



## Periodic limb movements during sleep: a narrative review

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**Objective:** Using narrative review techniques, this paper evaluates the evidence for separable underlying patho-mechanisms of periodic limb movements (PLMs) to separable PLM motor patterns and phenotypes, in order to elucidate potential new treatment modalities.

**Background:** Periodic limb movement disorder (PLMD) is estimated to occur in 5–8% of the paediatric population and 4–11% of the general adult population. Due to significant sleep fragmentation, PLMD can lead to functional impairment, including hyperactivity and delayed language development in children, and poor concentration and work performance in adults. Longitudinal data demonstrate that those with PLMD are at greater risk of depression and anxiety, and a 4-fold greater risk of developing dementia. PLMD has been extensively studied over the past two decades, and several key insights into the genetic, pathophysiological, and neural correlates have been proposed. Amongst these proposals is the concept of separable PLM phenotypes, proposed on the basis of nocturnal features such as the ratio of limb movements and distribution throughout the night. PLM phenotype and presentation, however, varies significantly depending on the scoring utilized and the nocturnal features examined, across age, and co-morbid clinical conditions. Furthermore, associations between these phenotypes with major neurologic and psychiatric disorders remain controversial.

**Methods:** In order to elucidate potential divergent biological pathways that may help clarify important new treatment modalities, this paper utilizes narrative review and evaluates the evidence linking PLM motor patterns and phenotypes with hypothesised underlying patho-mechanisms. Distinctive, underlying patho-mechanisms include: a pure motor mechanism originating in the spinal cord, iron deficiency, dopamine system dysfunction, thalamic glutamatergic hyperactivity, and a more cortical-subcortical interplay. In support of the latter hypothesis, PLM rhythmicity appears tightly linked to the microarchitecture of sleep, not dissimilarly to the apnoeic/hypopnoeic events seen in obstructive sleep apnea (OSA).

**Conclusions:** This review closes with a proposal for greater investigation into the identification of potential, divergent biological pathways. To do so would require prospective, multimodal imaging clinical studies which may delineate differential responses to treatment in restless legs syndrome (RLS) without PLMS and PLMS without RLS. This could pave the way toward important new treatment modalities.

**Keywords:** Periodic limb movements (PLMs); sleep; periodic limb movement phenotype (PLM phenotype)

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## Introduction

Periodic limb movements during sleep (PLMS) are involuntary, sleep-related phenomena characterized by periodic episodes of repetitive, stereotypical movements of the limbs (1-3). Lower extremities are commonly affected, with typical dorsiflexion of toes and ankles consistently reported, resembling the spinal flexor-reflex (Babinski sign), along with occasional flexion of the hip and knee. The involvement of upper limbs or other parts of the body is much less commonly recorded (4). PLMS are found in up to 80% of restless legs syndrome (RLS) cases (5), which are experienced as an unpleasant urge to move along with paresthesia- a burning or pricking sensation felt in the arms, legs or feet during periods of rest or inactivity (6). However, a much smaller percentage of patients with a polysomnographic (PSG) evidence of PLMS (22.5%) are found to have a comorbid RLS (4,7). PLMS are frequently comorbid with other sleep disorders, a variety of medical conditions (e.g., congestive heart failure, diabetes, migraine (8), cardiovascular, hepatic and renal disease, alcohol dependence, syringomyelia), and several major neurologic and psychiatric disorders (9). They can be triggered by medications and psychoactive substances, such as antidepressants and lithium (10), and they commonly increase with age, even without a comorbid sleep disorder (11). Movements similar to PLMS have been captured with polysomnography during nocturnal wakefulness (PLMW).

The diagnosis of periodic limb movement disorder (PLMD) is a diagnosis of exclusion according to the International Classification of Sleep Disorders Third Edition (ICSD-3) (12). In order for PLMD to be established, other sleep disorders associated with PLMS need to be excluded: namely the RLS (2,13), narcolepsy (14), REM sleep behavior disorder (RBD), and sleep-related breathing disorder (15). Moreover, PLMS should be linked to sleep complaints or/and daytime impairment (2,12,13,16).

Recent developments in the field of sleep medicine have changed our understanding of the impact of periodic motor activity on the microstructure and macrostructure of sleep

and their effect on daytime functioning (17), including the modulation of the autonomic system and inflammation (18-20). As mentioned, PLMS have also been associated with significant cardiovascular and cerebrovascular risks (21,22), likely due to associated sympathetic overactivity that can lead to surges in nocturnal blood pressure (BP) and heart rate (HR) without appropriate modification of the global autonomic balance (23).

Taken together, the relevant evidence summarized in this narrative review showcases accelerating research over the last two decades. The presented evidence increasingly posits that PLMS present a distinct sleep phenomenon with separate, if yet not fully delineated, physiopathology (11,24).

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/jtd-21-1353>).

## Scoring of PLMS

Pathological PLMS are detected when their index is higher than five distinct PLM events recorded per hour of sleep. This cut-off has been extensively used in correlation studies with sleep complaints and other medical conditions, though several studies have shown that healthy subjects without sleep disorders may score above 10 e/h (25,26). Based on epidemiological studies, ICSD-3 has set the PLMI cut-off to >15/h in adults and >5/h in children (*Table 1*) when a diagnosis of PLMD is considered (35). As a diagnosis of exclusion, the reported sleep disturbance or functional impairment should not be better explained by another medical or mental condition (16). Identifying PLMS can be challenging in clinical practice, given that they are also associated with primary motor disorders and sleep-related breathing disorders during associated respiratory events and arousals (13,34,36).

Two similar sets of updated scoring rules are currently available. The first, proposed by the World Association of Sleep Medicine (WASM), is a product of a joint task force from the International and European Restless Legs Syndrome Study group (IRLSSG and EURLSSG), and

**Table 1** Major polysomnographic parameters for PLMS

Traditional measures	Description	Measurement notes/proposed measures	Strengths	Limitations
PLMI	The number of PLMS per hour of sleep time (total number of PLMS/total sleep time, PLMS/h) (16). The criteria for the diagnosis of PLMD is PLMI >15/h, in adults and PLMI >5/h in children (16). The above PLMI cut-off for the diagnosis of PLMD in adults has been questioned as arbitrary (27)	Measurement notes: AASM criteria: $\geq 4$ consecutive LM, each lasting 0.5–5 s, with 8 $\mu\text{V}$ above resting EMG, and an inter-movement interval >5 s and $\leq 90$ s (16). WASM criteria: $\geq 4$ consecutive LM, each lasting 0.5–10 s ( $-15$ s for bilateral movements), with 8 $\mu\text{V}$ above resting EMG, and an inter-movement interval >10 s and $\leq 90$ s. The PLM series is stopped when a LM with an interval of <10 s intervenes (28). PSG also calculates and reports PLMW, as PLMW per hours per wake time (PLMW/h) (16)	Easy to produce. Widely used in clinical practice and research studies. Linked to CVD (29)	High night-to-night variability (30). Fails to characterise the basic periodicity of the movements which is a cardinal feature of the condition (30). Fails to correlate with the clinical symptoms (31)
PLMIar	The number of PLMS that are associated with an arousal per hour of sleep	Measurement notes: an arousal and a leg movement are associated with each other when there is a maximum of 0.5 s duration between them irrespective of which one comes first (16)	Easy to produce. Linked to increased risk of CVD in patients with PLMS (32,33) caution when there is comorbid OSA	Same with PLMI. Scoring needs due to possible interaction. Please also refer to the main text (28,34)
PI	Ratio of the number of LM that fulfill criteria for PLMS to the total number of LM (PLMS/LM) (28). Same ratio can be generated for PLM during wakefulness, PLMW/LMW (28)	Proposed measures: it ranges from 0 (no periodicity, to 1 (all intervals within the predetermined length, i.e., > 10 s to $\leq 90$ s for the WASM and >5 s to $\leq 90$ s for the AASM group (16,28)	PI has a significantly lower night-to-night variability compared to the PLMI (17). Data support a clinical importance with highest PI in RLS with daytime symptoms compared to controls, narcolepsy REM behavior disorder, and Parkinson's disease (28)	Night-to-night variability captured does not capture the intrinsic periodicity of PLMS (28,34). A minimum amount of LM overnight of approximately 10/h is required for accurate computation of PI. This limits the measurement of PI in controls for comparison reasons (17)
IMI	IMI is defined as the time between onsets of 2 consecutive LMs that are part of PLMS (28)	Proposed measures: time between events ranges from >10 s to $\leq 90$ s for the WASM and >5 s to $\leq 90$ s for the AASM group (16,28). The IMI approximates a log-normal distribution and considers putative biological process that causes periodicity in PLMS (28)	IMI night-to-night variability is significantly lower than that of the PLMI and PI. Log IMI is superior to IMI with significantly lower night-to-night variability (4–8% change) in RLS and controls (30). Log IMI is independent of the number of LM and current disease state. It is proposed as a marker to characterise disease state and sleep status along with the PLMI (30). IMI may have the potential to express intrinsic or inherent periodicity of PLMS	Limited studies available

PLMS, periodic limb movements during sleep; PLMD, periodic limb movement disorder; LM, leg movement; PLMI, periodic limb movement index; PLMIar, periodic limb movement arousal index; PI, periodicity index; IMI, inter-movement intervals; PLMW, periodic limb movement during wake; AASM, American Academy of Sleep Medicine; WASM, World Association of Sleep Medicine; EMG, electromyogram; PSG, polysomnographic; CVD, cardiovascular disease; RLS, restless legs syndrome; REM, rapid eye movement; OSA, obstructive sleep apnea.

the second is issued by the American Academy of Sleep Medicine (AASM) (28,35) (please refer to *Table 1* for in-depth list).

The AASM scoring criteria require that limb movements (LM) must occur in a series of at least four consecutive LM lasting 0.5–5 seconds each, with an amplitude of 8  $\mu$ V above resting electromyogram (EMG), with an inter-movement interval (both for monolateral and unilateral LM) between  $\geq 5$  s and  $\leq 90$  s to count as PLMS (35). By contrast, WASM criteria scores LM (called candidate leg movements, CLM) that may last longer, 0.5–10 s, for monolateral CLM, and 0.5–15 s for bilateral, keeps the same requirement of at least 4 consecutive CLM, and with an inter movement interval adjusted to  $\geq 10$  s and  $\leq 90$  s (both for monolateral and unilateral CLM), without any CLM preceded by an interval of  $< 10$  s interrupting the PLM series. The increase in the maximum duration of the CLM is proportionally increasing the inter-movement interval, to at least 10 s, which is found to characterize these PLMS that respond to dopaminergic treatment (37). It also reduces the number of leg movements that count as PLMW due to expected reduced periodicity of the movements during wakefulness (28) (*Table 1*).

Both AASM and WASM rules recommend that any LM occurring within 0.5 s of any type of a respiratory event to be scored as respiratory event-related LM and be excluded from the PLMI. Although both criteria are detailed, their definitions have been critiqued as possibly underestimating that number (28,35). Based on the results of a well designed study, the WASM group allows the extension of the time brackets to 2 s before and 10.25 s after a respiratory event, but cautions the reader that the study is yet to be replicated and was performed on a limited type of respiratory events (28,34) (*Table 1*).

The number of arousals related to PLMS (i.e., PLMIar) is an integral part of the polysomnographic report. It may be seen as a marker of sleep fragmentation, but several studies have failed to link the PLMIar with the severity of the reported sleep complaints nor with subjective or objective sleepiness. It is worth mentioning that almost a third of the PLMS are not associated with an EEG-arousal, and in 40% to 50% of the PLMS, the arousal precedes the onset of the motor event, which makes it difficult to maintain that the leg movement directly provokes the cortical arousal (38,39). The importance of PLMIar appears to lie more in relation to the increased hazard (5–26%) for cardiovascular events (CVE) seen in patients with PLMS (32,33).

## PLMS phenotypes

A number of studies over the last two decades have facilitated the identification of the phenotype of “genuine PLM” (18). Genuine PLM [inclusive of PLM during sleep (PLMS) and PLMW] comprise of two consistent features: approximately 20–40 s peaks in the inter-movement-interval (IMI) histogram, followed by a decline in frequency as the night progresses (40). These have consistently been observed in RLS (41–43), PLMD (27) and various other conditions, albeit with varying degrees of periodicity (44). The IMI of LM activity shows bimodal distribution in RLS with the first peak between two to four seconds and the second between 20–40 s (43). The second peak represents the periodic LM (42). These lognormal distributions intersect at ten seconds, which forms the lower threshold for genuine periodic peak with an established range between 10 s and 90 s (45) (*Table 1*).

Genuine PLMS can be computed using the periodicity index (PI), which is an independent measure of periodicity, and is defined as the ratio of the number of sequences with an inter-LM interval between 10 and 90 seconds/total number of inter-LM intervals (43). At least four consecutive LMs are required fulfilling the predetermined IMI interval to form PLMs, and theoretically, PI is scored as either 0 or 1, with conditions classified based on either complete absence or complete periodicity of interval lengths ranging between 10 s and 90 s (42,43) (*Table 1*).

Secondly, PLMS distribution throughout the night and inter-night variability also form their distinct phenotype (18). In RLS patients, PLMS are commonly recorded between 11 PM and 3 AM, predominantly in the first half of sleep (46), with a clear decline in PLMS from the beginning to the end of sleep cycles (27). Traditionally, this has been taken to suggest that PLMS in RLS follow a circadian distribution, correlated with levels of endogenous dopamine throughout the night (47). It remains unclear if this also causes inter-night variability in PLMS (18). Characterizing the PLMS phenotype is crucial to understanding the mechanisms underlying differences in LM activity and presentations in clinical cohorts (18). For instance, only genuine PLMS respond to treatment with dopaminergic agonists (48,49), and not the PLMW that tend to have a shorter IMI (50) (*Table 1*).

In keeping, several studies that monitored three independent parameters (i.e., PLMI, PI and time of the night LM distribution) in different clinical cohorts (27,37,51) during investigations of treatment efficacies



(52,53) indicate that the degree of PLMS periodicity expression varies significantly across clinical subgroups (18). This variability likely arises due to significant differences in genetic predisposition for PLMS (52,54,55).

The mean log IMI has shown the lowest night-to-night variability, compared to the PLMI, the PI and the mean MI (30). It is independent of the number of leg events at night, and reflects on the intrinsic periodicity of the PLMS, with changes over time believed to reflect individual changes (*Table 1*).

### *Paediatric phenotypes*

Predictably, there is marked variability in scoring criteria for PLMS in children, depending on the age group (18). Periodicity is a rare phenomenon in paediatric PLMS (27,42), which impacts the interpretation, but can be rectified by altering the diagnostic criteria to fit normative cut-offs (18). For example, the diagnostic criterion for ages five to 18 years is  $>5/h$  (56), whilst the criterion for children between ages two to five years is the same in some studies (57), and higher in others (58,59). Some studies indicate an increased PLMI score (up to 10.1/h) in children between ages 3–5 and living at higher altitudes (60).

### *Distribution during sleep*

PLMS commonly start during the non-rapid eye movement (NREM) stage N1, are predominant in N2, and less frequent in N3. PLMS are generally absent during REM, with exception of patients with REM behavior disorder, where PLMS are commonly recorded during REM (61,62). Historically, the association of PLMS to stages N1 and N2 has been argued to be due to the significant link (up to 92% of the PLMS) with the cyclic alternating pattern (CAP), especially with its fast activity subtypes (A2 and A3) (63). Gradual loss of cortical control with concomitant increase in arousal threshold from N1 to N3 coincides with the emergence of a major background oscillatory arousal mechanism, the CAP (64). It has been further argued that in patients with PLMS functional changes in cortico-subcortical-spinal networks involved in generating locomotion may induce these motor patterns (64).

There are two major nocturnal patterns of PLMS. One starts shortly after sleep onset and dominates initial sleep cycles, influenced by circadian, as well as homeostatic influences (65), and a second type, where PLMS are more evenly distributed throughout the sleep cycles, with a

predominant peak commonly occurring in the middle cycles of sleep. Of note is that, in both patterns, the PLMI can vary significantly between consecutive nights (17,65,66). Anecdotally, it has long been acknowledged that certain body positions in susceptible individuals may also affect the genesis of PLMS. For example, in a recently published case, the generation of PLMS occurred only during the time when patient was lying in a particular position (67). The authors hypothesized that changes in body position may act to generate a deep and complex proprioceptive tactile sensory input strong enough to activate the central pattern generators linked to PLMS (68,69).

### **Epidemiology**

PLMD is estimated to occur in four to eleven % of the general adult population (25,70–72), with age presenting an important risk factor (*Table 2*). As discussed previously, to date, PLMD remains a diagnosis of exclusion, and hence, most existing published studies predominantly focus on capturing the prevalence of PLMS ( $\geq 15$  e/h) in the community, rather than prevalence of PLMD itself (61,89,91,92). Several major studies, the Wisconsin sleep cohort (WSC) from the US (91), the HypnoLaus from Switzerland (61) and the SHIP-TREND/BiDirect from Germany (89), reported similar prevalence and mean age at baseline, with 28.8%, 28.6% and 33.3% of the participants presenting with a PLMI  $>15$ /hour with a baseline mean age of 56.1 years, 58.4 years and close to 54 years respectively. The Osteoporotic Fractures in Men (MrOS) study from US, which included only men of older age (76.5 years) showed prevalence of PLMI  $>15$ /hour at 61% (92). Prevalence also significantly differs across ethnic groups. In a younger group (mean age 41.9 years) of 592 adult participants in tri-county Detroit, prevalence of PLMI  $>15$ /hour was 7.6% overall, and lower in African Americans (4.3% versus 9.3% in Caucasian) (7). Similarly, even that up to 80% of RLS patients are reported with increased PLMS (5,21), this also significantly differs between various ethnic and genetic group (93). The first large-scale RLS Asian population study demonstrated two significant differences in PLMS expression: (I) lower prevalence of only 42.3%, and (II) evidence that lower prevalence rates could be due to underlying differences in genetic expressions (93). However, LM periodicity and time structure characteristics did not vary across ethnicities (93).

To date, the data regarding gender-related differences for PLMS or PLMD remain conflicting, especially when

**Table 2** Risk factors for PLMS/PLMD

Risk factor	Reference
Older age	(61,73)
Drugs	
Dopamine-receptor antagonists	(74-76)
Lithium	(10,77)
Antidepressant (SSRIs, TCA, SNRIs)	(10,61,77,78)
Hypnotics	(79)
Anticonvulsants	(77)
Other conditions	
Restless legs syndrome	(61,73,80)
Heart disease	(79,81)
Musculoskeletal disease	(79)
Narcolepsy with cataplexy	(79)
Chronic kidney disease	(61,81,82)
Pregnancy	(83)
Magnesium deficiency	(84)
Neuropsychiatric and neurodegenerative disorders	(85)
Iron deficiency	(86-88)
Diabetes	(61,89)
Increased caffeine consumption ( $\geq$ six cups/day)	(79)
Stress	(79)
Snoring	(79)
Habits	
Physical inactivity	(89,90)
High BMI	(61,89,90)
Doing physical activities close to bedtime	(79)
Being a shift or night worker	(79)

PLMS, periodic limb movements during sleep; PLMD, periodic limb movement disorder; SSRIs, selective-serotonin reuptake inhibitors; TCA, tricyclic anti-depressants; SNRIs, serotonin and norepinephrine reuptake inhibitors; BMI, body mass index.

polysomnography-based studies are considered (18). During pregnancy, though, and likely related to iron deficiency, there is a peak in the prevalence of RLS and PLMI  $>15$ /hour up to 25% (83).

### Prevalence in children

The prevalence of a pathologically increased PLMI in children, which is set at above five events per hour, ranges between 5.6% and 8% in community-based studies (56). There is no data yet

about the prevalence of PLMD in the community, with 14% prevalence reported in a pediatric sleep clinic population (94). PLMS commonly appear to precede the development of RLS in children (95,96) and they are more prominent in Caucasian children with sleep disordered breathing, than in African American children (97). A large-scale study reported 25.6% of children with growing pain exhibited a PLMI  $>5$ /h compared with 10.2% of children without growing pain, suggesting that growing pain could be a part of the pediatric phenotypic spectrum (98).

### Associated psychiatric and neurologic disorders

Theoretically, PLMS may cause significant sleep fragmentation and lead to functional impairment (18,99) through their disturbance of underlying sleep rhythms and their intrinsic functions. Unsurprisingly, patients with PLMD indeed commonly report a non-restorative sleep, excessive daytime sleepiness, poor concentration and work performances (95). In children, delayed language development and behavior problems such as increased irritability, hyperexcitability, hyperactivity, inattention, aggressiveness and social withdrawal (57), oppositional behaviors (100), and mood disorders such as anxiety and depression have all been reported (99).

Paediatric PLMD commonly presents co-morbid with the attention deficit hyperactivity disorder (ADHD). It has been suggested that up to 26–64% children with ADHD may meet PLMD diagnosis, and reciprocally, that up to 91% pediatric PLMD cases meet ADHD diagnosis (101,102). The PLM-related sleep fragmentation similarly appears to be linked to the hyperactivity behavior, with significantly more PLMS linked to an arousal in the PLMD-ADHD children group compared to the PLMD without comorbidities (102). Overall, the consensus is that, in children, PLMS may trigger or worsen the symptoms of ADHD (103). Moreover, in vulnerable and susceptible children, they may increase the likelihood of nightmares, difficulty in sleep initiation, as well as increase the risk of monosymptomatic and refractory enuresis (104).

In keeping with many other sleep disorders (105), PLMD and RLS share bidirectional links with several major psychiatric and neurologic disorders (106). Both are commonly diagnosed sleep comorbidities in numerous neurologic and neurodegenerative diseases (85) including alpha-synucleinopathies (62), Alzheimer's disease (107), multiple sclerosis (108), multiple system atrophy (109), corticobasal degeneration (76) and amyotrophic lateral

sclerosis (110), spinal cord injury (111), Gilles de la Tourette syndrome (112,113), stroke (114), and several functional disorders including chronic pain (115), chronic fatigue (116) and fibromyalgia (117). However, the mechanisms underlying those links are far from clear (118). Several studies have illustrated structural and functional alterations in distinct brain regions of the patients, with similar areas reported in animal models with RLS/PLMD, but no unifying mechanism has yet been identified (119).

A recent retrospective longitudinal study, conducted using the national health insurance research database in Taiwan, reported four major findings: (I) sleep-related movement disorders increased the risk of developing all-cause dementia by four times, (II) patients aged 45–64 years had higher associated risk, (III) women were more susceptible than men and (IV) dementia risk was time-dependent and increased progressively over time (107). In keeping, frequent PLMS have also been independently associated with cognitive decline, with largest effects on the cognitive domain of executive function among older men, even in the absence of an overt diagnosis of dementia (120). In the same vein, prevalence studies of PLMS in Parkinson's disease (PD) confirm an increased prevalence of PLMD in PD (121,122). Limited pathophysiologic evidence suggests nigrostriatal degeneration, along with a reduced striatal dopamine transporter binding in PD patients with PLMS, as a shared pathophysiological basis for both disorders (123).

A small number of studies have over the years examined the link between PLMS and other neurologic disorders, and the links with multiple sclerosis have been amongst those most studied. MS patients with PLMS have been shown to have a significantly higher disability (124). Prevalence of 32.5%, of increased PLMI >15/h has been suggested in one study of MS patients (125). A disinhibition of the lower spinal network due to cervical or supraspinal MS lesions has been proposed as one of the possible underlying mechanisms (125). Yet another study suggested a 12% prevalence of PLMI >21/h in patient with MS (126). Critically, patients with MS may experience PLMS during REM, which arguably may explain a greater likelihood of disability noted (124).

The data linking adult PLMD and psychiatric disorders is potentially even more conflicting. For example, in a recent cross-sectional study of idiopathic RLS patients, presence of PLMS did not reflect on quality of life (127). In addition, lack of PLMS was found to be associated with significantly higher depression and anxiety among RLS patients, and RLS patients without PLMS had distinct PSG

parameters such as lower total arousal index, longer latency to REM, and a higher spontaneous arousal frequency than RLS patients with PLMS (127). The authors argued that high prevalence of RLS without PLMS in their carefully characterized clinical sample questions the presumed shared pathomechanism between RLS and PLMS for a substantial portion of RLS patients. Moreover, the authors of the study argued that their findings may be taken to suggest separate neuromechanisms at play. Another distinct finding in this study was the high prevalence (65.1%) of clinically significant depression in the RLS patients who did not have co-morbid PLMS (127). Previous reports also go some way to support this notion, with patients with RLS and without PLMS reported to have higher rates of psychiatric comorbidities and higher risk for clinical depression (127,128). Of note, patients with RLS without PLMS have been shown to be treatment-resistant to dopaminergic therapy (128). Interestingly, another Korean study reported significantly more severe anxiety and depressive symptoms in RLS patients with lower PLMI (129). In keeping, another study that compared neuropsychiatric symptoms in patients with PLMD to those with RLS highlighted a higher psychosomatic burden in the RLS patients (130). In this study, RLS patients also showed a higher somatization burden (130). Future prospective studies should closely examine whether PLMS status has any bearing on the pain-depression-anxiety relationship in RLS, and whether it independently predisposes for any distinct neurologic or psychiatric phenotype.

### Risk factors

Amongst recognized risk factors (*Table 2*), age, male gender and RLS have all been recorded as independent risk factors for PLMS in adults (PLMI >15/h) in community-based studies (61,73,80). The impact of lifestyle-related factors on PLMS exacerbation, on the other hand, remains controversial. Physical inactivity has been linked to higher PLMI and vice versa (89,90). Moreover, two small-scale studies in PLMD patients reported a reduction in PLMI following a single session of maximum effort physical training (131,132) and an increase in  $\beta$ -endorphin values (132). Such studies suggest the involvement of the opioid system, albeit large-scale epidemiologic and intervention studies are needed. Data on smoking habit and PLMS remain controversial (133).

Several psychotropic medications have been linked to PLMI above 15 events per hour (78). For example, whilst

dopamine-receptor antagonists, anticonvulsants, and lithium can potentially precipitate PLMS symptoms, it is typically the antidepressants, including selective-serotonin reuptake inhibitors (SSRIs; including sertraline), tricyclic anti-depressants (TCA; e.g., amitriptyline), and serotonin and norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine and mirtazapine) which have been linked to pharmacologically induced PLMs (77). However, several antidepressants have been identified that do not appear to precipitate PLMs and are hence clinically recommended in affected or vulnerable patients, namely trazodone, bupropion (134), nefazodone and doxepin (10,135).

Serum ferritin has been the focus of several studies with controversial results likely reflecting different phenotypes (89,136). However, iron supplementation remains a part of the treatment pathway in patients with RLS/PLMD and with serum ferritin levels at the lower end of normal range (137). Studies on magnesium ( $Mg^{++}$ ) and PLMS are rare, with one community based study supporting low levels as an independent determinant of PLMI  $>15/h$ , and a small interventional study showing reduction in the PLMI in patients with RLS or insomnia (84).

Chronic kidney disease (CKD) and renal failure have been similarly linked with RLS and PLMS (81,82). Diabetes has also been reported as potential risk factors for PLMI  $>15/h$ , however, this relationship weakens when adjusting for other confounding factors is done (61,89). Although PLMS and obstructive sleep apnea (OSA) may commonly coexist, community-based studies have to date failed to detect any overt relationship between PLMI and AHI (61,80).

### Pathomechanisms

The mechanistic framework that underlies PLMS pathophysiology and aetiology is far from clearly defined. Over the years, three major anatomical loci have been similarly fervently argued as the potential *locus minoris resistentiae*: a neocortical, subcortical and the spinal cord. The hyperexcitability of spinal flexor pathways, especially during NREM sleep, could arguably link to increased PLMS, with dopamine deficiency triggering these pathways in some susceptible individuals (1). Nonetheless, EEG, autonomic and sympathetic cortical activations following PLMS are a well-established finding. However, the data on whether similar activations reliably precede all the PLMS remains contradictory. Post PLMS cortical activation has been reported in the alpha and beta EEG bands, with increased heart rate and systolic and diastolic blood pressure

too (138-140). Other studies have shown an increase in EEG activity in the delta band and HR seconds before the leg movement (141-143). Conversely, these findings have been taken by some clinicians to suggest that the PLMS are simply the motor manifestation of an increased sympathetic/autonomic status. Interestingly, when cortical arousals and PLMS are iatrogenically disconnected by benzodiazepine intake, this minimizes the EEG activation but it does not appear to affect the PLMS (144,145). Conversely, dopamine agonists have been reported to have the opposite effect (144,145). Two distinctive underlying pathomechanisms have been argued in that background: a pure motor, and possible originating in the spinal cord, and a more cortical-subcortical interplay. In putative support of the latter hypothesis, it has been shown that the PLMS rhythmicity appears tightly linked to the microarchitecture of sleep, and its CAP periodicity, not dissimilarly to the apnoeic/hypopnoeic events in OSA (146). Moreover, PLMS are rarely recorded during the B phase of CAP, a period of a low EEG activation which does not appear to support the emergence of PLMS, which are instead typically confined to CAP's A phases.

PLMS are, however, less stereotyped than previously believed, with individual variations recorded widely in motor patterns, muscle sequence activation and the groups of muscles involved (17,147). PLMS commonly occur either on one leg or they can as easily alternate between the two limbs (10). According to the EMG activity the distinct motor patterns in PLMS may include: (I) tonic activity lasting several hundreds of milliseconds followed by myoclonic activity, (II) an initial myoclonic jerk followed by tonic activity, (III) several clusters of myoclonic jerks sometimes followed by tonic activity (148).

Typically, PLMS are most prominent in the tibialis anterior (TA) muscle (75%) and therefore are primarily recorded there during clinical investigations (96). Other activated muscle groups include gastrocnemius (60%), biceps femoris (55%), and rectus femoris (40%) (149), and less frequently their antagonistic muscles groups (21). Upper limb muscles are infrequently involved, and axial muscles even less frequently (18). On EMG, 53% of the PLMS initiate in the TA, 18% in the gastrocnemius, 13% in the biceps femoris and 7% in the rectus femoris muscle groups respectively (149). Several groups have argued that based on this anatomical distribution, TA muscle activity likely falls under the category of "central pattern generators" (CPG), and that this spread of PLMS activity may reflect a subcortical origin of PLMS. Furthermore,



it has been argued that this asynchronous activations of the leg muscles with partially or totally disconnected supratentorial and spinal structures (39,150,151) may theoretically suggest the possibility of two distinctly independent spinal pattern generators (one on either side of the body) which integrate to form a more complex mechanism, sharing anatomical as well as functional pathways. Accordingly, multiple supraspinal mechanisms that can work in a coordinated manner have been identified thus far (152). The descending supraspinal mechanisms have further been implicated in modulating PLMS, which according to this hypothesis, could initially arise from the brainstem reticular system (7). An indirect evidence from a transcranial direct-current stimulation (tDCS) study in RLS patients suggest that the periodicity of PLMS arises due to spinal motor and brainstem hyperexcitability (153). Some imaging studies, on the other hand, have been potentially taken to implicate the role of the sympathetic nervous system and the red nucleus of the brain stem in triggering PLMS (154). Synchronization of large-scale cortical motor neurocircuitry comprising pericentral, dorsolateral, prefrontal and cingulate regions of the brain has been recorded in delta band prior to motor demonstration of PLMS (155). In addition, activity in those areas and the default mode network, appeared significantly associated with PLMI severity scores (155).

### *Iron, dopamine and glutamate*

The role for iron deficiency in the pathophysiological processes of RLS is recognized (88). 25% of RLS patients suffer with iron deficiency (86), and 43% of iron deficient patients experience symptoms of leg restlessness (87). Moreover, RLS symptom severity is associated with low-normal range of serum ferritin (156). Conversely, the role of iron deficiency in PLMs without RLS remains largely unexplored, despite its well-established role in RLS with PLMS (157).

Similarly, considerable pharmacological and clinical evidence supports dopamine system dysfunction as critical in RLS pathophysiology (158). It is well-established that RLS symptoms improve when patients are administered dopaminergic medications (159), but can also experience worsening of their symptoms (augmentation effect) at a rate of 8% per year on treatment (160,161). Dopamine agonists need to cross the blood brain barrier in order to alleviate RLS symptoms suggesting that dopamine plays a central role in RLS pathophysiology (162). Moreover, iron is a co-

factor of tyrosine hydroxylase, a rate limiting step enzyme involved in the conversion of levodopa to dopamine in the brain (163). Thus, inadequate iron supply to the brain can alter dopaminergic signaling in the brain (157). Animal studies report a decrease in extracellular dopamine levels, of its D1, D2 receptors, and of the dopamine-transporter density in the striatum of iron-deficient rodents (164). Furthermore, neurodevelopmental studies reveal short- and long-term alterations associated with neonatal iron deficiency, leading to major biological alterations in dopamine pathways (165). For instance, impaired dopamine function in the nigrostriatal pathway may result in poorer motor sequencing during tests (166). Dopaminergic A11 cells are located in the midbrain, and they are the sole source of dopamine in the spinal cord via long and diffuse axonal projections (167) that cross over from the dorsal horn into the motor neuronal junction (157,168). Reduced drive or damage of this system, as evidenced by stereotaxic bilateral 6-hydroxydopamine lesion in animal studies, can cause changes consistent with RLS (169).

Of note, in animal studies, opioid treatment and an intact endogenous opioid system have been shown to have a neuroprotective effect on the dopaminergic cells in cases of iron deficiency (170), suggesting a new set of molecular pathways for newer therapies.

Thalamic glutamatergic hyperactivity has also been recently associated with both RLS and PLMS (171,172). This pathomechanism may underlie the clinical benefit that the RLS and PLMD patients receive from the  $\alpha$ -2- $\delta$  anticonvulsants (e.g., pregabalin and gabapentin), with more significant effects on the quality of sleep, than on the reduction of PLMI (173). The link between all three systems has been suggested by the findings in iron deficient animal models where an increased glutamate activity has been demonstrated in several brain regions (174,175).

### *Genetics*

Familial cases of early-onset RLS and PLMS have been identified (Table 3), with heritability greater than 60% (189,190). Genetic linkage studies in familial RLS identified several chromosomal loci (179), namely-*RLS1* on chromosome 12q discovered in a French-Canadian family (177), *RLS2* on Chr14q observed in an Italian family (176), *RLS3* on Chr9p in 15 extended American families (178), *RLS4* ON Chr2q and *RLS5* on Chr20p (180) respectively. These transmissions are autosomal dominant with incomplete penetrance (191). Additionally, high

**Table 3** Genetic causes of RLS and PLMS

Gene/gene locus	Function	Reference
Familial		
<i>RLS1</i> (autosomal recessive)	–	(176-180)
<i>RLS2, RLS3, RLS4, RLS5</i> (autosomal dominant, incomplete penetrance)		
Sporadic		
<i>MEIS1</i>	Motor neuron development Iron metabolism BTBD9 regulation	(80,157,181-187)
<i>BTBD9</i>	Regulation of brain dopamine levels Dopamine biosynthesis Regulation of IRP2 Embryonic limb development and neuronal development	
<i>MAP2K5/SKOR1</i>	Development of the dorsal horn of sensory pathways Neuroprotection of dopaminergic neurons	
<i>PTPRD</i>	Axon guidance and termination of motor neurons	
<i>TOX3/BC034767</i>	Mediating calcium-dependent transcription in neurons	(186,188)

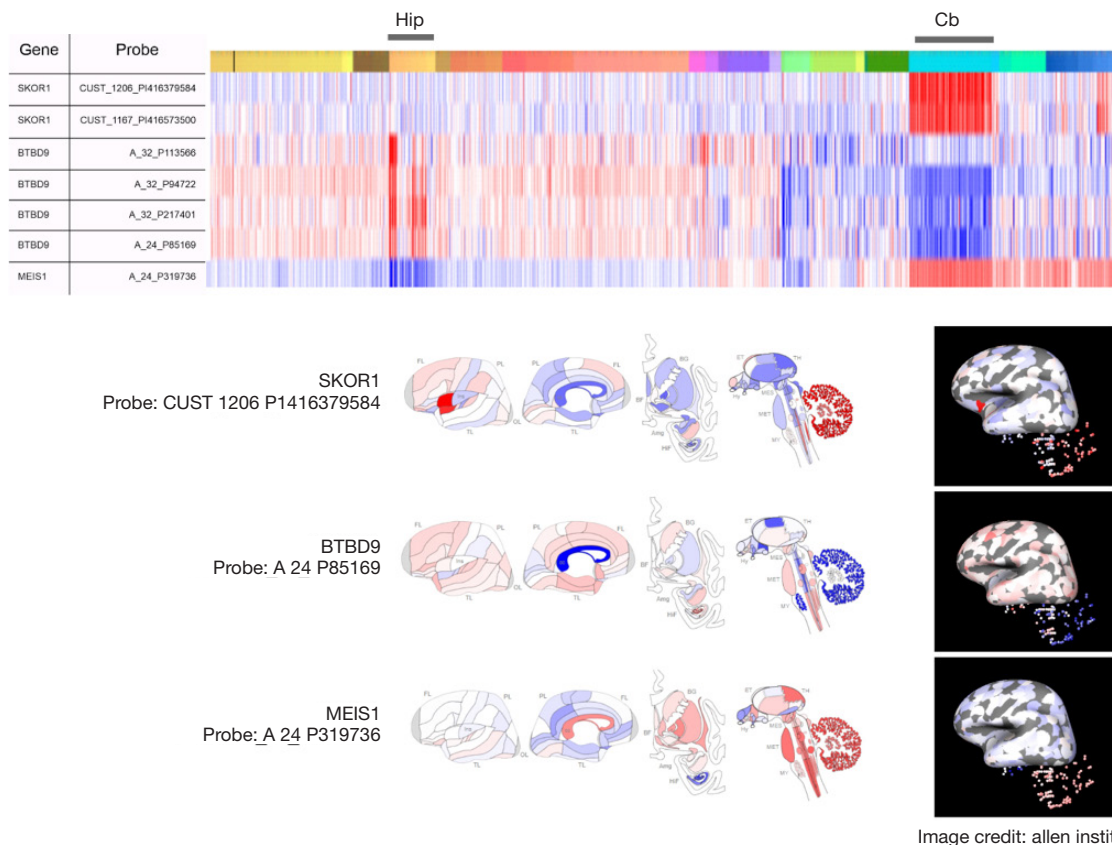
RLS, restless legs syndrome; PLMS, periodic limb movements during sleep.

concordance has been reported in monozygotic twins (169,192).

Genome wide association studies (GWAS) have similarly identified four susceptibility candidate genes and single nucleotide polymorphisms (SNPs) strongly associated with PLMS, namely: rs12469063 and rs2300478 of *MEIS1*, rs3923809 and rs9357271 of *BTBD9*, rs6494696 of *MAP2K5/SKOR1* (80,187) and *TOX3/BC034767* on chromosome 16q12.1 (Figure 1) (194,195). Each genetic variant carries an increased risk of up to 50% in RLS (187). These genes have been suggested to play role in embryonic limb development and neuronal development (162). For example, *MEIS1* gene (chromosome 2p14) is involved in regulatory network crucial for motor neuron development, and it is expressed in substantia nigra (196). On the other hand, each risk allele of *BTBD9* (chromosome 6p21.2) has been associated with a 13% decrease in ferritin levels, a known risk factor for RLS (195). Moreover, *SKOR1* gene, previously called *LBXCOR1* has been suggested to play the role in regulation of development of the dorsal horn of sensory pathways (191). Additionally, two SNPs have been expressed in the rs1975197 of Protein Tyrosine Phosphate, Receptor type, D (*PTPRD*) gene (chromosome 9p24.1-p23), which is involved in neuronal development (194). In the Wisconsin sleep cohort

(WSC), the most prominent genetic associations were established in *TOX3/BC034767*, *MEIS1* and *BTBD9* with both RLS and PLMs (197). Moreover, *MEIS1* SNPs were most strongly linked with PLMs in the absence of RLS (80). In RLS patients autopsy studies, the *MEIS1* gene was also found to be associated with increased thalamic expression of H-ferritin, L-ferritin and divalent metal transporter-1RNA (181), which suggested that *MEIS1* mutant alleles predisposed patients to iron deficient conditions.

Similarly, another study has reported that blocked *MEIS1* mRNA expression leads to increased transferrin-2 receptor, ferroprotein mRNA and *BTBD9* gene expression, while hepcidin mRNA expression decreased after 48 hours, thereby inferring the role of *MEIS1* gene in controlling intracellular iron transfer to mitochondria, extracellular iron export and potential effects on the *BTBD9* gene expression and its function in the downregulation of iron (184). While *MEIS1* regulates iron homeostasis, *BTBD9* was observed to significantly reduce brain dopamine levels and led to an abnormal sleep pattern in mutant flies (182). The *BTBD9* gene modulates transcription of ion conductance, cytoskeletal arrangement and protein ubiquitination and it enhances activity in rat striatum, a part of basal ganglia involved in voluntary movement in addition to largely



**Figure 1** Genes associated with PLMS. Levels of gene expression for *SKOR1*, *BTBD9* and *MEIS1* across different anatomical regions of the human brain as heatmaps or as drawings are shown. *SKOR1* and *MEIS1* show highest expression in the Cb, while *BTBD9* shows highest expression in hippocampal regions (Hip). Donor H0351.1016; adapted and data available from Human Brain Atlas of Allen Institute (193). Amg, amygdala; BG, basal ganglia; Cb, cerebellum; ET, epithalamus; FL, frontal lobe; HiF, hippocampal formation; Hy, hypothalamus; INS, insula; MES, mesencephalon; MET, metencephalon; Mid, midbrain; MY, myelencephalon; OL, occipital lobe; Pons, pons; PL, parietal lobe; TH, thalamus; TL, temporal lobe; PLMS, periodic limb movements during sleep.

comprising of dopaminergic neurons containing both D1 and D2 receptors (157). A study reported under expression of this gene causes hyperactivity and hyperexcitability in the calcium-gated dopaminergic neurons in striatum (198).

In summary, clinical implications and diverse phenotypes of PLMS are increasingly recognized. Several computerized and data-driven assessment techniques have been proposed to facilitate the analysis of intrinsic periodicity of PLM during both sleep and wakefulness. However, their phenotype and presentations vary vastly, across age and co-morbid clinical conditions. These motor patterns are influenced not just by their intrinsic regulatory and oscillatory mechanisms, but also neurophysiological co-factors- dopamine and iron. Furthermore, sensory inputs can alter the activity of these intrinsic motor pattern generators and fluctuations in iron and dopamine reportedly

cause significant exacerbations of symptoms.

Their links with major neurologic and psychiatric disorders remain controversial. In the future, prospective, multimodal imaging clinical studies should help delineate differential responses to treatment in RLS without PLMS and PLMS without RLS. This could pave a way toward identification of potential divergent biological pathways and the important new treatment modalities.

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