Periodic limb movements during sleep *vs* seizures and epileptiform discharges: some supposedly shared pathomechanisms

Movimentos periódicos dos membros durante o sono *vs* crises e descargas epileptiformes: alguns patomecanismos supostamente compartilhados

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SUMMARY

This is a narrative review that assesses some possible underlying abnormal mechanisms shared between periodic limb movements during sleep (PLMS) and interictal epileptiform discharges (IEDs) or epileptic seizures.

The underlying abnormal mechanisms of PLMS are not clearly defined, but the hypotheses raised include a pure motor mechanism originating in the brainstem, spinal cord or a cortico-subcortical interaction, influenced by predisposing factors, through neural networks.

PLMS rhythmicity appears to be closely linked to sleep microarchitecture, and also to cortical arousals, as with some types of epilepsy, which involve both the underlying sleep rhythms and their intrinsic functions as well as the so-called central pattern generators that produce rhythmic motor patterns. However, the relationship between PLMS and epilepsy has not yet been fully clarified. Rhythmicity and sleep fragmentation appear to be common denominators between them, at least more closely in sleep-related hypermotor epilepsy. To some extent, the electroencephalographic changes of PLMS would express an epiphenomenon of the involvement of some underlying brain networks common to epileptic seizures and IEDs.

Keywords: Periodic limb movements, sleep, seizure, pathophysiology

RESUMO

Esta é uma revisão narrativa que avalia alguns possíveis mecanismos anormais subjacentes compartilhados entre os movimentos periódicos dos membros durante o sono (MPMS) e as descargas epileptiformes interictais (DEIs) ou crises epilépticas.

Os mecanismos anormais subjacentes dos MPMS não estão claramente definidos, mas as hipóteses levantadas incluem mecanismo motor puro originado no tronco cerebral, medula espinhal ou uma interação córtico-subcortical, por influência de fatores predisponentes, através das redes neurais.

A ritmicidade dos MPMS aparece estar intimamente ligada à microarquitetura do sono, e também aos despertares corticais, como acontece com alguns tipos de epilepsia, o que envolve tanto os ritmos subjacentes do sono e suas funções intrínsecas quanto os chamados geradores de padrões centrais que produzem padrões motores rítmicos.

No entanto, a relação entre PLMS e epilepsia ainda não foi totalmente esclarecida. Ritmicidade e fragmentação do sono parecem ser denominadores comuns entre eles, pelo menos mais intimamente na epilepsia hipermotora relacionada ao sono. Em certa medida, as alterações eletroencefalográficas de PLMS expressariam um epifenômeno do envolvimento de algumas redes cerebrais subjacentes comuns a crises epilépticas e IEDs.

Palavras-chave: Movimentos periódicos dos membros, sono, convulsão, fisiopatologia

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INTRODUCTION

There is a spectrum of motor events related to sleep and paroxysmal nocturnal epilepsy that have clinical similarities and perhaps also shared neurophysiological mechanisms, not yet fully characterized.

Rhythmic movements during sleep include normal variants of physiological movements, some related disorders, and types of epilepsy such as sleep-related hypermotor epilepsy (SHE). Recently, models for sleep arousal have sought to clarify their etiology[12].

Periodic limb movements during sleep (PLMS), one of these rhythmic movements, are involuntary, sleep-related phenomena characterized by periodic episodes of repetitive and stereotyped limb movements that can cause significant sleep fragmentation and daytime functional impairment[3].

Polysomnographically, PLMS are recognized only if they occur in a series of at least four consecutive movements, each lasting 0.5 to 5 seconds but separated by 4 to 90 seconds. The number of PLMS per hour of sleep constitutes its index (PLMI) and according to the ICSD-3, it is considered abnormal when >15/h in adults and >5/h in children[11]. Their identification can be a challenge in clinical practice, as they are also associated with primary motor disorders and respiratory disorders related to sleep and associated awakenings[3].

Regarding periodic limb movement disorder (PLMD), it refers to patients with an abnormal PLMI, and clinical sleep disturbance that cannot be explained by another sleep disorder[1]. So other associated sleep disorders need to be excluded: namely RLS, narcolepsy, REM sleep behavior disorder (RBD) and sleep-related respiratory disorder[3].

There are recent advances that have clarified some aspects of the impact of periodic motor activity on the microstructure and macrostructure of sleep and its effect on daytime functioning[3]. However, it is still unclear whether the electrophysiological changes would be functional epiphenomena of some common underlying brain networks of sleep and periodic movements. Here we try to clarify the pathogenetic similarities between the electroencephalographic expression of the PLMS and the phenomena linked to epileptic seizures, regarding predisposing factors and the neural networks of both seizures and PLMS.

EPIDEMIOLOGY OF PERIODIC LIMB MOVEMENT OF SLEEP: PREVALENCE AND RISK FACTORS

The prevalence of PLMS is estimated to be 4%–11% in adults[17]. In population studies, age, male gender, and restless legs syndrome (RLS) were all recorded as independent risk factors for PLMS in adults (PLMI > 15/h)[3].

PLMS usually increase with aging. They are often comorbid with other sleep disorders such as restless legs syndrome (RLS) and various clinical comorbidities (eg, congestive heart failure, diabetes, migraine, cardiovascular, liver and kidney disease, alcohol dependence, syringomyelia), in addition to neurological or psychiatric [3]. PLMS can be precipitated by medications and psychoactive substances, such as antidepressants and lithium[3], and several psychotropic drugs have been associated with PLMI, increasing or decreasing them.

Serum ferritin has been the focus of several studies with controversial results, probably reflecting different phenotypes, but iron supplementation is routine for patients with RLS/PLMD and low serum ferritin levels[1,3] .

The efficiency of dopaminergic agonists in PLMD[16] seems to be linked to iron and dopamine deficiencies in the CNS which supports the idea that the brain dopaminergic hypoactivity is under PLMS pathophysiology.

Chronic kidney disease and renal failure were similarly associated with RLS and PLMS. Diabetes has also been listed as a potential risk factor for PLMI > 15/h, but this relationship decreases when proper adjustment of confounding was undertaken[3].

MACRO AND MICROSTRUCTURE OF SLEEP VS PERIODIC LIMB MOVEMENT AND SEIZURES

Sleep is generally analyzed through its macrostructural stages, which, by themselves, cannot provide information about its functional structure and stability. Sleep is characterized by the cyclical occurrence of REM (rapid eye movement) and NREM (non-rapid eye movement) sleep phases, the latter comprising slow-wave sleep (N3 stage) and the lighter stages of sleep (N1 and N2). However, the microstructure characteristics and the phasic phenomena that occur during sleep also provide complementary information about it. In NREM sleep, the cyclic alternating pattern (CAP) is a recurrent physiological EEG activity that occurs in the brain during sleep and captures the microstructure of sleep and can be used to identify its instability[10].

The CAP is composed of a higher excitation A phase (k complexes, delta bursts, polyphasic bursts, arousals) and a lower excitation B phase (baseline interval between consecutive A phases)[9]. The different A phases express the arousability-reactivity of the sleeping brain at different ages and sleep stages; A1 is prevalent in younger subjects during N3, whereas A2 and A3 express more sleep disruption in adults[12].

Regarding the segments of REM sleep, it also has two distinct microstates: phasic and tonic. Phasic REM sleep is the portion of REM sleep during which there are bursts of rapid eye movements, which may be associated with brief bursts of EMG activity and/or sudden increases in sympathetic activity. Tonic REM sleep is the portion of REM sleep that exists between the phasic bursts, in which low muscle tone is consistent[6]. Consequently, sleep stages and cycles represent the macrostructure of sleep and the CAP

and segments of REM sleep, their microstructure.

PLMS are more frequent during stages 1 and 2 of NREM sleep, especially with their CAP and their rapid activity subtypes (A2 and A3). Besides, PLMS become less frequent during stage 3 of NREM sleep and REM sleep[1,3] . Furthermore, PLMS are rarely recorded during the CAP B-phase, a period of low EEG activation that does not appear to support the emergence of PLMS, which are typically confined to CAP A-phases[3].

The number of PLMS-related awakenings (ie, PLMIar) can be seen as a marker of sleep fragmentation, but several studies have failed to relate PLMIar to the severity of reported sleep complaints or subjective or objective sleepiness[3].

There are two main PLMS night patterns. One begins shortly after sleep onset and dominates early sleep cycles, influenced by circadian as well as homeostatic influences, and a second type, where PLMS are more evenly distributed across sleep cycles, with a predominant peak commonly occurring in the middle of sleep cycles. Being that in both patterns, the PLMI can vary significantly between consecutive nights. Furthermore, it is recognized that certain body positions in susceptible individuals can affect the genesis of PLMS[3].

Regarding sleep and interictal epileptiform discharges (IED) or seizures, the main physiological issues are presented as follows[4].

Epileptic discharges may occur only during sleep or potentialize during the sleep, or the wake-up time. Besides, sleep deprivation may trigger seizures in some kinds of seizures, mainly genetic generalized epilepsies, like juvenile myoclonic epilepsy. Also, electrical activity in different areas of the brain tends to be synchronized during NREM sleep when IEDs and seizures are most activated, and epileptiform activity during lighter stages of sleep is related to sleep instability and the CAP patterns[4].

Neuronal networks commonly shared between sleep and epilepsy produce a vicious cycle, as nocturnal seizures can disrupt sleep, on the other hand, antiepileptic drugs and sleep disorders can contribute to sleep fragmentation, which can worsen seizures. Most sleep-related seizures are followed by arousal. In addition, many predisposing factors can facilitate the occurrence of micro-arousals and sleep instability, which increases or modulate the occurrence of minor motor events and other sleep disorders, which in turn induce IEDs and sleep-related seizures[4].

SIMILARITIES AND DIFFERENCES BETWEEN PERIODIC LIMB MOVEMENT AND SEIZURES

Neural oscillations or brain waves are observed throughout the central nervous system and at all levels of the organization, and synchronization is a widespread natural phenomenon occurring in networks of oscillators. The types of brain waves are usually divided into the delta, theta, alpha, beta, and gamma, measured in cycles per second or hertz. However, specific types of neural oscillations and also synchronization can appear in functional situations, such as sleep and consciousness, and also in abnormal situations, such as epilepsy – currently understood as a network disease. Besides, neocortical synchronization along sleep and wakefulness is frequently linked with rhythmic oscillations of neuronal activity: slow oscillation, delta, spindle, beta, gamma and ripples[14]. In this section, we intend to outline the main known pathological mechanisms for epileptic seizures and IED, as well as PLMS, unfolding the questionable common neuronal pathways.

The epileptic activity must be considered in terms of the functional and dynamic connectivity of dysfunctional neuronal networks[13]. Since some of these networks are interconnected through reentrant connections, this means that some nodes tend to receive connections from others, such as the cortico-thalamic-cortical system[13]. It is also known that seizures occur in neuronal networks due to a change in the dynamic balance between excitatory and inhibitory processes, with the predominance of the first[13]. At the local neuronal network level, neurons and associated glia became increasingly coupled in the transition to a seizure, recruiting more distant neuronal networks[13]. Consequently, these circuits have been described in various forms of epilepsy, such as the thalamocortical system involved in absence epilepsies, and also in several other forms of epilepsy[13].

It has been postulated that in seizures with altered consciousness or with certain motor behaviors, such as those of a repetitive nature or innate behavior, there is the involvement of circuits in both cortical and subcortical pathways[8].

On the other side, PLMS is often associated with transient autonomic arousal, with tachycardia and oscillation of blood pressure. This involves several cortical and subcortical centers in the so-called “central autonomic network” modulators of the brainstem mechanisms that directly regulate autonomic functions[15]. Consequently, this also involves many subcortical areas of the brain, but their origin and pathophysiology remain unclear[5,16].

In the review by Drakatos *et al*.[3], three main anatomical loci were discussed as the potential *locus minoris resistentiae*: neocortical, subcortical, and the spinal cord. Two distinct underlying pathological mechanisms were discussed in this context: a pure motor, possibly originating in the spinal cord, and a more cortico-subcortical interaction given the PLMS rhythmicity closely linked to sleep microarchitecture and its CAP periodicity, not unlike the events apneic/hypopneic in obstructive sleep apnea.

The link between the periodic limb movement and intrinsic periodic fluctuations of the nervous system affecting motor and autonomic systems during NREM sleep

suggested the existence of a common brainstem generator[16]. Central pattern generators (CPG) have been shown to exist in the spinal cord of many animals[7]. These CPGs are genetically determined networks of neurons capable of generating rhythmic motor patterns that have been found to underlie vital functions like respiration, locomotion and mastication[10]. CPGs are independent of higher brain centers or peripheral sensory input[7]. Such generators modulate their periodicity by descending influences, probably reticular. This concept is supported by previous studies with functional MRI, which point to the red nucleus and other regions of the brainstem as generators of PLMS. The lack of EEG cortical potentials and other findings in the literature support the origin and induction mechanism of the PLMS as subcortical[16].

It has been considered that in patients with PLMS, functional alterations in the cortico-subcortico-spinal networks involved in the generation of locomotion may induce these motor patterns. However, it is still unknown whether this reflects a process in which dysfunction in the brainstem leads to an immediate movement of the legs with delayed processing through the thalamus to the cortex or somatosensory feedback of the leg movement to the cortex, or perhaps a combination of the two mechanisms[2].

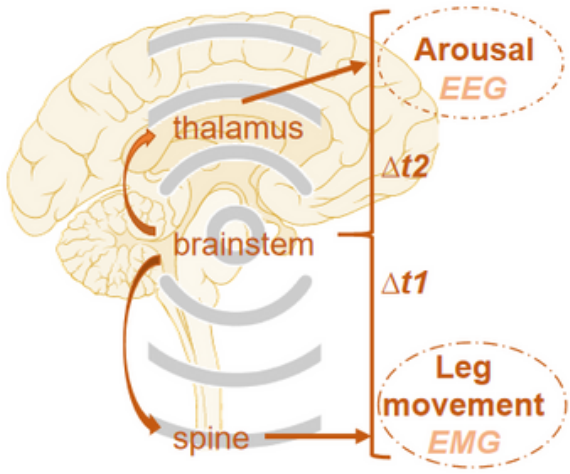

Figure 1. The hypothesis regarding CNS areas involved in the leg movements during sleep is associated with cortical arousals. Δt1: quick delay from the brainstem event to the beginning of the leg movement. Δt2: slow delay between the brainstem event and its transmission to the cortex. Diagram based on Bansal et al[2]. The oscillations would be generated from the brainstem, with supraspinal influence and electroencephalographic manifestation, as well as with spinal influence and motor repercussion and electromyographic manifestation.

A fascinating question relates to some possible shared pathogenesis of NREM sleep parasomnias and sleep-related hypermotor epilepsy - SHE - the only type of epilepsy that has rhythmic features. The description of the different nosological entities belonging to these groups elucidates a possible common origin of the pathology of awakening and outlines relevant characteristics that allow a differential diagnosis. In particular, recognition of an epileptic disorder requires specific medications, while most disorders of arousal do not require any treatment. Also, PLMS are often associated with EEG arousals. Bansal *et al*.[2] in an approach with neuro-extremity analysis researched the causal link between neural activity and leg movements. The initial implementation was consistent with the hypothesis of brainstem dysfunction as a potential source of leg movements during sleep associated with cortical arousals.

Here, we discuss supposedly shared pathomechanisms of sleep movement disorders such as PLMS and the seizure motor phenomenon. The most important researchers on the subject, Parrino *et al*.[10], have already addressed the topic for several years. They recognize the role of arousal systems in giving rise to a continuum of EEG modifications ranging from high-voltage slow rhythms to low-amplitude rapid activities with different characteristics, such as the A-phase subtypes of CAP. These researchers recognize the physiological, paraphysiological, and pathological motor activities during NREM sleep. They suggest that there are CPG expressed by an automatic sequence of EEG-vegetative events that need a trigger (excitement), spontaneous or internal epileptic outburst or external stimuli, expressed by a spectrum of behaviors that appear the same, whether they are part of a seizure or a parasomnia/sleep motor event. These results will depend on several continuum factors (sleep stage, delta power, neuromotor network), but all events share the common trait of arousal-activated phenomena10. The CPG would be a possible mechanism involved and has been seen as a similarity between automatic motor behaviors in both sleep disorders and frontal lobe epilepsy[8].

Along with this, there is the CAP phase A with instability and micro-arousals. Previous studies showed that most seizures occurred in the CAP and always during phase A. Contrarily, there are sleep-related movements, epileptic or not. The PLM periodicity is parallel to the recurrence of CAP cycles. The great majority of limb movements occur during phase A of CAP, which occurs during NREM sleep[10]. And CPGs bring an embryonic origin of these movements that share a final common path to neurophysiological expression. Hyperkinetic automatisms in patients with epilepsy may resemble stereotyped behaviors of our ancestors. Defensive postures, violent gestures, emotional behaviours and sudden arousals resemble archaic automatic motor sequences triggered by CPG situated in subcortical structures[10].

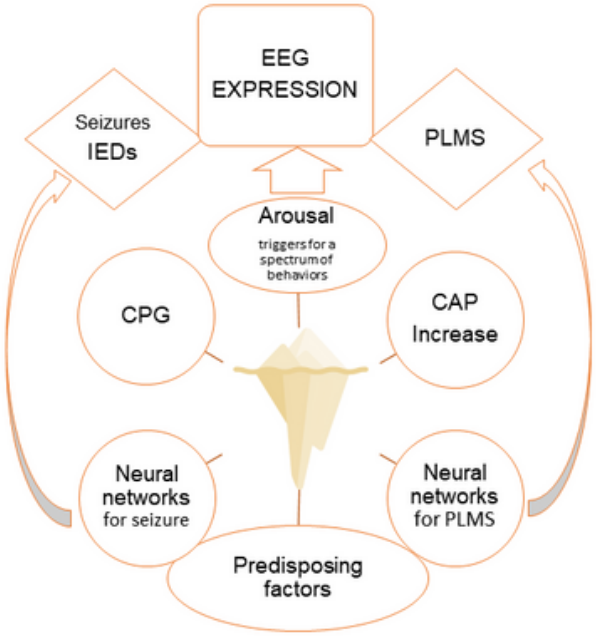

Figure 2. Do PLMS and epileptic seizures have some shared pathomechanisms? Would the electroencephalographic alterations represent an epiphenomenon of some dysfunctions, underlying structures, common neural networks?
CAP: cyclic alternating pattern; CPG: central pattern generators; IEDs: interictal epileptiform discharges; PLMS: periodic limb movements of sleep

Regarding arousals, there is a variable temporal relationship between EEG arousals and PLMs: arousals may precede, follow, or accompany PLMs, suggesting that arousals are not only a consequence of PLMS but can be separated expressions of a common mechanism[1]. Sieminski *et al*.[11] evaluated the temporal distribution of arousals around PLMS and the results suggest that PLMs are followed by arousals, but the work described a temporal relation, not a causal one[11].

As briefly presented by Sieminski *et al*.[11] , the appearance of PLMS in their study showed cortical and autonomic activation initiated after PLMS. This was expressed by a significant increase in alpha+beta wave power and heart rate, and shortly thereafter by an increase in systolic blood pressure, moreover, they did not detect changes in EEG, BP, and HR before PLMS. However, some studies demonstrate that some forms of activation begin before PLMS, and those leg movements are part of a continuous activation process as presented by Ferillo et al. apud Sieminski *et al*.[11] showing an increase in EEG activity just before PLMS - about 3 s earlier for delta band activity and 1 s earlier for the other EEG bands[11]. Although, in any case, it appears that there is not a fully shared underlying pathological mechanism, as the manifestations are different. Despite the differences in motor phenomenology between sleep-related epilepsies and PLMS, as these have long duration and long inter movement intervals, they have stereotyped movements as happens in SHE[12].

Concerning sleep fragmentations, it really can be triggered by some limb movements, which are related to cortical arousals[2]. And it is also caused by epileptic activity during sleep. Any sleep disorder can aggravate seizures and it reinforces that the link between epilepsy and sleep is reciprocal[4].

Kim *et al*.[5] investigated the brain regions associated with PLMS and the results suggest that the brain regions activated before PLM onset indicates the cortical contribution of PLMS pathomechanism.

Furthermore, stereotypies and repetitive motor patterns observed in several physiological and pathological conditions are linked to networks between the cortex and basal ganglia. Thus, this framework could be related to the phenomenon of seizures or even PLMS[8].

Previous neurophysiological studies have studied the relationship between sleep and PLMS[2,5,11]. They pointed out the cortical contribution of the MPMS[5] pathomechanism, the temporal relationship of arousals around the MPMS[11] and the hypothesis of brainstem dysfunction as a potential source of leg movements during sleep associated with cortical arousals[2].

Probably, future studies combining functional neuroimaging with stereoelectroencephalography may contribute to testing hypotheses about cortico-subcortical circuits and deeper brain subcortical regions of the brain[8].

CONCLUSIONS

It is already known that PLMs involve transient autonomic arousal and activation of cortico-subcortico-spinal networks also favoring rhythmic motor patterns. However, a possible shared pathophysiological relationship between PLMS and epilepsy remains an understudied área. There seems to be a temporal relation between PLMs and arousals, but not a causal one, unlike IEDs and seizures, which lead to arousals. EEG changes would furthermore be an epiphenomenon of some common underlying brain networks to both seizures, IEDs and PLMs, all related to arousal mechanisms.

REFERENCES

1. Alessandria M, Provini F. Periodic Limb Movements during Sleep: A New Sleep-Related Cardiovascular Risk Factor? Front Neurol. 2013; 4:116.
2. Bansal K, Garcia J, Feltch C, Earley C, Robucci R, Banerjee N. "Understanding Cortical Arousals during Sleep from Leg Movements: A Pilot Study.". bioRxiv; 2021.
3. Drakatos P, Olaithe M, Verma D, Ilic K, Cash D, Fatima Y, Higgins S, Young AH, Chaudhuri KR, Steier J, Skinner T, Bucks R, Rosenzweig I. Periodic limb movements during sleep: a narrative review. J Thorac Dis. 2021;13(11):6476-6494.
4. Gomes MM. At the crossroads of epilepsy and sleep: some issues. Rev. Bras. Neurol. 2021;57(4): 23-30.

5. Kim TJ, Cha KS, Lee S, Yang TW, Kim KT, Park BS, Jun JS, Lim JA, Byun JI, Sunwoo JS, Shin JW, Kim KH, Lee SK, Jung KY. Brain regions associated with periodic leg movements during sleep in restless legs syndrome. Sci Rep. 2020;10(1):1615.
6. Kirsch D, Harding SM, Eichler AF. Stages and Architecture of Normal Sleep. In: Post TW, ed. UpToDate. Waltham, MA: UpToDate. Last updated: November 08, 2021. Accessed: November 18, 2021.
7. Lu Q. Coupling relationship between the central pattern generator and the cerebral cortex with time delay. Cogn Neurodyn. 2015;9(4):423-436.
8. McGonigal A. Semiology and Epileptic Networks. Neurosurg Clin N Am. 2020 Jul;31(3):373-385.
9. Mutti C, Bernabè G, Barozzi N, Ciliento R, Trippi I, Pedrazzi G, Azzi N, Parrino L. Commonalities and Differences in NREM Parasomnias and Sleep-Related Epilepsy: Is There a Continuum Between the Two Conditions? Front Neurol. 2020;11:600026.
10. Parrino L, Halasz P, Tassinari CA, Terzano MG. CAP, epilepsy and motor events during sleep: the unifying role of arousal. Sleep Med Rev. 2006;10(4):267-285.
11. Sieminski M, Pyrzowski J, Partinen M. Periodic limb movements in sleep are followed by increases in EEG activity, blood pressure, and heart rate during sleep. Sleep Breath. 2017;21(2):497-503.
12. Silvestri R, Walters AS. Rhythmic movements in sleep disorders and in epileptic seizures during sleep. Sleep Science Practice 2020:4, 5.
13. Stefan H, Lopes da Silva FH. Epileptic neuronal networks: methods of identification and clinical relevance. Front Neurol. 2013 Mar 1;4:8.
14. Timofeev I, Bazhenov M, Seigneur J, et al. Neuronal Synchronization and Thalamocortical Rhythms in Sleep, Wake and Epilepsy. In: Noebels JL, Avoli M, Rogawski MA, et al. , editors. Jasper's Basic Mechanisms of the Epilepsies Internet. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK98144/
15. Valenza G, Passamonti L, Duggento A, Toschi N, Barbieri R. Uncovering complex central autonomic networks at rest: a functional magnetic resonance imaging study on complex cardiovascular oscillations. J R Soc Interface. 2020;17(164):20190878.
16. Vetrugno R, Montagna P. Periodic Limb Movements: Diagnosis and Clinical Associations. Practical Neurology March/April 2009; 23-27.
17. Vetrugno R, D'Angelo R, Montagna P. Periodic limb movements in sleep and periodic limb movement disorder. Neurol Sci. 2007;28 Suppl 1:S9-S14.