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ORIGINAL ARTICLE

Periodic leg movements in sleep in patients with supratentorial cerebral infarction

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Abstract The pathophysiology of periodic leg movements in sleep (PLMS) is complex, and still lacks a consensus. Consecutive 35 patients with the diagnosis of acute supratentorial ischemic stroke and 35 age- and sex-matched control subjects were prospectively investigated. Clinical and sociodemographic evaluation and a whole-night polysomnographic recording were performed. In patients with supratentorial ischemic stroke, 27 patients (77.2%) had PLMS-index more than 5/h, and 19 out of 35 patients (54.3%) had PLMS-index more than 15/h; while only 10 participants (28.5%) in control group had PLMS-index more than 5/h, and 6 participants (17.1%) had PLMS-index more than 15/h ($p < 0.05$). None of the demographic variables showed statistically significant relationship with PLMS, such as gender ($p = 0.952$) and age ($p = 0.435$). Territorial localization of ischemic lesions showed no relation with the presence of PLMS ($p = 0.867$), PLMS-index ($p = 0.432$), or restless legs syndrome ($p = 0.833$). All patients demonstrated PLMS contralateral to ischemic lesion except eight patients with bilateral PLMS; these were also more prominent contralaterally. Our study supports the hypothesis that destructive lesions causing the loss of cortical or subcortical inhibition exerting on the reticular formation on spinal pathways could lead to the development of PLMS.

Keywords Periodic leg movements in sleep · Supratentorial cerebral infarction · Subcortical disinhibition · Restless legs syndrome

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Introduction

Periodic leg movements in sleep (PLMS) are sleep related phenomena characterized by periodic episodes of repetitive and highly stereotyped limb movements [1]. These movements are characterized by the dorsiflexion of ankle and toes, a partial flexion of knee and sometimes hip, and connected to the nocturnal awakenings and unrefreshing sleep. PLMS were first described by Symonds [2, 3] as 'nocturnal myoclonus' and polysomnographic (PSG) recording was first performed by Lugaresi et al. [4]. The term 'periodic leg movement disorder' (PLMD) is defined by the International Classification of Sleep Disorders as PLMS accompanied by a clinical sleep disturbance or a complaint of daytime fatigue [5]. Although various conditions such as uremia, iron deficiency, peripheral neuropathy, radiculopathy, and spinal cord and brainstem lesions are well-known to induce PLMS; [6–8] the underlying pathophysiology is still not well-known. It was suggested that the loss of cortical or subcortical inhibition exerting on the brainstem generator might cause PLMS [9]. There are three case reports, wherein focal supratentorial cerebral infarctions involving the corona radiata, lenticulostriate region, pallidum and internal capsule were accused of PLMS [10–12], supporting the hypothesis that PLMS arise from suprasegmental disin-hibition of lower spinal circuitry [13]. On the basis of these data, we aimed to investigate patients with supratentorial infarctions for the PLMS.

Methods and materials

Consecutive 35 patients hospitalized in our neurology department with the diagnosis of ischemic cerebrovascular

diseases were prospectively investigated for PLMS within 1 week of stroke onset. Only the patients with supratentorial lesions were included into the study. The diagnosis of stroke was confirmed by the cranial magnetic resonance imaging (MRI) in all patients and lesion localizations were recorded. An age- and sex-matched control group consisted of 24 healthy participants, who are relative to the patients and who had no history of stroke or transient ischemic stroke, were consecutively included to the study and investigated within the same procedure. None of the participants were on medications that might affect the central nervous system, and none of them had treatment for PLMS or restless legs syndrome (RLS). The clinical evaluation of all participants was performed by one neurologist (G.B.) specialized in sleep and disorders. The study was approved by the institutional ethics committee in our faculty, and the informed written consents were obtained from all participants or their first-degree relatives (for patients who were unable to give informed consents).

All participants had a whole-night polysomnographic recording performed on Embla a-10 (Flaga, Reykjavik, Iceland) system. Sleep was recorded and scored according to the AASM (American Academy of Sleep Medicine) Manual for the Scoring of Sleep and Associated Events [14]. Leg movements were recorded from both left and right tibial electromyogram recordings using surface electrodes placed on the lower third of the anterior tibialis muscle. The electromyography signal was recorded at a time-constant of 0.3 s and a high band-pass filter setting of 90 Hz, and electrode impedance of 5,000 ohms or less. In the definition of PLMS, the most recent standards for recording and scoring periodic leg movements proposed by the American Association of Sleep Medicine were used [5]. The number of periodic movements per hour of total sleep time (PLMS index), number of periodic movements followed by an arousal per hour of total sleep time (PLMS-arousal index), minimum, maximum and mean durations of movements, and PLMS indices in NREM and REM sleep stages were calculated. Respiratory events were also accurately assessed in PSG recordings. PLMS associated with respiratory events were not included in PLMS-related parameters, but scored and analyzed separately as PLMS-associated with respiratory disturbance. The respiratory disturbance index (RDI), minimum and average oxygen saturation levels were also recorded.

In statistical analysis, Pearson Chi-square test and nonparametric Mann–Whitney U test were used, as appropriate. PLMS parameters in two groups were analyzed by using the Student's t test for parametric values, and Spearman's or Kendall correlation analysis for nominal or ordinal nonparametric values, respectively. The threshold level for statistical significance was established at $p < 0.05$.

Results

Demographic data

Of 35 stroke patients, 22 patients were males (62.9%) and 13 were females (37.1%). In the control group, 24 participants were males (68.6%) and 11 were females (31.4%). The mean age of patients was 68.1 ± 9.9 years (ranging between 50 and 92 years) and the mean age of control group was 65.7 ± 10.1 years (between 46 and 88 years). The age ($p = 0.687$, Mann–Whitney U test) and gender ($p = 0.842$, Pearson Chi-square test) were matched between patients and controls. The mean body mass index was also not different (26.6 ± 4.6 kg/m^2 in patients versus 24.9 ± 6.8 kg/m^2 in controls; $p = 0.646$, Mann–Whitney U test). The RLS was diagnosed in five patients (14.3%) and in seven control subjects (20%). None of these had a previous diagnosis of RLS. Among stroke patients, 23 patients (65.7%) had atherothrombotic cerebrovascular diseases and 12 had embolic strokes (34.3%). The territorial localizations of strokes are given in Table 1. None of the patients showed a pure cortical lesion.

Polysomnographic data

All patients with ischemic stroke were examined by PSG within the first 48 h of stroke. The polysomnographic data of all participants are summarized in Table 2. On clinical evaluation of stroke patients, 7 patients had a clinical sleep disturbance accompanying PLMS (fulfilling the criteria for PLMD) and 18 patients had obstructive sleep apnea syndrome (OSAS) symptomatology. Upon PSG recordings, 27 patients (77.2%) had a PLMS index more than 5/h and 19 out of 35 patients (54.3%) had a PLMS index more than 15/h. On the other hand, only 10 control subjects (28.5%) had a PLMS index more than 5/h and 6 of them (17.1%) had a PLMS index more than 15/h. PLMS index values

Table 1 The territorial localizations of strokes

Anatomical localizations	Number of patients		
	Right-sided	Left-sided	Total
Middle cerebral artery (MCA) territory	9	4	13
Anterior cerebral artery (ACA) territory	1	–	1
Posterior cerebral artery (PCA) territory	–	1	1
Corona radiata	5	2	7
Basal ganglia	1	4	5
Thalamus	3	1	4
Centrum semiovale	2	2	4

Table 2 The polysomnographic findings of all participants

Polysomnographic data	Patients with ischemic lesion		Control subjects	
	Mean ± SD	min.–max.	Mean ± SD	min.–max.
Total sleep time (min)	303.1 ± 77.4	123.0–485.1	358.5 ± 46.7	292.0–498.5
Sleep efficiency (%)	73.7 ± 15.7	29.0–99.1	81.4 ± 9.4	65.1–96.4
Sleep continuity (%)	74.6 ± 15.1	33.1–99.5	83.7 ± 8.6	65.5–96.6
Sleep latency (min)	15.9 ± 18.5	0.4–70.8	12.2 ± 15.1	0.6–57.3
REM sleep latency (min)	152.7 ± 95.3	17.5–441.0	178.5 ± 86.6	49.5–284.0
Wakefulness (%)	24.4 ± 15.2	0.5–66.9	9.8 ± 10.6	2.4–34.5
N1 sleep stage (%)	13.7 ± 8.7	1.5–36.1	12.1 ± 6.2	1.6–18.1
N2 sleep stage (%)	68.8 ± 71.1	19.9–468.7	59.6 ± 13.8	34.2–83.5
N3 sleep stage (%)	21.2 ± 15.1	0–73.5	18.3 ± 10.4	6.2–44.1
REM sleep stage (%)	8.2 ± 7.1	0–24.4	9.7 ± 9.3	6.6–32.2
Apnea-hypopnea index	21.9 ± 18.7	0.2–78.0	17.8 ± 19.8	0–56.0
RERA index	16.9 ± 11.3	0–46.3	23.1 ± 19.0	4.3–40.2
RDI index	38.9 ± 20.4	0.2–83.0	40.8 ± 21.2	4.3–68.6
Average O_2 saturation level	93.5 ± 2.2	85.6–97.1	93.4 ± 1.4	90.2–96.3
Minimum O_2 saturation level	80.9 ± 9.3	51.0–94.0	76.8 ± 10.5	50.0–88.0

* p value is more than 0.05 for all variables

were significantly higher in stroke patients than in control subjects ($p = 0.020$ for PLMS index >5/h, and $p = 0.038$ for PLMS index >15/h; Mann–Whitney U test). PLMS parameters are given in Table 3. The mean PLMS index was found as 44.1 ± 52.5/h in stroke patients and 21.8 ± 19.6/h in controls ($p = 0.026$, Mann–Whitney U test). In case if only stroke patients with a PLMS index more than 15/h were analyzed, the mean PLMS index was calculated as high as 70.7 ± 61.0/h.

RLS was diagnosed in five patients (14.3%) with ischemic stroke; three of them (60.0%) had PLMS, which constituted only 15.7% of patients with PLMS in stroke patients. PLMS parameters did not show any difference in patients with or without RLS. In the control group, on the other hand, seven participants (20%) were diagnosed as having RLS; six of them (85.7%) had PLMS.

None of the sociodemographic or polysomnographic variables, including gender ($p = 0.952$, Mann–Whitney U test), age ($p = 0.435$, Student's t test), or RDI ($p = 0.921$, Student's t test) showed statistically significant relationship with PLMS. In correlation analysis, PLMS index was indeed positively correlated with age ($p = 0.246$, Kendall correlation) and RDI ($p = 0.609$, Kendall correlation), though not significant. The effect of the body position on PLMS could not be analyzed, because stroke patients were hemiplegic and spent the night lying on supine position.

Clinical data

The anatomical localizations of stroke in accordance with the presence of PLMS are given in Table 4. The territorial localizations of ischemic lesions showed no relation with

Table 3 The characteristics of periodic leg movements in sleep in patients and controls

PLMS data	Patients with ischemic lesion		Control subjects		p value
	Mean ± s.d.	min.–max.	Mean ± s.d.	min.–max.	
PLMS index	44.1 ± 52.5	0–252.7	21.8 ± 19.6	0–62.8	**0.026**
PLMS-arousal index	10.4 ± 8.4	0–36.4	17.8 ± 8.4	0–36.4	0.243
PLMS index—associated with respiratory disturbance	6.8 ± 10.1	0–39.1	6.3 ± 10.1	0–31.4	0.852
Minimum duration (min)	0.5 ± 0.06	0.5–0.7	0.5 ± 0.07	0.5–0.8	1.000
Maximum duration (min)	6.9 ± 2.5	2.1–10.0	5.4 ± 3.2	2.5–10.0	0.992
Mean duration (min)	2.4 ± 0.5	1.4–4.3	2.1 ± 0.5	1.6–3.6	0.874
PLMS index in NREM sleep	50.6 ± 54.6	0–256.9	36.4 ± 24.5	0–86.8	0.083
PLMS index in REM sleep	13.7 ± 25.0	0–98.0	10.4 ± 18.2	0–59.4	0.234

Bold value is statistically siginificant

Table 4 The anatomical localizations of strokes in accordance with the presence of PLMS

Anatomical localizations	Number of patients		
	PLMS ≥ 15/h	PLMS ≥ 5/h	No PLMS
Middle cerebral artery (MCA) territory ($n = 13$)	6	9	4
Anterior cerebral artery (ACA) territory ($n = 1$)	1	1	0
Posterior cerebral artery (PCA) territory ($n = 1$)	–	–	1
Corona radiata ($n = 7$)	3	5	2
Basal ganglia ($n = 5$)	4	5	0
Thalamus ($n = 4$)	3	4	0
Centrum semiovale ($n = 4$)	2	3	1
Total ($n = 35$)	19	27	8

the presence of PLMS ($p = 0.867$, Pearson Chi-square test), PLMS index ($p = 0.432$, Mann–Whitney U test), and the presence of RLS ($p = 0.833$, Pearson Chi-square test). Stroke volume was not associated with the presence of PLMS ($p = 0.448$, Mann–Whitney U test), and did not show any correlation with PLMS index, either ($p = 0.622$, Spearman's correlation). Of 27 patients with ischemic stroke and a PLMS index higher than five per hour, 19 patients displayed PLMS in the lower extremity contralateral to the ischemic lesion. In eight patients, however, PLMS were bilateral, but more prominent on the contralateral extremity as well. In the control group, on the other hand, all participants had bilateral PLMS; in two participants PLMS were more prominent on the right side.

Discussion

In this prospective study, we found that 54.3% of patients with supratentorial infarction had PLMS, with a high mean PLMS index of 44.1 ± 52.5/h. Moreover, 77.2% of patients had a PLMS index over 5/h. In contrast, PLMS were present in 17.1% of the age- and sex-matched control group. The largest epidemiological study evaluating the presence of PLMS documented a 3.9% prevalence in 18,980 subjects from the general population aged 15–100 years, though the prevalence of PLMS was found to increase with advanced age [15, 16]. Studies showed that about 30–58% of elderly population had PLMS greater than 5 [17, 18]. A recent study investigating 70 healthy, middle-aged subjects between 40 and 60 years, showed that the mean PLMS index was 9.6 + 1.9, and there was no significant relationship between age and PLMS index [19]. The age did not show a significant correlation with PLMS index in our study, as well. The female gender was found to be associated with PLMS [20], though a significantly higher proportion of men than women was shown in another study [19]. We did not observe any association between gender and PLMS parameters in our study.

Nineteen patients out of 27 patients with ischemic stroke and PLMS had leg movements contralateral to the lesion. In eight patients, the leg movements were recorded bilaterally, but they were much more prominent on the contralateral extremity, as well. The temporal relationship between stroke and PLMS, the contralateral settlement of PLMS, together with the absence of a previous history of neurological or sleep disorders support the causal relationship rather than a simple coincidental occurrence.

There are only few case reports on cerebrovascular diseases and PLMS. The first report came from Kim et al. [8], who presented two patients with right-sided PLMS following small infarctions on left mid-pons. Kang et al. [10]. reported a 40-year-old man who developed right-sided PLMS beginning 7 days after an ischemic stroke on the left corona radiata. Lee et al. [11] later reported a similar case of 58-year-old man, who developed right-sided PLMS 2 days after an ischemic stroke on the left pallidum and internal capsule. Both cases were confirmed by polysomnography, showing that PLMS were predominated in the leg opposite to the hemisphere affected by stroke. Rosetti et al. [21] reported a patient with unilateral periodic leg movements during wakefulness and sleep after a parietal hemorrhage. Finally, RLS associated with PLMS and disruption of sleep architecture was reported by Sechi et al. [12], occurring in a patient following ischemic infarction on the right lenticulostriate region.

The anatomical structure responsible for PLMS still remains unclear; however, several reports have suggested related anatomical substrates. Electrophysiological and functional MRI studies showed a strong association between dysfunction at brainstem level for both primary and secondary PLMS [22]. It has been proposed that disinhibition of reticular formation at brainstem could result in reticulospinal excitatory responses and pathological recruitment in propriospinal or spinal jerks [23]. The destructive lesions causing the loss of cortical or subcortical inhibition exerting on the reticular formation on spinal pathways could therefore lead to the development of PLMS [8, 10, 13]. The results of our study support this hypothesis, showing a high prevalence of unilateral or asymmetrically bilateral PLMS in patients with supratentorial cerebrovascular diseases.

Among other diseases that are commonly found in association with PLMS are RLS and OSAS. The RLS was identified in 5–15% of general population, but in up to 80% of patients with PLMS [24, 25]. In our study, RLS was present in 14.3% of stroke patients, and 60% of them had PLMS. From another point, only 15.7% of patients with PLMS had RLS. Furthermore, we did not observe any differences in PLMS parameters between patients

with or without RLS. PLMS may also occur in OSAS patients in temporal association with abnormal respiratory events [26]. OSAS was present in 68.6% of our patients with ischemic stroke and 33.3% of them had PLMS. Of patients with PLMS and ischemic stroke, 42.1% had OSAS. On the other hand, the other PSG parameters such as RDI or oxygen saturations did not showed any statistically significant relationship with the polysomnographic PLMS parameters.

Besides sleep disorders, an elevated PLMS index was also shown in patients with alcohol dependency [26] or essential hypertension [27]. Some observational studies described an increase of PLMS in patients treated with psychoactive substances [28]. None of our patients had psychoactive drug treatment or alcohol dependency. Hypertension, together with the other medical disorders such as cardiac diseases, diabetes mellitus, hyperlipidemia or history of neuropathy were questioned in our study, and no significant relation was found with the presence of PLMS or PLMS index. Recently, there is a growing body of the literature implicating RLS and/or PLMS in cardiovascular risks. These patients were reported to be more likely to suffer from coronary artery disease, hypertension, and stroke [29]. Increased sympathetic activation secondary to RLS or arousal reactions following PLMS have been suggested as the underlying pathophysiology. Although the emergence of PLMS/PLMD was after the cerebrovascular event and contralateral to the lesion in majority of our study population, the possibility of premorbid PLMS before the ischemic events and the increased risk for stroke could also be questioned.

Conflict of interest None.

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