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Original Article

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Large muscle group movements during sleep in restless leg syndrome: neurophysiological and clinical implications

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Abstract

Study Objectives: Recently, criteria have been drawn up for large muscle group movements during sleep (LMM), defined as movements lasting for 3–45 seconds in adults, which are often accompanied by changes in sleep stage, arousals, and increases in heart rate. The aim of this study was to characterize LMM in restless legs syndrome (RLS) in order to better evaluate their impact on the neurophysiology of the disorder and, therefore, the possible clinical implications.

Methods: Consecutive, drug-free patients diagnosed with RLS and controls, aged 18 years or more, were retrospectively enrolled. Leg movement activity—short-interval (SILMS), periodic (PLMS), and isolated (ISOLMS) leg movements during sleep—and LMM were detected and scored.

Results: In total, 100 patients and 67 controls were recruited. All movement measures were significantly higher in RLS. A significant positive correlation was found between LMM and ISOLMS index but not PLMS index in both groups. LMM index showed a significant negative correlation with total sleep time, sleep efficiency, and percentage of sleep stages N3 and R, as well as a significant positive correlation with the number of awakenings, and percentage of sleep stages N1 and N2 only in patients with RLS. No significant correlation was found between either LMM or PLMS index and RLS severity.

Conclusions: Different types of movements, including SILMS, ISOLMS, and LMM, play somewhat distinct roles in sleep neurophysiology in RLS. Notably, LMM, a newly recognized category of movements, demonstrates associations with sleep architecture instability and fragmentation, arousals, and awakenings, suggesting potential clinical implications.

Key words: large muscle group movements during sleep; sleep-related movements; periodic leg movements during sleep; restless legs syndrome; isolated leg movements during sleep; arousals

Statement of Significance

In this study, the newly recognized category of movements called large muscle group movements during sleep (LMM) shows associations with sleep architecture instability and fragmentation (arousals and awakenings) in restless legs syndrome (RLS), suggesting potential clinical repercussions. However, further investigation is warranted to delineate their clinical significance and treatment implications as LMM are likely to not respond to dopaminergic drugs. There is a need for a comprehensive assessment of LMM and their clinical correlates in RLS.

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Restless legs syndrome (RLS) is a highly heterogeneous sensorimotor disorder, not only in terms of clinical manifestations, onset, and evolution of symptoms (with sex- and age-related differences) but also in terms of response to pharmacological treatment [1, 2]. The etiopathogenesis is still largely under study, with the complexity of the biological mechanisms [3] and the neuronal networks involved being highlighted [1]. In particular, regarding this latter aspect, studies outline the presence of dopaminergic dysfunction, which could be connected to involvement of cortico-striatal-spinal structures [4–6], resulting in sensorimotor activation and the onset of sleep disturbances and insomnia symptoms, often present in patients with RLS [1]. An hyperglutamatergic state has also been proposed in RLS, leading to hyperarousability, often causing sleep fragmentation and insomnia [1, 7]; furthermore, both dysfunctions of dopaminergic circuits and those of glutamate and GABA seem to be related to hypoadenosinergic state [1]. Therefore, the pathology is based on an intricate and connected neurotransmitter network that modulates the clinical presentation, phenotype variability, as well as the severity of RLS, and its response to treatment.

In this perspective, neurophysiology, reflecting the functioning of neuronal and neurotransmitter networks, can provide valuable assistance for a better understanding of RLS; over time, several studies have therefore investigated its neurophysiological characteristics, demonstrating hyperarousability [7] and the presence of periodic leg movements during sleep (PLMS) in a high percentage of patients, both adults and pediatric [8, 9].

The clinical utility of this approach also lies in the demonstration that therapies used according to guidelines can modulate different polysomnographic aspects: α2delta ligands of calcium channels reduce hyperarousability and increase deep sleep [10, 11], while dopamine agonists do not act on these parameters, being however very effective in reducing PLMS and associated arousals [12, 13]; both these pharmacological categories bring about a clinical improvement documented by the International RLS Study Group (IRLSSG) severity scale (IRLS) [14].

Recently, criteria have been drawn up for large muscle group movements during sleep (LMM), defined as movements with a duration ranging from 3 to 45 seconds in adults or from 3 to 30 seconds in children, characterized by an increase in electromyographic activity and/or the appearance of movement artifacts in any combination of at least two recommended channels and that do not meet the criteria for any other type of movement, PLMS in particular [15]. The current literature on LMM is still limited and involves essentially studies in children [16, 17]. Considering that LMM are often accompanied by changes in sleep stage, arousal [18], and increases in heart rate [15], the aim of this study was to characterize LMM in RLS, in order to better evaluate their impact on the neurophysiology of the disorder and, therefore, the possible clinical implications, also in light of the fact that in adults, literature data on these movements is only available for healthy people [18].

Materials and Methods

Participants

Consecutive, drug-free patients diagnosed with RLS, aged 18 years or more, who provided their informed consent according to the Declaration of Helsinki, were retrospectively enrolled.

The diagnosis of RLS was carried out according to the following IRLSSG diagnostic criteria [19], through a semi-structured interview: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching; (4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night; and (5) these criteria are not solely accounted for as symptoms of another medical or behavioral condition. Patients with a sleep disorder diagnosis other than RLS, any psychiatric diagnosis, neurodevelopmental delay, use of central nervous system drugs within the year prior to the study, or use of any drug or medication for 3 weeks before the PSG recording were excluded. Also, participants with an apnea–hypopnea index > 10/hour of sleep were excluded.

Control participants were also enrolled, similar to patients with RLS, and included participants without sleep problems, physical, neurological, or psychiatric disorders. The study was approved by the Oasi Research Institute Ethics Committee.

Polysomnographic recording and scoring

All participants underwent a full-night PSG recording, which included electroencephalogram (at least 3 channels, one frontal, one central, and one occipital, referred to the contralateral earlobe); electrooculogram (two channels), electromyogram (EMG) of the submentalis muscle and of both tibialis anterior muscles, and electrocardiogram (one derivation). The EMG signals from the chin and both tibialis anterior muscles were band-pass filtered at 10–100 Hz, with a notch filter at 50 Hz. At the beginning of each recording session, the amplitude of the EMG signal from the two tibialis anterior muscles was assured to be below 2 μV at rest.

Sleep stages were visually scored on 30-second epochs and all leg movements during sleep (LMS) were identified following standard criteria [20], followed by the computation of a series of parameters including, in particular: (1) total LMS index, n/hour; (2) PLMS index, n/hour: LMS included in regular and non-interrupted sequences of at least 4 movements with onset-to-onset intermovement interval (IMI) 10-90 s; (3) short-interval LMS (SILMS) index, n/hour: LMS with preceding IMI < 10 s; (4) isolated LMS (ISOLMS) index, n/hour: LMS with IMI > 90 seconds and LMS with IMI 10–90 seconds not meeting all the criteria for PLMS; (5) Periodicity index: PLMS index/total LMS index ratio. Respiratory-related LM were not excluded from the counts because participants with an apnea–hypopnea index > 10/hour of sleep were excluded and not enrolled. In addition, there is no general agreement on the definition of the rules for the identification of these movements [20] and respiratory-related LMS can be true PLMS [21].

In addition, LMM activity was quantified by two scorers (M.P.M. and P.C.), blinded to the group (controls or RLS). For this scoring, the recently published PSG-only criteria defining LMM were applied [15] and LMM with a duration between 3 and 45 seconds, characterized by an increase in electromyographic activity and/or the occurrence of movement artifact in any combination of at least two recommended channels and not meeting the criteria for any other type of movement were detected. Following the above rules [15], movements were classified as LMM or associated with an arousal or an awakening and counted separately in REM and non-REM (NREM) sleep.

Statistical analysis

Differences between the two groups were assessed by means of the Student's t-test or ANCOVA, using age as a covariate; for the analysis of frequencies, the chi-square test was used. Correlations were assessed by multiple regression analysis. The

commercially available Statistica software package (StatSoft, Inc., 2001. STATISTICA data analysis software system, version 6.) was used. Differences and correlations were considered significant if $p < .05$.

Results

In total, we recruited 100 patients (42 men and 58 women) and 67 controls (29 men and 38 women). The demographic characteristics of patients and controls are reported in Table 1. There was no statistically significant difference in sex composition between the two groups, while patients with RLS tended to be older than controls and the difference was statistically significant for women. For this reason, age was used as a covariate in the subsequent comparisons and correlations, in order to take its effects into account.

LMM activity and LMS activity

Table 2 shows the comparison between the various sleep movement measures (LMS and LMM) obtained in the two groups of participants enrolled for this study, while considering age as a covariate. As expected, all LMS measures were significantly higher in RLS. In addition, the total LMM were significantly higher in patients with RLS than in controls. However, when LMM associated with arousals or awakenings were considered separately for REM and NREM sleep, they were not significantly different during REM sleep, although always tendentially higher in patients with RLS.

The multiple regression analysis of SILMS index, PLMS index, ISOLMS index, and age (independent factors/predictors), and total LMM index in total sleep time (TST; dependent variable) is reported in Table 3, separately for controls and patients with RLS. A significant positive correlation was found only between total LMM index and ISOLMS index by multiple regression analysis. This correlation is also graphically displayed in Figure 1 and contrasted to the same graphical description of the correlation between total LMM index in TST and PLMS index. In both Table 3 and Figure 1, it can be noticed that the positive correlation between the ISOLMS index and total LMM index in TST was much stronger in controls than in patients with RLS.

Table 1. Demographics of the Two Groups of Participants Enrolled for This Study

Sex	Group	N	Age, years		Student's *t*-test	
			Mean	SD	*t*	*P*<
Women	Controls	38	47.9	16.33	−2.334	.022
	RLS	58	55.3	14.54		
Men	Controls	29	47.8	21.53	−0.909	NS
	RLS	42	51.9	16.76		

Sex distribution controls versus RLS: chi-square 0.03, not significant (NS).

Table 2. Comparison Between the Sleep Movement Measures (LMS and LMM) Obtained in the Two Groups of Participants Enrolled for This Study, While Including Age as a Covariate

	Controls (n = 67)		RLS (n = 100)		ANCOVA		Effect size
	Mean	SD	Mean	SD	*F*	*P*<	Cohen's d
PLMS index	5.8	11.38	30.8	22.75	62.788	.000001	−1.390
SILMS index	2.2	3.23	6.2	7.62	14.297	.00022	−0.680
ISOLMS index	8.4	4.83	12.5	6.38	19.989	.000015	−0.713
Total LMS index	16.4	15.63	49.4	30.42	60.578	.000001	−1.365
Periodicity index	0.220	0.229	0.605	0.185	141.626	.000001	−1.850
Total LMM index, TST	7.3	3.92	10.9	6.56	18.035	.000036	−0.655
Total LMM index, NREM	7.1	4.07	11.0	6.64	21.067	.000009	−0.713
Total LMM index, REM	6.9	5.10	9.6	9.68	7.390	.0073	−0.349
LMMA index, TST	3.8	2.51	5.4	4.04	11.078	.0011	−0.502
LMMA index, NREM	3.5	2.68	5.3	4.11	11.465	.00089	−0.523
LMMA index, REM	4.3	4.17	5.6	6.09	2.981	NS	−0.243
LMMW index, TST	2.3	1.32	3.0	1.60	6.848	.0097	−0.492
LMMW index, NREM	2.2	1.42	3.1	1.69	10.334	.0016	−0.532
LMMW index, REM	2.5	1.84	2.6	1.99	0.001	NS	−0.057
LMM duration (s), TST	10.7	3.69	10.6	2.56	0.058	NS	0.074
LMM duration (s), NREM	11.1	4.21	10.7	2.70	0.075	NS	0.242
LMM duration (s), REM	10.3	4.01	10.6	3.48	0.243	NS	−0.112

PLMS, periodic leg movements during sleep; SILMS, short-interval leg movements during sleep; ISOLMS, isolated leg movements during sleep; LMS, leg movements during sleep; LMM, large muscle group movements during sleep; LMMA, LMM associated with arousals; LMMW, LMM followed by awakening; TST, total sleep time; REM, rapid eye movement sleep; NREM, non-REM sleep.

Table 3. Simultaneous Association of SILMS Index, PLMS Index, ISOLMS Index, and Age, (Independent Factors/Predictors) and Total LMM Index in TST (Dependent Variable), Separately for Controls and Patients With RLS, Assessed With the Multiple Regression Analysis

	Controls				RLS			
	Partial correlation	*t* value	*P*<	β	Partial correlation	*t* value	*P*<	β
SILMS index	−0.177	0.571	NS	−0.184	0.153	1.512	NS	0.252
PLMS index	−0.203	−1.636	NS	−0.177	−0.105	−1.031	NS	−0.129
ISOLMS index	0.658	−1.413	.000001	0.839	0.198	1.972	.05	0.280
Age, years	0.118	0.939	NS	0.093	−0.068	−0.661	NS	−0.066

PLMS, periodic leg movements during sleep; SILMS, short-interval leg movements during sleep; ISOLMS, isolated leg movements during sleep.

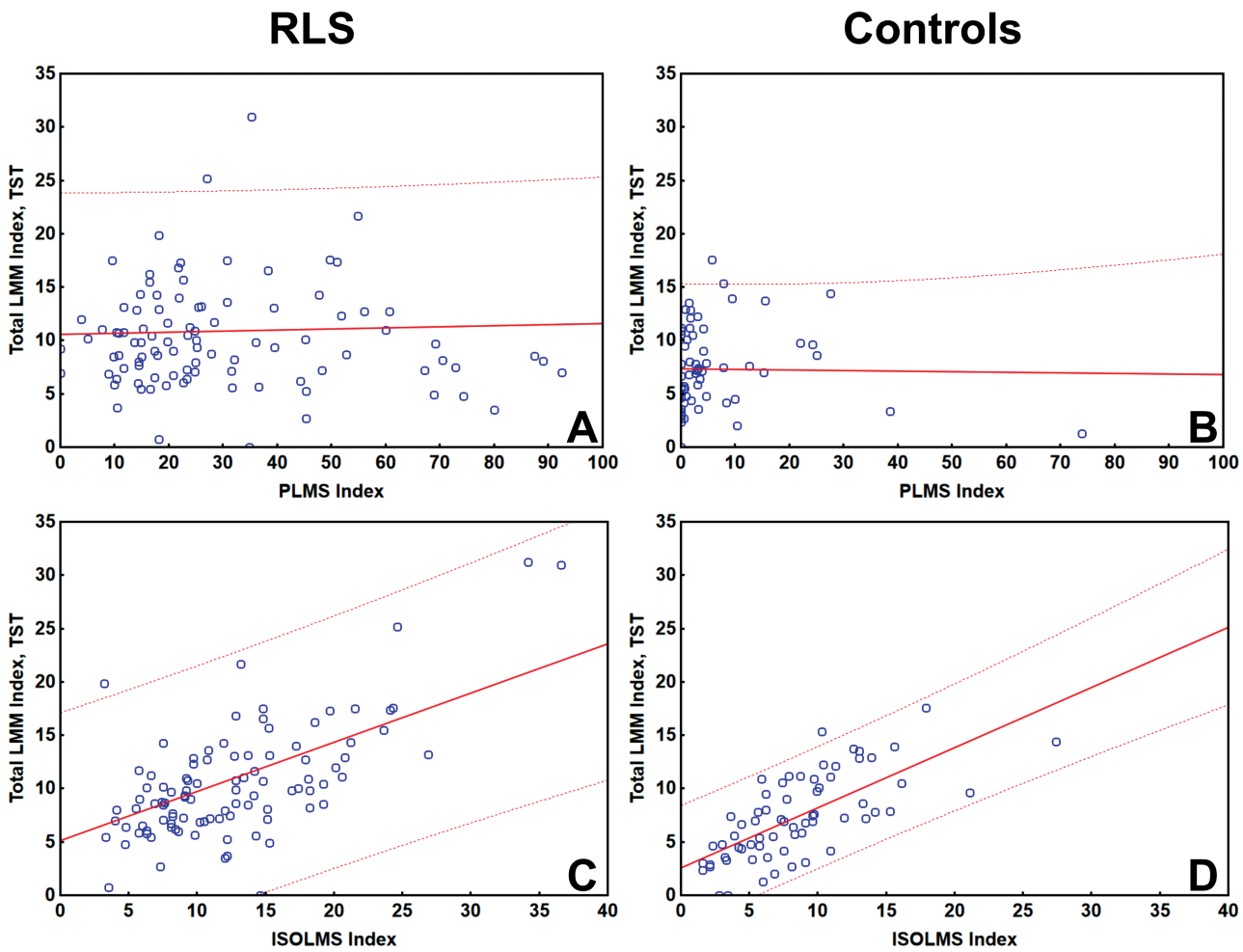

Figure 1. Top graphs: graphic representation of the correlation between total LMM index in TST and PLMS index in patients with RLS (panel A) and controls (panel B). Bottom graphs: a graphic representation of the correlation between total LMM index in TST and ISOLMS index in patients with RLS (panel C) and controls (panel D). In each panel, also the linear regression line (continuous line) is shown along with the 95% prediction lines indicating the area of the graph within which new observations would be expected to occur, with a 95% probability.

LMM activity and sleep architecture

Table 4 reports the comparison between the sleep architecture parameters obtained in the two groups of participants enrolled for this study, also considering age as a covariate. Although some differences can be observed, especially those accompanied by a medium effect size (~0.3 [22]), involving slightly lower sleep efficiency and percentage of REM sleep and a higher percentage of sleep stage N1 in patients with RLS, none of the differences were found to be statistically significant.

In order to obtain information on the eventual association between LMM and sleep architecture parameters, especially those indicating fragmentation and superficialization, the correlation between different sleep architecture parameters (dependent variables) and total LMM index in TST or PLMS index, taking into account their simultaneous effect, as well as that of age (independent factors/predictors), was assessed by multiple regression analysis separately for controls and patients with RLS (Table 5). In controls, only PLMS were found to be positively correlated with the

Table 4. Comparison Between the Sleep Architecture Parameters Obtained in the Two Groups of Participants Enrolled for This Study, While Including Age as a Covariate

	Controls (n = 67)		RLS (n = 100)		ANCOVA		Effect size
	Mean	SD	Mean	SD	F	P<	Cohen's d
Time in bed, min	491.1	81.03	511.2	87.54	0.944	NS	–0.238
Sleep period time, min	466.3	74.38	477.2	93.38	0.177	NS	–0.129
Total sleep time, min	387.2	77.58	388.4	103.06	0.339	NS	–0.012
Sleep onset, min	17.9	20.28	23.8	28.88	1.182	NS	–0.234
REM sleep latency, min	101.8	74.23	119.1	67.61	1.451	NS	–0.244
Stage shifts/hour	12.2	4.74	12.6	5.06	0.890	NS	–0.079
Awakenings/hour	4.9	3.01	5.1	3.07	0.012	NS	–0.059
Sleep efficiency, %	80.2	16.37	75.6	14.83	0.828	NS	0.296
Wakefulness after sleep onset, min	79.1	80.90	88.9	61.39	0.083	NS	–0.136
Sleep stage N1, %	7.2	6.45	9.6	7.23	3.216	NS	–0.344
Sleep stage N2, %	55.2	10.47	53.3	10.81	2.782	NS	0.180
Sleep stage N3, %	16.8	9.70	18.7	9.38	2.570	NS	–0.202
Sleep stage R, %	20.8	6.80	18.5	6.58	2.487	NS	0.353

Table 5. Multiple Regression Analysis Between Different Sleep Architecture Parameters (Dependent Variables), and Total LMM Index in TST, While Taking Into Account Their Simultaneous Effect as Well as That of Age (Independent Factor/Predictor), Separately for Controls and Patients With RLS

	Controls				RLS			
	Partial correlation	t value	P<	β	Partial correlation	t value	P<	β
LMM index in TST								
Total sleep time	0.218	1.772	NS	0.216	–0.266	–2.702	.0082	–0.250
Stage shifts/hour	0.183	1.478	NS	0.187	0.184	1.834	NS	0.0178
Awakenings/hour	0.214	1.736	NS	0.195	0.317	3.277	.0015	0.318
Sleep efficiency, %	0.065	0.521	NS	0.051	–0.254	–2.575	.012	–0.235
Stage N1, %	0.076	0.601	NS	0.066	0.223	2.243	.027	0.221
Stage N2, %	0.062	0.490	NS	0.059	0.262	2.665	.009	0.262
Stage N3, %	–0.083	–0.660	NS	–0.078	–0.243	–2.456	.016	–0.245
Stage R, %	–0.044	–0.349	NS	–0.043	–0.342	–3.561	.0006	–0.325
PLMS index								
Total sleep time	0.130	1.038	NS	0.138	–0.313	–3.226	.0017	–0.312
Stage shifts/hour	–0.091	–0.728	NS	–0.100	–0.127	–1.253	NS	–0.127
Awakenings/hour	–0.034	–0.268	NS	–0.033	–0.027	–0.269	NS	–0.027
Sleep efficiency, %	–0.096	–0.769	NS	–0.083	–0.254	–2.573	.012	–0.246
Stage N1, %	0.359	3.050	.0034	0.363	0.193	1.925	NS	0.199
Stage N2, %	–0.223	–1.815	NS	–0.238	–0.043	–.426	NS	–0.044
Stage N3, %	0.100	0.800	NS	0.103	–0.080	–.791	NS	–0.083
Stage R, %	–0.115	–0.920	NS	–0.124	–0.030	–.026	NS	–0.028

percentage of sleep stage N1; conversely, in patients with RLS total LMM index in TST showed a significant negative correlation with TST, sleep efficiency, and percentage of sleep stages N3 and R, as well as a significant positive correlation with number of awakenings, and percentage of sleep stages N1 and N2. Conversely, PLMS index only correlated negatively with TST and sleep efficiency.

LMM activity and RLS severity

Information on the score at the International RLS Study Group rating scale (IRLS) [23] was available for 51 patients (mean score 25.3 ± 4.43 SD, range 17–37) and was used to assess the eventual correlation between total LMM index in TST and RLS severity in this subgroup of patients. Also in this case, the multiple correlation analysis between IRLS score (dependent variable) and total LMM index in TST (partial correlation –0.122, t value –0.840, NS), PLMS index (partial correlation 0.242, t value 1.572, NS) and age (partial correlation 0.187, t value 1.304, NS), used as independent factors/predictors, showed small-to-medium correlations [22], but none of them was statistically significant.

Discussion

RLS is associated with a complex movement disorder during sleep that has long been assessed almost exclusively by taking into account its most evident and attention-catching phenomenon, i.e. PLMS. However, solid evidence has been reported on the important presence of different types of LMS in these patients, distinguished basically on their typical intermovement interval and classified as SILMS and ISOLMS [20, 24–27]. These different categories of movements behave strikingly differently with age [8, 28, 29] and are associated with different impacts on sleep neurophysiology [30–33]. In addition, they respond differently to treatment with dopamine agonists [34].

Based essentially on pediatric evidence, criteria have more recently been established to score and quantify another category of movements that are, most likely, important impacting events on sleep neurophysiology, i.e. LMM [15]. It has already been reported that, in healthy adult controls, these movements correlate positively with sleep stage N1 percentage, arousal index, sleep stage shifts, and negatively with sleep stage N3 [18]. It has also been reported that LMM, which characterizes a recently introduced pediatric sleep-related movement disorder called restless sleep disorder [35–37], might be frequent in children with RLS [38] and is associated with important clinical consequences, such as excessive daytime sleepiness and decreased quality of life [17], or cognitive functions, such as selective attention [39].

With this study, we aimed to expand our knowledge on the correlates of LMM in adults and to characterize them in RLS, also in order to better evaluate their impact on the neurophysiology of the disorder and, therefore, obtain the first information on their potential clinical repercussions. However, as they coexist with LMS in the same patients, as also recognized by the scoring criteria which state that LMM cannot be counted if they coincide with PLMS [15], the first step of this study was to assess the correlation between LMM and all types of LMS (SILMS, PLMS, and ISOLMS). Our results clearly demonstrate that LMM correlate clearly with ISOLMS and are not correlated with the other two types of LMS. This implies that when LMS are scored, the criteria allow several ISOLMS to be scored also as LMM, and vice versa. It is important to underline that the guidelines for scoring LMM [15] clearly state that they should not be labeled as such if they are PLMS but do not exclude their correspondence with ISOLMS; thus, some movements could have been labeled as both LMM and ISOLMS. Therefore, the LMM scorers of the present study were not aware of an eventual previous scoring of ISOLMS and only PLMS were excluded. However, there are substantial differences that make the two scorings correlated but not the same. First of all ISOLMS duration can range between 0.5 and 15 seconds [20] while LMM duration ranges from 3 to 45 seconds [15]; in addition, ISOLMS can involve only tibialis anterior EMG signals while LMM can be scored also without the involvement of such channels. This accounts, at least to some extent, for the small-to-medium correlation found between these two activities in patients with RLS, which explains approximately 6% of the variance [22]. Interestingly, in controls the same correlation was very large, indicating a higher degree of correspondence between these two types of movements, with a correlation coefficient explaining approximately 43% of the variance [22]. Based on these considerations, it is possible to suggest that movements that, following the current scoring criteria, can be classified either as ISOLMS [20] or LMM [15] should only be labeled LMM (i.e. when they last ≥ 3 seconds and involve other additional channels, beside tibialis anterior EMG).

Differently from PLMS they have been indicated to be dependent on a dopaminergic dysfunction involving the dorsoposterior hypothalamic dopaminergic A11 cell group projecting to spinal networks [40] and respond promptly and dramatically to dopamine agonists [13, 41, 42], ISOLMS have been reported to be unchanged after acute administration of pramipexole [34]. In this respect, it is interesting to note that in the present study, more than 80% of LMM were associated with arousals (49% in controls and 48% in RLS) or awakenings (35% in controls and 31.5% in RLS). It has already been reported that increased arousal activity is present in RLS and that it is not influenced by dopaminergic drugs [43, 44], but responds to benzodiazepines [42]. This indicates the need, in future controlled studies, to assess which treatments would be most effective to reduce LMM in RLS, considering their association with sleep architecture indicators of instability and fragmentation, as shown by the current study.

Arousals and awakenings from sleep are subserved by a complex neural network with important functions performed by serotonergic neurons located within the raphe nuclei and noradrenergic neurons within the locus coeruleus and with neuromodulatory glutamatergic, acetylcholinergic, dopaminergic, histaminergic, and orexinergic influences [45, 46]. The effects of benzodiazepines are mediated by widespread specific receptors that are anatomically closely associated with gamma amino butyric acid (GABA)—the major inhibitory neurotransmitter of the central nervus system—receptors [47].

Although we did not find significant differences in sleep architecture between controls and patients with RLS, it is interesting to note that, in the latter only, LMM rather than PLMS correlated significantly with a series of sleep parameters pointing at sleep fragmentation and instability, such as decreased TST, sleep efficiency, and percentage of sleep stages N3 and R, as well as increased number of awakenings, and percentage of sleep stages N1 and N2. These features of sleep architecture in RLS have been reported by several previous investigations [48]. Moreover, considering that the main indicators of homeostatic sleep pressure are NREM and slow-wave sleep, regulated by neurotransmitters also implicated in RLS, we underline the importance of modulating these sleep stages and the factors that can modify them (such as LLM) for possible therapeutic implications. Therefore, it is now needed to better establish the eventual presence and severity of the clinical significance of LMM, it is possible to speculate that alternative strategies, appropriately targeting one or more of the above neurotransmitters, might be sought in the future, with the aim of reducing LMM and counteract their negative effects on sleep neurophysiology, with possible beneficial clinical effects.

In this regard, in accordance with neurophysiological data, it is important to take into account some evidence from the literature in the genetic field, which supports involvement of dopaminergic transmission and iron metabolism, such as genome-wide association studies which have found the involvement of the MEIS1, BTBD9, and PTPRD genes [49]. In addition, a recent transcriptome analysis found a series of biological pathways involved in dysregulated networks linked to neurotransmitter mechanisms (particularly cholinergic synapses), synaptic plasticity, and axon guidance [3]. All of these studies provide valuable information that should guide scientists in their search for new and innovative treatment strategies.

It is important to underline that we did not find a significant correlation between either PLMS or LMM and IRLS. However, this is not surprising because IRLS investigates subjectively reported symptoms of RLS, most of which occur in the evening or at night, and only few questions investigate daytime consequences. Indeed,

the IRLS has strengths and weaknesses that likely interfere with a detailed assessment of eventual clinical correlates of nocturnal motor events [50]. Additional studies should, in the future, focus on this topic, using more adequate and sensitive instruments to assess this point, possibly with a prospective design.

Finally, it is also necessary to compare our results in controls with those recently reported by Ibrahim et al. [18] who also reported a prevalence of LMM very similar to ours in a sample of 100 healthy participants: 6.8/hour in TST (7.3/hour in our study), 6.2/hour in NREM sleep (7.3/hour in our study), and 8.4/hour in REM sleep (6.9/hour in our study). Moreover, similar to our findings, these authors reported a higher proportion of LMM associated with arousals or awakening (88.9% of total LMM). Also, Ibrahim et al. [18] reported that LMM correlated with sleep fragmentation, and added an important analysis on the correlation of LMM with anxiety and depression which was found to be significant. Taken together with our results in controls and patients with RLS, this further reinforce the need to better characterize the clinical correlates of LMM in patients with RLS, who are at increased risk for these psychiatric conditions [2, 51–53].

The limitations of this study include its retrospective enrollment of patients and the limited information available on daytime symptoms and their iron status; its strengths are the relatively large number of patients and controls, the accurate diagnostic process carried out by specialized Centers in Sleep Medicine, and the accurate consideration of covariates in the statistical analysis.

In conclusion, this discussion sheds light on the complexity of assessing and understanding nocturnal motor events in patients with RLS, beyond the traditional focus on PLMS. It has become evident that different types of movements, including SILMS, ISOLMS, and LMM, play somewhat distinct roles in sleep neurophysiology and exhibit varying responses to treatment. Notably, LMM, a newly recognized category of movements, demonstrate associations with sleep architecture instability and fragmentation, arousals, and awakenings, suggesting potential clinical repercussions. While this study elucidates correlations between LMM and ISOLMS in patients with RLS, further investigation is warranted to delineate their clinical significance and therapeutic implications. Moreover, comparisons with findings in healthy controls underscore the need for comprehensive assessments of LMM and their potential links to psychiatric comorbidities in RLS. As we navigate these complexities, future studies utilizing more sensitive instruments and prospective designs will contribute to a deeper understanding of the clinical correlates and management strategies for nocturnal motor events in patients with RLS. Despite the limitations of this study, its findings underscore the importance of a multidimensional approach to evaluating sleep disturbances in RLS, emphasizing the need for targeted interventions that address the diverse neurophysiological mechanisms underlying this disorder.

Disclosure statement

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Data availability

The datasets generated and analyzed during the current study are not publicly available due to privacy concerns but deidentified data are available from the corresponding author upon reasonable request.

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