Periodic leg movements during sleep: phenotype, neurophysiology and clinical significance

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Abstract

Periodic leg movements during sleep (PLMS) are the most important objective finding in restless legs syndrome (RLS). During the last decade, PLMS have been very important for the assessment and comprehension of their pathophysiological correlates, which have been paralleled by the emergence of new computer-assisted and data-driven rules for their identification, scoring and analysis. The present article focused on the most relevant PLMS-related findings of the last decade, and sought to provide a coherent and comprehensive overview on this enigmatic motor phenomenon. First, a clear description was made on the identification, quantification and scoring of PLMS and their associated events. This was followed by a description of the current knowledge of their neurophysiologic aspects. Then, the typical phenotype of genuine PLMS in RLS and other clinical conditions was described, allowing for their careful separation from other sleep leg motor activities. In addition, the most recent findings on the genetics of PLMS were briefly summarized, followed by the current evidence on their clinical correlates, which is another rapidly advancing field of research. The description of the specific aspects of PLMS in children was also carefully reported, with important clues on their evaluation in this age group. Finally, further research was proposed, which may lead to consideration of PLMS as a clinically significant concern, independent of the association with RLS.

Keywords:

Periodic leg movements during sleep (PLMS) scoring

PLMS neurophysiology

PLMS genetics

PLMS consequences

PLMS in children

Introduction

The identification and description of leg movements during sleep are entwined with those of restless leg syndrome (RLS) and date back, at least, to the year 1672 when Sir Thomas Willis identified the key features of the syndrome, including a possible implicit description of periodic leg movements during sleep (PLMS) in *De Anima Brutorum* [1]. Two centuries later, in 1880, Beard hypothesized that the origin of the motor disturbance was at the level of the spinal cord [2]. In 1943, Allison first noticed the involuntary nature of some motor aspects of RLS [3], while in the 1940s and 1950s, Karl Axel Ekbom described in detail its clinical features and introduced the term “restless legs” [4]. Finally, PLMS were clinically recognized by Symonds in 1953 [5], and recorded polysomnographically by Lugaresi et al. in 1965 [6,7]. The polysomnographic documentation of PLMS constituted a crucial step in support of the organic nature of RLS, which had long been considered to lack any physiological correlate [8].

However, notwithstanding the fact that for decades PLMS have been the most important objective finding in RLS, for many subsequent years, scientists and clinicians devoted little attention to them, in part due to studies reporting a lack of clinical significance [9-11], a lack of specificity for RLS [12], and a high night-to-night variability [13-20]. Because of this night-to-night variability, there is an increase in the likelihood that an individual will meet threshold PLMS criteria with an increased number of nights sampled [17]. However, individual PLMS variability from night to night is random and unlikely to affect group-level analysis [13,17].

Conversely, the last decade has been very important for the assessment and comprehension of the pathophysiological correlates of PLMS that include their association with sympathetic nervous system bursts [21,22] and cardiovascular disease [23]. This increased understanding of PLMS has been paralleled by the emergence of new and data-driven rules for their identification, scoring and analysis, in part also based on computer-assisted approaches [24,25]. Although much more prevalent in adults of older age [26], this phenomenon has also started to be understood in children. The following review focused on the most relevant PLMS-related findings of the last decade, with the aim of providing a coherent and comprehensive overview of this enigmatic motor phenomenon.

Identifying, quantifying and scoring PLMS and their associated events

Defining PLMS is an ongoing, dynamic process. The first scoring criteria were proposed by Coleman in 1982 [27], and provided the basis for the first international criteria in 1993 [28]. Currently, two sets of similar, but not identical, rules exist: the first were proposed by the International Restless Legs Syndrome (RLS) Study Group and the World Association of Sleep Medicine (IRLSSG/WASM) [24], while the second set was issued by the American Academy of Sleep Medicine (AASM) [25,29].

Both sets of rules are expected to be updated and modified in the future, as new and consolidated evidence concerning the features of PLMS emerge. Among the reasons for an eventual modification of the rules is the anticipated shift from expert-consensus-based to evidence-based criteria – the current standard of high-precision digital recordings that allows for a systematic investigation of the criteria – and the challenge of characterizing PLMS in populations without RLS. Indeed, as it has become apparent in the last decade that significant levels of PLMS are observed in varying proportions in populations with a particularly wide range of sleep disorders such as: narcolepsy [30-32], rapid eye movement (REM) sleep behavior disorder (RBD) [33,34], and sleep-related breathing disorders [35,36], but also in patients with cardiovascular [37,38] or other diseases [39,40], as well as in the healthy population [41]. The challenge in defining PLMS is therefore no longer based on the identification of these leg movements in RLS, where a large majority of nocturnal leg movements are classified as PLMS [12], but to identify them in populations with possibly unspecific increased leg movements due to a variety of different reasons, including, but not limited to, sleep-related respiratory events [42] or primary motor disorders such as Parkinson's disease [39]. Indeed, one recent concern has been that some of the current PLMS criteria may act as a “pattern extractor” by ignoring all “non-fitting” leg movement activity and that in situations where there is a high number of leg movements (LMs), the PLM index will reflect the number of LMs rather than the true periodic ones [43] (also see below).

Leg movement activity during nocturnal sleep recordings is frequent, and PLMS scoring rules identify those leg movements that are thought to be periodic. Currently, leg movement activity (LMA) during sleep is first categorized based on the duration of movements, and only LMs

between 0.5–10 s duration are considered further (Fig. 1). From these, LMs associated with respiratory events are excluded and the remaining, called candidate LMs, are classified as periodic or non-periodic, based on the inter-movement interval (IMI) and the number of LMs in a series with IMIs in the periodic range of 5–90 s. While research has focused almost exclusively on the periodic LMs, it is currently not well known whether non-periodic LMs during sleep are of significance. For example, in patients with RLS, it has been shown that only the periodic LMs respond to dopaminergic treatment and that non-periodic LMs with IMIs <5 s are unaffected [44]. On the other hand, LMs associated with respiratory events may be associated with clinical variables independent of PLMS, such as number of apnea episodes, presence of chronic obstructive pulmonary disease, hypertension and ethnic factors [45]. Thus, the investigation of nocturnal non-periodic leg movement activity deserves further attention.

Concerning the definition of PLMS, Table 1 lists the most important rules according to the WASM/IRLSSG [24] and AASM [46] rules. A series of recent studies has begun to investigate the evidence base for the current rules, at least in patients with RLS. Among the criteria that have received empirical support is the definition of the association of PLMS with arousals [47]. Periodic leg movements with sleep are considered to be associated with an arousal event when the two events are separated by <0.5 s, regardless of which is first [47]. It could be shown that this is indeed the case in >98% of the time when PLMS and arousals are within 10 s of each other, and when they actually overlap or are separated by <0.5 s [47]. Interestingly, this study also showed that in roughly half of all cases, the arousal onset preceded the onset of PLMS, while the opposite was true for the other half of cases [47]. A further criterion that has received empirical support is the definition of bilateral LMs. The definition of bilateral LMs is one of the areas where the current WASM/IRLSSG [24] and AASM rules [25,29] differ, as the former define LMs as bilateral when the offset of the first is separated by no more than 0.5 s from the onset of the second, while the latter assumes bilateral LMs when the onset of the first is separated by no more than 5 s from the onset of the second movement. Results of a recent study indicated that for patients with RLS, in the overwhelming majority of events, bilateral LMs overlap with each other and at the same time are correctly identified by both the current WASM/IRLSSG and AASM rules [48]. Although the two sets of rules differ considerably in their definition of bilateral LMs, they do provide largely corresponding classifications in subjects with RLS and could be considered equivalent in a clinical context [48].

One criterion that has been critically evaluated but not supported is the definition of respiratory event-related LMs. Also here, the WASM/IRLSSG rules and the AASM rules differ. The WASM/IRLSSG rules consider LMs as associated with a respiratory event when the LM occurs at the end (± 0.5 s) of an apnea or hypopnea [24]. In contrast, the AASM rules define LMs occurring during a period from 0.5 s preceding to 0.5 s following a respiratory event [25,29]. A systematic evaluation, however, has shown that both sets of rules critically underestimate the number of LMs associated with respiratory events, which are systematically increased around the end of respiratory events, over a period significantly longer than specified in either set of rules (-2 to $+10.25$ s) [42].

In summary, the development of scoring rules for PLMS is a dynamic process, which has recently received increased scientific attention that is expected to critically inform future modifications of these rules. Importantly, the scoring of PLMS can be seen as post-processing (ie, the classification and selection of periodic LMs within all identified LMs according to the current rules). For the time being, to promote sustainability of research results, a strong recommendation for research projects is to identify all LMs during nocturnal recordings; this will allow post hoc application of different rules to the identified LMs and fluent generation of updated data sets. By extension, this is also a strong recommendation for the development of automatic scoring algorithms: algorithms that have been shown to correctly identify single LMs, and not only PLMs, which can be considered validated even if PLMS scoring rules change – at least as long as the basic definition of a leg movement remains the same.

The neurophysiology of PLMS and their associated events

Periodic leg movements during sleep are typically recorded from the tibialis anterior (TA) muscle and closely resemble the triple flexion reflex, which consists of dorsiflexion of the ankle and flexion of the knee and hip, obtained with the contraction/relaxation of several muscles and with a visible involvement of the TA muscles [12]. The TA muscles are the most frequently involved muscles (~75%), followed by the gastrocnemius (~60%), biceps femoris (~55%), and rectus femoris (~40%); antagonist muscles can be activated, while axial muscles are rarely involved; muscles of the upper limbs are sometimes involved too [49]. The electromyography (EMG) activity

usually starts in the TA (53% of PLMS), gastrocnemius (18%), biceps femoris (13%), or rectus femoris (7%) muscle; rarely, PLMS starts in the upper limb muscles and more rarely in the axial muscles [49].

The activity of the TA muscles can also be considered within the concept of the so-called “central pattern generators” because asynchronous activations of the two sides can be seen in patients in whom there is a partial or total “disconnection” between spinal and supratentorial structures [50]; thus, it is possible that there are two unrelated specific spinal pattern generators, one on each side, that become integrated into a more complex mechanism, with the anatomic and functional integrity of the complex pathways interconnecting the spine to the brain through the brainstem [51]. The supraspinal mechanisms identified so far are multiple and possibly act in a complex and coordinated synergy [51].

Periodic leg movements in sleep are involuntary movements [52] that are most often synchronized with a generalized oscillatory pattern during sleep, such as the cyclic alternating pattern (CAP) [53], but this synchronization far from indicates a cause/effect relationship between PLMS and CAP or other transient EEG components. Dopaminergic agents that are able to dramatically reduce PLMS do not modify CAP, and benzodiazepines, which are able to reduce EEG oscillations and arousals, do not affect PLMS [54]; nor can experimentally induced arousals elicit PLMS in healthy controls [55]. The interaction between PLMS, cortical activity (arousals) and autonomic nervous system activity, however, is complex and dynamic. The most frequently observed pattern is an increase in slow EEG activity, soon followed by a small increase in heart rate, and then by the occurrence of a PLMS event, which, in turn, heralds or is coincident with an increase in fast EEG activities and a much more consistent increase in heart rate [56]. However, this pattern is not strictly stereotyped and several variations can occur [47].

It is particularly important to consider that not only heart rate, but also significant blood pressure rises are associated with PLMS [21,22], with corresponding important cerebral hemodynamic changes, in a constant pattern: activation (hyperoxygenation), followed by deactivation (hypo-oxygenation), and again activation, with the hypo-oxygenation component being clearly prevalent [57]. This observation might constitute a link between PLMS and their suspected increased risk of cerebrovascular disease [58-60].

Particularly evident is the synchronization between PLMS, arousal-related EEG transients, heart rate rises, and the resumption of respiration after apnea episodes, but also in this case the resolution of apnea is not always followed by the disappearance of PLMS, which only show some changes in their time structure and occur with shorter intermovement intervals [61-63]. Despite the lack of cause/effect relationship, the interaction between all these components is important, and the modification of any of them might influence the impact of the others [64]. In support of this view, it has also been reported that the length of arousals is positively correlated with the PLMS duration [47], and that the amplitude of PLMS-related rises in heart rate can be reduced by dopamine agonists [65].

In order to better understand the clinical significance of PLMS, research will need to consider them as part of a complex framework of interactions, including supraspinal and autonomic neurophysiologic correlates, which act synchronously and in a possibly mutually reinforcing manner. Future research should focus on a better understanding of these interactions and on the assessment of the mutual and/or global effects of the different oscillatory processes, which, if taken together, might correlate significantly with different clinical aspects of RLS, especially in patients with a long disease history [66].

The phenotype of PLMS in RLS and other clinical conditions

In the last decade, a series of studies has analyzed in detail the features of “genuine” PLMS that have depicted the phenotype of PLMS. These features include: a clear peak at approximately 20-40 s in the intermovement interval histogram, along with a gradually decreasing frequency during the night [12], which have consistently been observed in RLS [44,67,68], PLMD [69] and with different amounts and degrees of periodicity in other conditions such as narcolepsy [32] and REM sleep behavior disorder [34]. In the latter, the presence of PLMS seems to be a factor aggravating the severity of the clinical course [70].

It has been repeatedly reported that the intermovement interval distribution of the leg activity during sleep in RLS shows a clearly bimodal distribution of inter-LM intervals with one peak at 2–4

s, and another at around 20–40 s, which can be modeled by a distribution mixture analysis with two lognormal distributions, the second of which represents the occurrence of PLMS [67,68]. The intersection of the two lognormal distributions at 10 s indicates that this might be used as a low cut-off value for the identification of “genuine” periodic LM. An easy way to condense the degree to which leg movement activity in individual patients is characterized by the “genuine” periodic peak between 10–90 s has been the computation of the Periodicity Index (PI), which represents the ratio of the number of this specific type of LM intervals (regular sequences of at least three intervals between four movements, all between 10–90 s), divided by the total number of intervals found [67]. Theoretically, this index can vary between 0 (absence of periodicity, with none of the intervals having a length between 10–90 s) to 1 (complete periodicity, with all intervals having a length between 10–90 s). The PI has been found to be independent of both the absolute number of LMs and the PLMS index, and therefore represents an independent measure [67,68]. Based on these studies, an alternative index for PLMS and periodic leg movements during wakefulness has recently been proposed that counts as PLMS – those leg movements that also contribute to the PI (ie, LMs in a series of at least four with all inter-movement intervals between 10–90 s). Initial studies have shown that in patients with RLS and in healthy controls, this new alternative index is similar to the PLMS index when leg movement activity is genuinely periodic, but significantly lower when periodicity of leg movement activity is low [43].

Another feature of the PLMS phenotype is their distribution throughout the night: RLS patients are most likely to have PLMS in the time period from 23:00 to 03:00, during the first half of their usual sleep period [19,71,72], and the hourly distribution of “genuine” PLMS shows a clear decline in their number from the first to the last hour of sleep [32,34,68,69]. The higher expression of PLMS during the first part of the night clearly parallels the circadian distribution of RLS symptoms [73], and both are possibly correlated with the levels of endogenous dopamine [74]. On the contrary, it is unclear if the factors playing a role in the night-to-night variability of PLMS [13-20] are also based on a possible variability in the levels of endogenous dopamine. However, it should be noted that the measures of periodicity and intermovement interval have been reported to be much more stable than the PLMS index [16,75].

The characterization of the PLMS phenotype is important, and also allows some considerations to be made on the mechanisms underlying the different types of LM activity recorded in patients. As

an example: only “genuine” PLMS promptly respond to the administration of dopamine agonists [44,76,77], while other less periodic activities, such as LM recorded during wakefulness in RLS patients, do not [78]. An imbalance between serotonin and dopamine availability, with the latter being decreased, seems to be the basis of the well-known effects of several antidepressants, which are able to increase the number of PLMS [79-82].

In summary, three independent parameters for the description of nocturnal PLM phenotypes have emerged: PLMS index, periodicity (interval distribution histograms and PI), and time distribution of LMs throughout the night. These parameters have been analyzed in several conditions (see Fig. 2) [32,34,69,83,84], and in response to treatment [44,65,76,77,85,86]. The data available so far seem to indicate that numerous, high-periodic, and progressively decreasing PLMS during the night constitute a well-defined pattern of a specific LM activity, rather than of different types of PLMS, which is expressed especially in RLS and PLMD patients [12,67,69]. However, it can be found with different degrees of expression in a variety of other clinical conditions [32,34,83,84] and even controls, probably depending on a common genetic predisposition [40,50], which is most probably based on the genes involved and also in the clinical expression of RLS [87-90].

By applying the three above-mentioned measurements, it has also been shown that sleep LM patterns are significantly influenced by age [68], with periodicity probably being a less-common phenomenon in children and adolescents [68,83,91]; this has significant repercussions on the interpretation of pediatric data (see below). In this respect, it should be said that assessing normative cut-offs is a difficult issue and the best data to support >15/hour in adults are reported in two studies [92,93]. For children aged 5–18 years, there is good data to support a cutoff of >5/hour [94]; slightly higher normative values may be appropriate for children aged 1–5 years [95] and children living at high altitudes [96].

In contrast to RLS, where women are affected about 2:1 over men [97], gender differences have not consistently been found for PLMS. A study that classified PLMD by survey questions (not polysomnography or accelerometry) reported PLMD to be more common in women (OR 1.47; CI 1.23–1.75) [98]. However, most polysomnography based studies in adults and children have not found a gender effect [92,94,99,100].

Genetics of PLMS

Genome-wide association studies have identified that the presence of PLMS is associated with genetic variants or single nucleotide polymorphisms on different genes. In an Icelandic population, Stefansson et al. [87] found that there was a significant association between an intronic variant on BTBD9 and having RLS with PLMS. This association was present in people who were PLMS positive and RLS negative, but not RLS positive and PLMS negative, which suggested that there was a greater genetic association with PLMS than RLS. In the same study [87], homozygotes for the A allele of Marker rs3923809 of the BTBD9 gene had the lowest levels of ferritin and the highest PLMS indexes; this could suggest an involvement of the iron metabolism in the PLMS physiopathogenesis. More recent work in at least two cohorts (Wisconsin and Switzerland) [88], has shown that variants within TOX3/BC034767, MEIS1 (two unlinked loci), MAP2K5/SKOR1, and PTPRD as well as BTBD9 are significantly associated with the presence of PLMS, and that this association is only modestly reduced when adjusting for the presence of RLS symptoms [89]. In an elderly male cohort, variants in some of these genes (BTBD9, MEIS1, and MAP2K5/SKOR1) were associated with PLMS [90]. In all, the phenomena of PLMS were significantly associated with genes that have also been identified in genome-wide studies of RLS. Associations with PLMS have been shown in three separate populations across five genes, suggesting that there is not only a biological basis, but also a genetic basis for these periodic movements of the legs.

The search for the clinical correlates of PLMS

The fact that PLMS are associated with discrete increases in both heart rate and blood pressure suggests that these recurrent motoric phenomena may be associated with cardiovascular disease. Furthermore, it is possible that PLMS may mediate a putative association between RLS and cardiovascular disease. Early research demonstrating that cardiovascular risk may be aggravated by PLMS studied the sickest of patients who were afflicted with these movements: those with end-stage renal disease (ESRD) and congestive heart failure.

In ESRD patients, PLMS predicted mortality. In one study, people with ESRD that also had PLMS demonstrated 90% cardiovascular mortality over approximately 2 years, compared with 50% mortality in ESRD patients without PLMS [101]. In another study of ESRD patients, PLMS was associated with a nearly doubling of an estimated 10-year risk of stroke [102]. Similarly, it has been

shown that patients with congestive heart failure with PLMS compared with those without PLMS have a higher mortality rate. In a study of 218 patients with heart failure, after adjusting for significant confounding factors including age and heart failure severity, PLMS remained a significant predictor of mortality with a hazard ratio of 2.4. It is important to note that in this study, people with PLMS were older and had more severe heart failure [103].

It has been reliably demonstrated by independent groups that individual movements that constitute PLMS are associated with discrete increases in blood pressure to the order of 20 mmHg [21,22,104]. What is less clear is whether PLMS is associated with daytime hypertension. It is important to note that it might be the nighttime blood pressure that is particularly important to measure, as nighttime blood pressure is superior to daytime blood pressure at predicting incident cardiovascular disease [105,106]. Unfortunately, thus far, no study has evaluated whether PLMS is associated with nighttime hypertension.

Population-based studies have supported a link between PLMS and both hypertension and cardiovascular disease. In a large multiethnic cohort ($n=1740$), PLMS frequency was associated with hypertension in African-Americans, such that for every 10-unit increase in PLMI, there was a 20% increased odds of prevalent hypertension and a 1.01 mmHg increase in systolic blood pressure [107]. There were trends for a similar but smaller magnitude relationship between PLMS and hypertension in Chinese-Americans, but not in Caucasian- or Hispanic-Americans. This is interesting, as African-Americans were least likely as an ethnic group to have PLMS, but when PLMS did occur, it seemed to have a larger effect on blood pressure than in other ethnicities. The lower prevalence of PLMS in African-Americans has previously been reported [92].

In a separate population study of elderly men, PLMS were not associated with incident hypertension; rather, PLMS were associated with a composite outcome, the incidence of coronary heart disease, cerebrovascular disease, and peripheral arterial disease. Associations were strongest for those who had a PLMI ≥ 30 or a periodic limb movement arousal index (PLMAI) ≥ 5 , especially for peripheral arterial disease and coronary heart disease. Individuals in these high categories of PLMS had an approximately 25% increased hazard ratio for incident coronary heart disease and a near doubling of peripheral arterial disease incidence [23]. Furthermore, there was an interesting interaction between the PLM indices and prevalent hypertension, whereby the frequency of PLMS

only differentiated cardiovascular event rates in persons without prevalent hypertension. In those without hypertension, the high PLMS index categories, compared with the referent low index categories, were associated with a significant 74–89% increased odds of the composite incident cardiovascular outcome, whereas the event rate was the same for those in different PLM groups with prevalent hypertension.

In summary, these findings argue for a possible association between PLMS and hypertension as well as cardiovascular disease. While these findings are interesting, they do not show causality. Further studies investigating whether PLMS are associated with entities that may mediate such associations should be carried out. Such mediating factors could be insulin resistance and diabetes, increased cholesterol, or instability in breathing.

Further research is needed to clearly determine the clinical significance of PLMS. As reported above, PLMS are commonly found in RLS and PLMD, but also in a number of different sleep disorders (sleep apnea, REM sleep behavior disorder, and more) [12], are related to increased cardiovascular risk [23,101-103,107], are associated with insomnia symptoms [69,92] and, in children, may be a predictor of developing RLS [108]. Periodic leg movements during sleep are embedded in a general sleep instability pattern [86], and dopamine agonists are very effective in suppressing limb movements, but benzodiazepines are more effective for the associated sleep disturbance in patients with RLS [54]. Treatment parameters and outcomes have not been adequately defined, so far; thus, no definite evidence is available that treating PLMS either changes cardiovascular risk or improves sleep; however, treating PLMS based on a clinical judgment may help on a case-to-case basis, but should always be followed up to ascertain improvement.

Pediatric PLMS

In children and adolescents, PLMS have been found to occur more frequently in RLS, OSA, narcolepsy, and iron deficiency than in control groups [109-118]. More limited data suggest increased rates in pediatric nocturnal enuresis [119-121], REM sleep behavior disorder [122], migraine [112,123,124], seizures [112,125], sickle cell disease [126], and Williams syndrome [127]. There is discordant data for ADHD [112,128-133] and autism [112,134,135]. Based on single-night polysomnography for pediatric RLS, PLMS >5/hour have been found in 63-74% of cases

[109-111]. The diagnostic criteria for periodic limb movement disorder (PLMD) in children include PLMS >5/hour and clinically significant sleep disturbance [97]. This entity has been described more extensively in children than in adults and, in many cases, may antedate the development of RLS [108,109,136].

There are substantial PLMS normative data for children aged 5–17 years, less for ages 2–5 years, and very little for infants and children aged <2 years. The largest study assessed 195 healthy, non-snoring 5–17-year-old children and adolescents; it found a median PLMS index of 0/hour and support for a clinical cutoff of 5/hour [94], which has also been found in multiple smaller studies [41,95,99,100,117,130,137]. For children aged 2–5 years, some data support the 5/hour cutoff [99,100], while another study has indicated a slightly higher cutoff [95]. However, PLMS during REM sleep, which are unusual in older children and adults, significantly contributed to the increase in the latter study [95]. Interestingly, PLMS normative data in the 3–5 year age range have been found to be increased at high altitude (mean 10.1/hour) [96].

Polysomnographic characteristics of pediatric PLMS have been examined in a limited number of studies. In contrast to adults with RLS, small cohorts of children and adolescents with RLS [68], ADHD [138], sickle cell disease [139], or a past history of iron deficiency [117] have not shown high periodicity or clear decrement of PLMS activity over the night. Although PLMS indices in these groups are elevated, low periodicity leg movements appear to be typical. However, as in adults with RLS, night-to-night variability of PLMS is prominent [13,139]. Also, children show blood pressure spikes in association with PLMS, as seen in adults [140].

Limited work has explored the response to treatment of pediatric PLMS. Case series with subjective outcome measures have indicated responsiveness to dopaminergic medications [109,136]. However, only three pediatric studies have used objective outcomes for PLMS. Oral iron given open-label was found to reduce the mean polysomnogram PLMS index from 27.6 to 12.6/hour, which was coincident with a rise in serum ferritin from 40.8 to 74.1 mcg/L [116]. In a randomized, blinded study, the polysomnogram PLMS index fell from 9.0 to 3.2/hour with the use of levodopa [141]. In an open-label study using the rotigotine patch, the PAM-RL ankle accelerometry derived PLMS index fell significantly by 1 mg/24 hour and 3 mg/24 hour dosages [142]. As in adults, PLMS in children can be exacerbated by serotonergic medications [79-81].

Considerable research is needed to determine the clinical significance, if any, of pediatric PLMS. Given the low prevalence of PLMS >5/hour in normal children and adolescents, PLMS have the potential to act as a biomarker for pediatric RLS and future development of RLS, particularly in young children and children with delayed language skills. However, polysomnography is expensive and impractical, especially if night-to-night variability and treatment response are to be assessed. Validated actigraphic and/or video devices would greatly enhance pediatric PLMS research opportunities. In addition, further data on the clinical significance, time structure, associated conditions, associated genetic markers, and treatment response of pediatric PLMS are clearly needed.

Conclusions and research agenda

The study of PLMS is a highly active research field and the present review has summarized some key aspects of recent developments. As it is apparent from all sub-chapters, and despite recent advances, there is a need for further investigation, particularly in populations without RLS. There is a real need to assess the clinical significance of PLMS. This can be done by precisely defining time structure, examining associations with other physiologic systems, including those that affect breathing and circulation, and by studying this motor phenomenon in those least affected by disease – children.

More studies are needed that:

- characterize the time structure of periodic and non-periodic LMs in subjects without RLS
- investigate non-periodic leg movement activity
- explore the clinical significance and characterization of respiratory event-related LMs
- investigate the complex relationship, including possible interactions between the different oscillatory processes during sleep at the level of arousal, movement, and autonomic system activity
- continue to characterize the association of PLMS with cardiovascular outcomes and cardiovascular risk factors in different populations

- assess whether or not these motoric phenomena should be treated in particular circumstances
- address the clinical significance and age-specific features of pediatric PLMS.
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Periodic leg movements during sleep, which have been entwined with RLS for a long time, are well underway to be established as an independent, clinically significant concern.

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Table 1. Scoring of periodic leg movements according to the guidelines of the WASM/IRLSSG ² and the AASM^{1,32}.

	WASM/IRLSSG	AASM
<i>Definition of leg movement</i>		
Onset	EMG increase $\geq 8 \mu\text{V}$ above the resting baseline	
Offset	EMG decrease to $< 2 \mu\text{V}$ above the resting level for $\geq 0.5 \text{ s}$	
Duration	time between onset and offset 0.5–10 s	
<i>Scoring of periodic leg movements</i>		
Intermovement interval (IMI)	onset-to-onset: 5–90 s	
Number of leg movements	≥ 4	
IMI $> 90 \text{ s}$	PLM series ends	
IMI $< 5 \text{ s}$	PLM series goes on, LM with IMI $< 5 \text{ s}$ is disregarded	<i>Not specified</i>
Sleep/Wake	All LMs form PLM series For PLMS, only those during sleep are counted	Only LMs during sleep form PLM series
Bilateral leg movements	offset-to-onset $< 0.5 \text{ s}$	onset-to-onset $< 5 \text{ s}$
Respiratory-related leg movements (RRLM)	Excluded from PLM series	

RRLM definition	Any leg movement occurring within: ± 0.5 s around the ending of an apnea/hypopnea event	Any leg movement occurring within: 0.5 s before the start to 0.5 s after the end of an apnea, hypopnea, respiratory effort related arousal or sleep-disordered breathing event
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Fig. 1. Classification of nocturnal leg movement activity according to current rules.

IMI, inter-movement interval; LM, leg movement

Fig. 2. The different patterns of the PLMS index, Periodicity index, inter-LM interval distribution, and night distribution of PLMS in different groups of adult controls and patients (reprinted with permission from [12]).