict relationship to the wake-sleep transition period: the jerks arise in a semirhythmic fashion only during the relaxation phase prior to sleep and disappear with the earliest stages of sleep and throughout all sleep stages, while PLM appear with the initiation of sleep and typically persist during light NREM sleep. In PLMS we could not detect any orderly propagation from a defined spinal segment to the caudal and rostral innervated muscles [33,35]: they rarely affected the axial muscles, and they almost never started in these muscles. Our findings also exclude any descending direct activation of spinal segments along pyramidal pathways [36] according to the pattern of brainstem myoclonus [37].

(4) The variability of the recruitment pattern and of the initiating muscles seems to indicate the engagement of different, independent, and sometimes unsynchronized generators for each PLMS event, as previously suggested [7,15,38,39]. As a possible explanation of the findings above, we postulate an abnormal hyperexcitability of the entire spinal cord, but especially its lumbosacral and cervical segments. Excitability of spinal cord changes during sleep has been documented by monosynaptic (H reflex) and polysynaptic spinal reflex studies in man and animals [40,41]. Hyperexcitability of polysynaptic reflexes has been disclosed in RLS [12,42]. A diffuse hyperexcitability of the spinal cord may explain the changing of origin of the PLMS in the same patient and in subsequent PLMS.

(5) Why the L4–S1 and the C6–C7 muscles are preferentially activated remains obscure. Even a flexion reflex pattern of the type of the triple flexion reflex [12,42,43], or the Babinski sign [44] when more localized, cannot fully explain the variability of the recruitment pattern and the initiating muscle. The involvement of the four limbs, however, with a preference for the legs, may suggest that PLMS are fragments of a locomotor pattern embedded within the spinal cord [45].

(6) We acknowledge that a pathophysiological model of PLMS confined to the spinal cord cannot account for several characteristics of PLMS itself: its occurrence during light NREM sleep, the synchronous periodicity with periodic oscillations of other EEG and autonomic functions [9], and the alternation of sides, with both sides retaining the same periodicity. Of two possible explanatory models, one could account for a dual pathophysiologic mechanism in which the primary causative event consisting of an increased spinal cord excitability allowing PLMS is set into motion by other sleep-related factors located at a supraspinal level. It has been shown that phase A of the cyclic alternating pattern [46], whose physiological fluctuations are probably organized at a supraspinal level, offers a permissive window for the activation of many motor phenomena during sleep, including PLMS [10]. A second model could account for abnormal activity arising from the supraspinal subcortical region, projecting dysfacilitatory influences to the spinal cord, but especially to the lumbosacral enlargement, triggering a sort of locomotor circuitry intrinsic to the cord.

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