Periodic limb movements (PLMs) are characterized by stereotyped, repetitive, non-epileptic movements of the limbs, more frequently in legs. They occur during wakefulness preceding sleep onset (PLMW) and during sleep (PLMS). The first polygraphically documented cases occurred in restless legs syndrome (RLS). In fact, most of what we know about PLMs derives from studies of patients with RLS. In their simplest form, PLMs consist of withdrawal-like dorsiflexion of the big and other toes and of the ankle, resembling the spinal flexor-reflex, occurring more frequently at the beginning of the night and exponentially declining across sleep cycles according to circadian influence(s). However, although the leg muscles are the most frequently affected, followed by the upper limb muscles, which are sometimes involved, and by axial muscles that are rarely involved, the movements are less stereotyped than previously believed, with individual variations of the movement patterns. What's more, the EMG activity during PLMS may assume different forms. They include: a tonic activity lasting several hundreds of milliseconds possibly followed by myoclonic activity, an initial myoclonic jerk followed by tonic activity or several myoclonic jerks in clusters sometimes followed by tonic activity. Sometimes PLMS may be seen to occur only in one leg or on one side of the body or to alternate between the two sides.

From a polysomnographic point of view, PLMS are scored only if they occur in series of at least four consecutive movements each lasting 0.5-5 seconds and separated by intervals of 4-90 seconds. These criteria have recently undergone re-evaluation. An index (number of PLMS per hour of sleep) greater than five for the entire night is considered pathologic, but data supporting this contention are rather limited.

The standard method to detect PLMs is a polysomnography recording. However, there have been efforts to detect PLMs by means of actigraphy, which is more convenient for both patient and investigator, since it permits multiple-night recordings in an outpatient setting. Actigraphy offers a convenient and economical alternative to polysomnography in the study of large populations to increase our understanding of the epidemiology and clinical significance of the PLMs. Physicians must note that actigraphy alone should not be used for diagnostic decisions. Periodic limb movement disorder
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(PLMD) is defined as a PLMS index of five or greater that is associated with otherwise unexplained sleep-wake complaint and requiring a polysomnographic confirmation along with the exclusion of other causes of sleep disturbances.

Physiology and Pathogenesis

PLMS are frequently associated with arousal and transient autonomic activation (tachycardia, tachypnea, and an increase in blood pressure) (Figure 2). The link between this common sleep-related motor phenomenon and the intrinsic periodic fluctuations of the nervous system affecting motor, autonomic and vigilance systems during light sleep suggested the existence of a common brainstem generator. This generator modulates their periodicity by descending, probably reticular, influences.12,13 Later the physiologic fluctuations that reoccur every 20-40 seconds during NREM sleep were termed the “cyclic alternating pattern,” infraslow oscillations whose periodicity is embraced with motor and autonomic fluctuations.14 The concept of a brain stem oscillator received some support in functional MRI studies implicating the red nucleus and other brainstem regions in the generation of the PLMS.15 Other MRI studies showed changes in thalamic structures at voxel-based morphometry analysis.16 Altogether, the findings support an involuntary mechanism of induction and a subcortical origin for PLMs. This is also suggested by transcranial magnetic stimulation investigations17 and the lack of EEG cortical potentials prior to PLMS’ and PLMW.18 However, clinical and neurophysiological observations demonstrate that PLMS are actually generated within the spinal cord from the activation of several central spine generators, most likely set into motion by state-dependent descending supraspinal modulating influences.19-25

Impairment in brain iron availability26,27 and the link between iron deficiency and reduction in central dopaminergic tone28,29 coupled with the knowledge that central dopamine signaling exhibits a daily rhythm with a nadir in the evening,30 support the pathophysiologic role of brain dopaminergic hypoactivity in PLMS.31 It may also explain the circadian recurrence and the efficacy of dopaminergic drugs in PLMD.32 In particular, a dysfunction or atrophy of a supraspinally located dopaminergic region in the hypothalamus (hypothalamic A11 nucleus) with descending pathways that target the preganglionic sympathetic neurons—the dorsal horn region, the interneurons, and the somatic motor neurons, has been hypothesized as being intimately involved in the etiology of PLMS.33,34 Striatal regions35 and thalamic structures4 also may be involved.

PLMS still appear as a complex and multivarious movement disorder that implicates many brain areas, including regions belonging to the medial pain system (thalamus, anterior cingulate and insula) where abnormal dopamine and opioid activity has been found.35,36 Several genetic variants associated with susceptibility to PLMS have also been recently discovered.37

Prevalence

The prevalence of PLMS is four to 11 percent in the general population with an age-associated increase up to 25-58 percent in the elderly population.38,39,40 PLMS are present in 80 percent of patients with RLS.41 PLMS may also occur in children, with prevalence rates from 3.9 percent to 50 percent, although the coexistence of other medical conditions like sleep apnea, attention-deficit hyperactivity syndrome, migraine, seizures, narcolepsy and other neuropsychiatric conditions may raise the rate (ICSD-2, 2005).42,43 The highest prevalence of PLMS was 85 percent, reported in a community-based study of elderly patients with a mean age of 67 years.44 The latter finding underscores the controversy about the clinical relevance of the PLMS. Some authors contend that PLMs are associated with adverse consequences for health,45 whereas others do not.46 PLMs have been reported to occur predominantly during the activation phase of the “cyclic alternating pattern” of sleep,47 associated with transient tachycardia and blood pressure increase.48-52 These findings led some authors to maintain that PLMs imply a cardiovascular risk and should be treated even in the absence of any subjective impairment. Other authors cast doubt about the clinical significance of the PLMs and their associated arousals: arousals are not a well-defined phenomenon and, since the exact arousal index leading to clinical manifestations remains nebulous, PLMs should not need attention.49 It thus remains to be seen whether PLMs constitute an incidental observation linked to developmental maturation or aging, or a defined medical entity with sequelas.

Clinical Conditions Associated with PLMS

Besides RLS, PLMs occur with a wide range of sleep-related pathologies, especially in patients with difficulties starting and maintaining sleep and in patients with excessive daytime sleepiness. To date, the largest epidemiological study evaluating the simultaneous presence of PLMs and sleep complaints reported a 3.9 percent prevalence in 18,980 subjects from the general population between 15 and 100 years of age.38 PLMS indeed occurs in various sleep disorders such as obstructive sleep apnea syndrome (OSA),53-56 insomnia57, hypersomnia,58 narcolepsy,59 REM sleep behavior disorders,60 sleep bruxism,61 and sleep-related eating disorders.62 In OSA, they may increase or decrease after continuous positive airway (CPAP) therapy. In moderate to severe OSA, the PLMs may increase due mainly to the “unmasking” of an underlying spontaneous PLMD, and may decrease post-CPAP in mild OSA due to resolution of secondary PLMS associated with respiratory effort-related arousals.63

PLMs have also been reported in disorders not primarily
affecting sleep, such as severe congestive heart failure, essential hypertension, end-stage renal disease, post-traumatic stress disorders, sarcoidosis, spinal cord injury, syringomyelia, multiple sclerosis, alcohol dependence, peripheral neuropathies sometimes associated with primary amyloidosis, diabetes mellitus, uremia, chronic lung disease, leukemia, rheumatoid arthritis, fibromyalgia, Isaac syndrome, stiff-man syndrome, Huntington chorea, amyotrophic lateral sclerosis, anemia with iron/ferritin deficiency, Parkinson disease, multiple system atrophy, Gilles de la Tourette syndrome, spinocerebellar ataxia, or after medical procedure ( epidural and spinal cord anesthesia, gastric surgery). They may also be related to medication intake, in particular psychoactive substances such as lithium, clomipramine, fluoxetine, venlafaxine and other serotonin reuptake inhibitor antidepressants, and neuroleptics.61,62

Psychiatric illness. Psychiatric illness such as depression and anxiety have been associated with chronic sleep loss and appear to be more prevalent in patients with PLMS (and RLS).63,64 Reports of depression varied from 20 percent up to 70 percent in patients with PLMS (and RLS), and the initiation of antidepressant therapy often provides a worsening of the PLMS. Remarkably, some epidemiologic studies have suggested an association of cardiovascular disease and PLMS-RLS leading to claims of an association between PLMS-related repetitive EEG arousals and autonomic hyperactivity and/or to sleep fragmentation as the causal link.51,52

Cardiovascular diseases. A number of studies suggest that PLMS may be a risk factor for cardiac diseases. PLMs are common in people with essential hypertension.70 EEG and autonomic activations are greater during PLMs than during other types of leg movements.71 PLMs have been associated with elevated systolic as well as diastolic blood pressure. An increase in systolic blood pressure by almost 17mmHg and 11mmHg was found during PLMs respectively with and without cortical arousals.52 Similar findings have been reported in another study,51 heralding the possibility that PLMS-related repetitive nocturnal EEG and blood pressure fluctuations could contribute to the risk of cardiovascular diseases. However, these changes may be unspecific, as they are comparable in magnitude to the changes in heart rate and blood pressure induced by a K-complex.72 Moreover, these changes may occur physiologically even in the absence of PLMS during light sleep.13 The latter findings question the pathophysiological relevance of the PLMS and do not exclude that PLMS represents an epiphenomenon of physiological arousal that, like sleep perturbations, ubiquitously increases with age.

It is important to remember clinical investigations addressing the correlations between PLMS and increased risk for hypertension and coronary artery disease are still contradictory. A possibility is also that sympathetic dysfunction is causally related to the PLMS and that the PLMS-related repetitive autonomic changes may have a potential clinical relevance.71 However, the recurrence of PLMS in multiple system atrophy, in which the central autonomic network is degenerated without the attendant heart-rate, blood pressure and EEG changes challenge any hypothesis of a direct provocation of the PLMS by an abnormal autonomic discharge. Further large-scale studies are needed to fully assess the extent of the PLMS to autonomic system relationships.

Excessive daytime sleepiness. PLMS may be responsible for difficulties in initiating and maintaining sleep and for sleep fragmentation with consequent daytime somnolence. Clinical
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investigations addressing the correlations of excessive daytime sleepiness and PLMS are, however, contradictory. Indeed, when searched for in patients with PLMD, no significant correlation may be found between polysomnographically scored PLMS and the subjective complaint of disturbed sleep, the objective measures of daytime sleepiness, or a sense of refreshed sleep on awakening. In 149 older subjects with complaints of excessive daytime sleepiness, PLMS were detected at in-laboratory sleep study, but they were not found to represent a significant risk factor associated with sleepiness. On the other hand, in another study PLMS (not scored in the sleep laboratory but according to a telephone interview) were among the factors having a significant relationship with subjective sleepiness.

A limitation of these studies may be the semantic distinction between sleepiness, tiredness, and fatigue. Though distinguishable on theoretical ground, these constructs may be too subtle to be adequately taken into account by the individual patient and to be distinguished.

Therapeutic Options

Several medications have been reported to influence PLMS. L-dopa and dopamine agonists are considered as the first-line treatments. However, due to the fact that the clinical significance of PLMS/PLMD is still debated, as many studies have failed to demonstrate an association between PLMS/PLMD and symptoms of sleep and non-sleep disturbances, it is not possible to indicate specific treatments for this sleep-related motor phenomenon. There are no established guidelines for treatment of PLMS, and those that exist remain undecisive. Moreover, recommendations for therapy of PLMS originate mostly from studies in RLS patients, and only a few trials investigated the effect of dopaminergic substances on the PLMS/PLMD. Clinical experience indicates also that therapy of the PLMS and its associated disorder may diverge. For instance, hypersomnias with PLMS respond positively to psychostimulants but not to treatment of the PLMS with dopaminergic agents (personal communication). It is also noteworthy that dopaminergic therapy for PLMS may even trigger RLS symptoms in the same patient, representing a complication of long-term dopaminergic treatment today called “augmentation.”

In patients who present with symptoms of sleep disturbance such as excessive daytime sleepiness, insomnia or frequent awakening, the clinician is thus faced with deciding whether or not to treat those that display a high PLMS index. The PLMS night-to-night variability makes the therapeutic decision still more complicated. The individual patient and his/her attending physician must make the final decision whether or not to treat the PLMs.