Bilateral leg movements during sleep: Detailing their structure and features in normal controls and in patients with restless legs syndrome

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ABSTRACT

Objective: The aim of this study was to analyze statistically the number of single leg movements (LMs) forming bilateral LMs during sleep, along with their combined duration, to eventually provide evidence-based data for the adjustment of the current scoring rules defining bilateral LMs.

Methods: Polysomnographic recordings of 111 untreated patients with RLS with a median age of 56.0 years, along with 42 normal controls with a mean age of 60.0 years, were included. In each recording, we identified all LMs that were considered as bilateral when two or more LMs were overlapping or the onset of the following movement was <0.5 second after the offset of the preceding LM. The remaining LMs were classified as monolateral. A series of parameters were computed for both bilateral and monolateral LMs.

Results: The duration of monolateral LMs in RLS patients was significantly longer than that of normal controls. For bilateral LMs, the maximum number of single LMs forming a bilateral movement and the maximum duration were slightly higher in RLS patients; however, the distribution of the number of individual LMs forming a single bilateral LM was similar. Only 0.12% and 0.27% of bilateral LMs consisted of >4 individual movements, and only 0.16% and 1.90% of bilateral LMs were >15 seconds in RLS patients and healthy controls, respectively.

Conclusion: Our results strongly suggest that bilateral LMs during sleep should be constituted by no more than 4 individual LMs and should have a maximum duration of 15 seconds.

1. Introduction

Two sets of rules for the scoring of periodic leg movements during sleep (PLMS), proposed by the International Restless Legs Syndrome (RLS) Study Group and the World Association of Sleep Medicine (WASM/IRLSSG) [1] and by the American Academy of Sleep Medicine (AASM), are the current standards [2,3]. Both sets are an admixture of rules based on data-driven analyses of leg movements (LMs) in polysomnographic recordings (PSG) and of historical, consensus-based rules inherited from the previous standards [4,5] and mostly developed for the visual scoring of PSG, as opposed to the current computer-based quantitative approaches and automatic analyses. Therefore, for some of the rules, hitherto based on expert consensus only, there is a continued need for critical and empiric investigations to provide an evidence base that could be incorporated into the decisional process toward an eventual improvement of the PLMS scoring criteria.

One such rule, for which evidence is lacking, concerns the definition of bilateral leg movements. The current WASM/IRLSSG standards [1] state that “Detections from the two sides can be combined, and bilateral movements are counted as one.” In a first step, we have recently reported a data-driven analysis of the rule that defines the time relationships between two LMs occurring on the two legs to be classified as a single bilateral LM [6]. With such an analysis, we observed that >95% of legs occurring over the two sides and not separated by >10 seconds meet the rule defining bilateral movements as including two or more monolateral LMs separated (offset-to-onset) by <0.5 second from each other. We thus could confirm that the current rule stating that LMs are considered as bilateral when they are overlapping or separated (offset-to-onset) by <0.5 second is supported by empirical data. Following the same rule, bilateral movements can include two or more monolateral LMs separated (offset-to-onset) by <0.5 second from each other. However, this poses two new questions that have not yet been answered: What is the maximum number of single LMs forming a bilateral LM? Is there is a maximum duration for bilateral leg movements derived from combining multiple, single, and unilateral LMs?

The focus of the present article is the investigation of these two specific aspects of bilateral LMs, by considering them in both normal controls and patients with RLS and in comparison with single monolateral movements recorded in the same subjects.

Therefore, the aim of this study was to analyze statistically the number of single LMs forming bilateral LMs during sleep and their combined duration, to eventually provide evidence-based data for the adjustment of the current scoring rules defining bilateral LMs.

2. Methods

2.1. Subjects

For this study, we retrospectively identified and included all recordings of sufficient technical quality that followed a standardized protocol in untreated RLS patients who participated in previous studies published by our groups [6–17]. In agreement with the International RLS Study Group [18,19], the minimal criteria accepted for the diagnosis of RLS were as follows: (a) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (b) the urge to move, or unpleasant sensations that begin or worsen during periods of rest or inactivity such as lying or sitting; (c) the urge to move or unpleasant sensations that are partially or totally relieved by movement, such as walking or stretching; (d) the urge to move or unpleasant sensations that are worse in the evening or night than during the day or that occur only in the evening or night. Routine blood tests and neurophysiological investigation (electromyography [EMG] and electroneurography of the lower limbs) findings were also normal. The sleep respiratory pattern of each patient was assessed by means of oral and/or nasal airflow (thermistor and/or nasal pressure cannula), thoracic and abdominal respiratory effort (strain gauge), and oxygen saturation (pulse oximetry), in a previous recording (within 1 week) or during the respective study; subjects with an apnea–hypopnea index of >5 were not included. Neurological examination results were unremarkable in all patients.

Drug-free control subjects as well were retrospectively identified and included in this study, and had been screened to exclude those with any current or prior symptoms suggestive of RLS, according to the same minimal criteria set by the International RLS Study Group for the diagnosis of RLS [18,19]. Control and RLS subjects had to be in general good health and were excluded if any of the following was present: a diagnosis of any (other) significant sleep disorder(s); major mental illness including any indications of cognitive problems as determined by history; any history of neuroleptic-induced akathisia; or use of any neuroleptic in the past year.

The original studies were approved by the local ethics committees, and all subjects had provided informed consent before entering the study.

2.2. Polysomnographic sleep recording

Each subject underwent a polysomnographic full-night recording, after an adaptation night, carried out in a standard sound-attenuated (noise level to a maximum of 30 dB nHL) sleep laboratory. Subjects were not allowed to have beverages containing caffeine during the afternoon

preceding the recording, and were allowed to sleep until their spontaneous awakening in the morning.

The following parameters were included in the polysomnographic study: EEG (at least three channels, one frontal, one central, and one occipital, referred to the contralateral earlobe); electrooculogram (electrodes placed 1 cm above the right outer cantus and 1 cm below the left outer cantus and referred to A1), electromyogram (EMG) of the submental muscle, EMG of the right and left tibialis anterior muscles (bipolar derivations with two electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of each leg, impedance was kept to $<10\text{ K}\Omega$), and ECG (one derivation). EMG signals, in particular, were digitally band-pass filtered at 10–100 Hz, with a notch filter at 50 Hz.

At the beginning of each session and before the start of recording, the sleep technician checked that the amplitude of the EMG signal from the two tibialis anterior muscles was $<2\text{ }\mu\text{V}$ at rest.

2.3. Sleep scoring and detection of leg movements

Sleep stages were visually scored following standard criteria on 30-second epochs [3]. LMs during sleep were detected by the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy). With this software, the detection is performed by means of a human-supervised automatic approach controlled by the scorer [20]. For this study, one scorer (R.F.) visually edited the detections proposed by the automatic analysis. LMs occurring during wakefulness were not analyzed.

2.4. Analysis of bilateral LMs

For the present analysis, we considered all LMs during sleep, irrespective of whether they were or were not classified as periodic. In each recording, we identified all LMs that were considered as bilateral according to the WASM/IRLSSG scoring rules [1], that is, when two or more LMs were overlapping or the onset of the following movement was <0.5 second after the offset of the preceding LM. The remaining LMs were classified as monolateral.

We then calculated a series of parameters for both bilateral (minimum, maximum, mean, and median of the number of single movements forming each bilateral LMs and of their duration) and monolateral LMs (minimum, maximum, mean, and median of the duration). We did include a range of different parameters beside the individual mean, because the distributions within each individual and often within each group were skewed. For this reason, nonparametric statistics for unpaired or paired datasets were used, as appropriate. All measurements were obtained for all LMs detected following the above procedure, irrespective of their classification as periodic or not periodic. However, we subsequently classified each movement as belonging to three separate categories,

following a recently introduced alternative definition of PLMS [12], as follows: PLMS defined as all movements included in regular sequences of at least four LMs separated by 10–90 seconds from each other, “short-interval” LMs (<10 s), and “isolated” LMs including all movements with an intermovement interval from the preceding one of >90 seconds and LMs included in regular sequences of less than four LMs separated by 10–90 seconds from each other.

Because the number of analyzed LMs differed widely between subjects, all results reported are based on weighted summary statistics giving equal weight to each subject. For example, for the computation of the average percentage of LMs classified as bilateral, we first computed the percentage for each subject and then averaged across subjects.

3. Results

We included 111 subjects with RLS (62 female and 49 male) with a median age of 56.0 years (interquartile range [IQR] 45–65 years) and 42 normal controls (22 female and 20 male) with a mean age of 60.0 years (IQR 30.3–66.0 years). Individual RLS patients contributed to the analyses 297 LMs (median, IQR 185–439) during sleep, whereas control subjects contributed on average 91 LMs (IQR 75–171) during sleep. Of these, a median of 108 (IQR 55–194) were identified as bilateral LMs, in RLS patients, which represented 37.5% (IQR 24.9–58.6) of all LMs during sleep. In controls, a median of 32.5 (IQR 17–42) were identified as bilateral LMs, representing 31.9% (IQR 21.8–42.6) of all LMs during sleep. RLS patients had a significantly higher percentage of bilateral LMs than normal controls (Table 1).

The comparison between RLS patients and normal controls concerning the features of bilateral or monolateral LMs is detailed in Table 1. The median duration of monolateral LMs in RLS patients was significantly longer than that in normal controls. For bilateral LMs, the median maximum number of single LMs forming a bilateral movement and the maximum LM duration were slightly but significantly higher in RLS patients; however, these comparisons would not withstand correction for multiple comparisons. Also the distribution of the number of individual LMs forming a single bilateral LM was somewhat similar between RLS patients and normal controls (Fig. 1) with, on average, only 0.12% and 0.27% of bilateral LMs consisting of more than four individual movements, in both groups.

Figure 2 shows the distribution of the duration of all bilateral LMs in RLS patients and healthy controls. In total, only 0.16% and 1.90% of bilateral movements were longer than 15 seconds in RLS patients and healthy controls, respectively.

Similar low proportions were found also for each LM subtype with the exception of short-interval LMs in controls, in whom 9.30% of all short-interval LMs were >15 seconds; however, this percentage corresponded to only four LMs.

Table 2 reports the results of the comparison between bilateral and monolateral LMs features found in RLS patients and controls. All parameters considered were found to be significantly different for bilateral vs monolateral LMs in both groups.

Finally, in both groups, the duration of bilateral LMs was longer for LMs that contained a higher number of individual LMs (Fig. 3).

4. Discussion

Although the maximum length of a monolateral LM is indicated to be 10 seconds, none of the current rules [1–3] for the scoring of LM activity during sleep specifies a maximum duration of bilateral LMs resulting from the combination of individual LMs or a maximum number of individual LMs that are combined to form a bilateral LM. Our analysis in two large groups of subjects has shown that bilateral LMs are formed by a maximum of four individual LMs and that only a very small number of LMs exceed this number (0.12% in RLS and 0.27% in controls). Given the rarity of bilateral LMs with more than four individual LMs and the fact that this was the median maximum number of movements in RLS patients, we believe that this maximum number of individual LMs forming a single bilateral LM might be considered to help identify other non-PLMS, alternating leg motor activities, such as the so-called alternating leg movement activity (ALMA) that can contain several individual movements over the two sides [21,22]. Currently [3], the minimum number of discrete and alternating EMG burst of leg movement activity events needed to score an ALMA series is four. Our results could suggest choosing five alternating EMG bursts as the minimum number to score ALMA to clearly differentiate it from bilateral LM activity as seen in RLS and control subjects.

Our results also indicate that the maximum duration of bilateral LMs can be set to 15 seconds. This limit is clearly evident in Fig. 2 and is supported by the fact that only 0.16% of bilateral LMs were longer than 15 seconds in RLS patients and only 1.90% in controls. In addition, the very small and statistically marginally significant differences between the features of bilateral LMs during sleep recorded in RLS patients and controls indicate that the rules for the identification of these bilateral LMs do not need to differ between these two groups and that common rules could be established, as is the case for all other criteria concerning LM activity scoring during sleep [1,3].

In this study, we have considered bilateral LMs as defined by the WASM/IRLSSG criteria [1]. These, however, differ from the AASM rules [3] that, in particular, consider LMs as bilateral if the onset of the first LM is <5 seconds before the onset of the subsequent LM in the contralateral leg, whereas the WASM/IRLSSG criteria [1] consider LMs as bilateral if the LMs overlap or if the offset of the first LM is <0.5 second before the onset of the subsequent LM in the contralateral leg. Despite this apparent important difference, we have previously reported that these two different definitions of bilateral LMs give largely equivalent results concerning the standard LM indices during sleep [6], at least when bilateral LMs formed by only two individual LMs are considered. Interestingly, in this study, bilateral LMs were formed of only two individual LMs in almost all cases (on average, in 94.69% in RLS patients and in 93.45% in normal controls). Thus, even if in this study we identified bilateral LMs by applying only the WASM/IRLSSG criteria [1], we think it reasonable to assume that our results would also apply reliably to the other set of rules by the AASM [3].

Finally, the clear difference between the features of monolateral and bilateral LMs found in this analysis indicates that these two activities need to be scored following different rules, especially concerning their maximum duration. This further supports the existence of a different rule for the duration of monolateral and bilateral LMs, whereas the lack of differences between the different subtypes of bilateral LMs (short-interval, PLMS, or isolated) indicates that there is no need for different values for this parameter in the definition of the different LM subtypes.

5. Conclusion

In conclusion, with this study we contributed to a data-based characterization of two important parameters of bilateral leg movements hitherto not specified by any previous or current rules for the scoring of LM activity during sleep. Our results strongly suggest that bilateral LMs during sleep should be constituted by no more than four individual LMs and should have a maximum duration of 15 seconds.

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Conflict of interest

The authors have no financial conflicts of interest in regard to this work.

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Table 1

Features of monolateral and bilateral LMs in RLS patients and controls.

	RLS (n = 111), median (IQR)	Controls (n = 42), median (IQR)	Mann–Whitney <i>U</i> p	
Bilateral LMs				
Number of LMs, min	2.0 (2.00–2.00)	2.0 (2.00–2.00)	2331.0	NS
Number of LMs, max	3.0 (3.00–4.00)	3.0 (2.00–3.00)	1751.5	≤0.018
Number of LMs, mean	2.0 (2.01–2.09)	2.1 (2.00–2.12)	2222.5	NS
Number of LMs, median	2.0 (2.00–2.00)	2.0 (2.00–2.00)	2331.0	NS
Duration (s), min	1.0 (0.81–1.26)	1.1 (0.82–1.26)	2211.0	NS
Duration (s), max	12.0 (9.96–14.15)	10.1 (8.77–13.19)	1708.0	≤0.01
Duration (s), mean	4.0 (3.46–4.72)	4.1 (3.47–4.88)	2107.5	NS
Duration (s), median	3.0 (2.93–4.00)	3.4 (2.70–4.00)	2205.5	NS
Monolateral LMs				
Duration (s), min	0.5 (0.50–0.52)	0.5 (0.50–0.59)	1772.0	NS
Duration (s), max	9.0 (6.83–9.96)	7.5 (6.23–9.88)	2075.0	NS
Duration (s), mean	2.1 (1.71–2.42)	1.9 (1.66–2.26)	1996.5	NS
Duration (s), median	1.7 (1.00–2.00)	1.2 (1.00–1.70)	1629.0	≤0.004
Bilateral LMs, %	37.5 (24.92–58.57)	31.9 (21.78–42.62)	1768.5	≤0.021
Monolateral LMs, %	62.5 (41.43–75.08)	68.1 (57.38–78.22)	1768.5	≤0.021
Abbreviations: IQR, interquartile range; max, maximum; min, minimum; RLS, restless legs syndrome; s, seconds. LM denotes leg movement with duration 0.5–10 seconds; Bilateral LMs denotes two or more LMs, recorded over the two sides, overlapping or with the onset of the following movement <0.5 second after the offset of the preceding LM.				

Table 2

Comparison between bilateral and monolateral LMs features in RLS patients and controls.

	Bilateral LMs, median (IQR)	Monolateral LMs, median (IQR)	Mann–Whitney	
			<i>U</i>	<i>p</i>
RLS patients (n = 111)				
Duration (s), min	1.0 (0.81–1.26)	0.5 (0.50–0.52)	2.0	≤0.000001
Duration (s), max	12.0 (9.96–14.15)	9.0 (6.83–9.96)	236.0	≤0.000001
Duration (s), mean	4.0 (3.46–4.72)	2.1 (1.71–2.42)	0.0	≤0.000001
Duration (s), median	3.0 (2.93–4.00)	1.7 (1.00–2.00)	0.0	≤0.000001
Controls (n = 42)				
Duration (s), min	1.1 (0.82–1.26)	0.5 (0.50–0.59)	2.0	≤0.000001
Duration (s), max	10.1 (8.77–13.19)	7.5 (6.23–9.88)	157.0	≤0.00023
Duration (s), mean	4.1 (3.47–4.88)	1.9 (1.66–2.26)	0.0	≤0.000001
Duration (s), median	3.4 (2.70–4.00)	1.2 (1.00–1.70)	0.0	≤0.000001

Abbreviations: IQR, interquartile range; max, maximum; min, minimum; RLS, restless legs syndrome; s, seconds. LM denotes leg movement with duration 0.5–10 seconds; Bilateral LMs denotes two or more LMs, recorded over the two sides, overlapping or with the onset of the following movement <0.5 second after the offset of the preceding LM.

Fig. 1. Percentage of bilateral LMs including two, three, four, or more than four individual leg movements (LMs) found in restless legs syndrome (RLS) patients and controls. Data are shown as mean (columns) and standard error (whiskers). Individual LM denotes leg movement with duration 0.5–10 s; Bilateral LMs denotes two or more LMs, recorded over the two sides, overlapping or with the onset of the following movement <0.5 second after the offset of the preceding LM.

Fig. 2. Distribution of the duration of all bilateral leg movements (LMs) found in both restless legs syndrome (RLS) patients and controls. Histograms represent all bilateral LMs or separated by type (short-interval, periodic leg movements during sleep [PLMS], or isolated). Data are shown as median (columns) and interquartile range (whiskers). Bilateral LMs denote two or more LMs, recorded over the two sides, overlapping or with the onset of the following movement <0.5 second after the offset of the preceding LM.

Fig. 3. Duration of monolateral and bilateral leg movements (LMs) containing two, three, four, or a higher number of individual LMs. Data are plotted as median (circles or squares) and interquartile range (whiskers). Monolateral LM denotes leg movement with duration 0.5–10 seconds involving only one side; Bilateral LMs denotes two or more LMs, recorded over the two sides, overlapping or with the onset of the following movement <0.5 second after the offset of the preceding LM.