

Case report

Restless legs syndrome and periodic limb movements after ischemic stroke in the right lenticulostriate region

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Abstract

We report the first instance of restless legs syndrome (RLS) associated with periodic limb movements (PLM) and disruption of sleep architecture occurring in a patient following ischemic infarction in the right lenticulostriate region. Recently, a role for the basal ganglia–brainstem system in the control of motor behaviors and in the regulation of awake–sleep states has been proposed. The purported roles of these structures may be relevant in explaining the occurrence of the RLS in our patient. The discrete brain localization observed in this patient may be a clue to a better understanding of the pathophysiology of RLS and PLM.

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1. Introduction

The pathophysiology of restless legs syndrome (RLS) remains uncertain, although it has been suggested that some brain loci may be involved and a central dopaminergic dysfunction has been hypothesized [1,2]. We report the first instance of RLS associated with periodic limb movements (PLM) and disruption of nocturnal sleep architecture occurring in a patient following ischemic infarction in the right lenticulostriate region. This discrete localization may be a clue to a better understanding of the pathophysiology of the RLS and PLM.

2. Case report

A 48-year old, right-handed woman with a eighth-grade education was admitted to our neurological ward in August 2003 following the acute appearance of a mild motor deficit involving the face, arm and leg on the left side

of the body. Her medical history was unremarkable. Family history was negative for neurological pathologies. A brain CT without contrast was normal. Her motor signs recovered completely within 36 h. She was treated with acetylsalicylic acid 325 mg daily. Four days after the admission, a further CT without contrast showed a low-density area consistent with a lacunar infarction in the right lenticulostriate region. One day following her recovery from the motor deficit, the patient began to experience uncomfortable sensations in the extremities, mainly the legs, that worsened during inactivity, in the evening and at night, mainly between 11 p.m. and 1 a.m. and which interfered with sleep. She reported an almost irresistible urge to move her legs and to pace in the floor at night. Each episode lasted at least 30 min and occurred nearly every night. Moreover, she reported frequent awakenings in the night with subsequent daytime somnolence. Her husband noted that she had frequent leg movements when she was asleep at night. She denied occurrence of any similar symptoms in her past. Her symptomatology did fulfil the minimal criteria of the International RLS study group for diagnosis of RLS [1]. A neurological examination was

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normal. Brain MRI studies, performed 1 month after admission, showed a small ischemic infarct in the territory of the lateral lenticulostriate arteries to the right, involving a tiny portion of the body of the caudate, the caudal part of the putamen, a tiny bit of the internal and external capsule, as well as a tiny part of the claustrum (Fig. 1). No other areas of ischemia were observed. Peripheral blood counts, serum electrolytes, erythrocyte sedimentation rate, glucose, liver, thyroid and renal function tests, iron, ferritin, folic acid, vitamin B12, antinuclear antibodies and rheumatoid arthritis factor were normal. Moreover, laboratory tests for Lyme disease, venereal diseases, monoclonal gammopathy and Sjogren syndrome were negative. Electroencephalogram, electrocardiogram, echocardiogram, echodoppler color flow imaging of carotids and vertebro-basilar arteries and chest-X-ray were unremarkable. She was not suffering from chronic venous insufficiency or varicose veins, nor had she used medications or substances associated with causing RLS. Electrophysiological investigations excluded peripheral neuropathy or lumbosacral radiculopathy. Treatment with amitriptyline 25 mg at 10 p.m. for the insomnia, for 4 days, had no effect. The patient was then treated with pramipexole 0.25 mg at night, obtaining a definite improvement of both the sensory and motor symptoms for about 3 weeks. After this period the symptoms partially resumed and pramipexole dose was increased to 0.50 mg daily with further little beneficial effect. About 1.5 year later, the brain MRI was unchanged, as were the RLS symptoms. The patient is still on pramipexole 0.50 mg daily.

3. Polysomnographic (PSG) study

The patient underwent PSG monitoring few months after the stroke using a portable device (Micromed Brain Spy 2100 16chs). Pramipexole was withdrawn 1 week before PSG study. EEG was acquired using a referential

technique with six electrodes (C4-A1, O1-A2, Cz-A2) positioned in accordance with the International 10-20 system (and referred to a common electrode placed in G2); other channels were dedicated to an electrooculogram (bipolar reconstruction); a chin electromyogram; arterial hemoglobin oxygen saturation level (HbSaO₂) (pulse oximeter with finger probe); body position; surface EMG on bilateral anterior tibialis and sural muscles, and ECG heart rate. Sleep stages were scored manually according to conventional criteria. Automatic analysis of sleep parameters was performed using “REMRANT Sleep Analysis Software” vers. 3.9[©] Medicare Automation. Periodic leg movements during sleep (PLMS) were scored accordingly to standard rules and quantified by a PLMS index (number of movements detected by PSG × 60)/total sleep time in mins = number of periodic leg movements per hour of sleep). Leg movements occurring both during sleep and during episodes of wakefulness were scored. Details of sleep structure and PLMS index are reported in Table 1.

4. Discussion

The temporal relationship between the ischemic stroke in the right lenticulostriate region; the onset of RLS symptoms associated with PLM and disruption of nocturnal sleep architecture supports a causative role of the lacunar ischemic damage in this patient. Moreover, recent data on the involvement of claustrum–basal ganglia both in the control of motor-sensorial crossmodal process, and in the regulation of awake–sleep states, support this relationship [3–5]. It is known that unilateral lesions of caudate nuclei and neighboring structures may induce bilateral restlessness and behavioral changes with hyperactivity and agitation [6]. This could be explained by the occurrence of a significant amount of bilaterality in the extrapyramidal pathways, which seems to be more pronounced in the female brain and in the right basal ganglia [7]. In

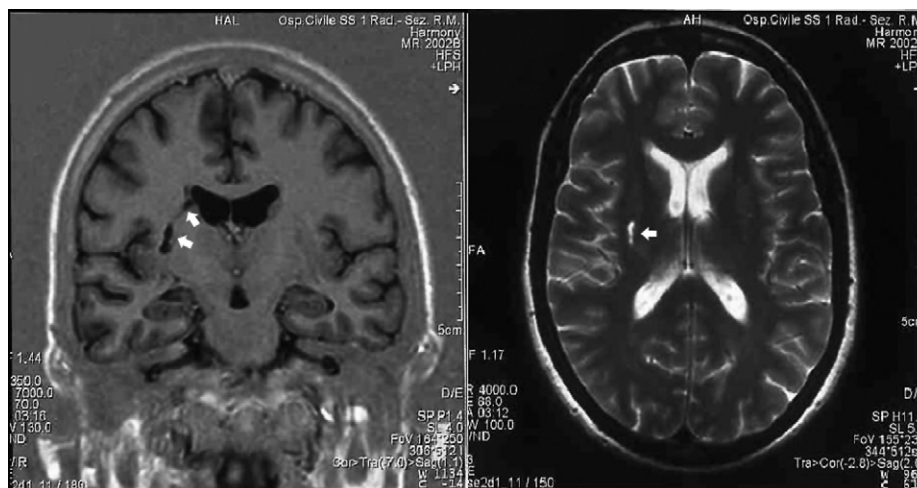


Fig. 1. Magnetic resonance images show an ischemic lesion in the right lenticulostriate region (A and B). The images are hypointense in proton density scans.

Table 1
Recording, sleep summary parameters and PLM by sleep stage

Time in bed	765.5 min	Sleep efficiency	68%
Number of awakenings (NW)	40	Total sleep period time	725 min
<i>Percentage of sleep stages</i>		<i>PLM by sleep stage</i>	
WASO	29.86	Total PLM/NREM	360
Stage 1	10.83	Total PLM/REM	0
Stage 2	42.90	Total number PLM	960
Stage 3	15.66	PLMS index	109.92
Stage 4	0.76	Mean duration PLM	2.35 s
Stage REM	0	Total sleep time	524 min

PLMS index: number of periodic leg movements per hour of sleep.

particular, experimental studies have shown that 10–20% of the globus pallidum internum output neurons project to the contralateral thalamus and tegmentum, and that cortico-striatal projections innervate both the ipsilateral and contralateral striatum. Thus, a disruption of neuronal circuits within the basal ganglia might influence the sensorimotor cortex either through antidromic excitation of cortico-basal ganglia fibers or through orthodromic activation of a basal ganglia–thalamocortical pathway [8]. These findings are consistent with the observation that patients with Parkinson's disease who have undergone unilateral stereotactic lesioning of the globus pallidus showed at least some improvement in extrapyramidal motor function of the ipsilateral side. However, the occurrence of a definite RLS, according to diagnostic criteria for this syndrome [1], secondary to a lacunar infarction in a discrete region of the brain has not previously been reported.

In this patient, other potential causes of RLS have been ruled out, and the neuropathology was confined to the right lenticulostriate region. In particular, as documented by the discrete lesion on MRI, the damage involved the body of the caudate, the caudal part of the putamen, the caudate and the external capsule, which mainly contains claustric connections. In patients with RLS a mild dopaminergic hypofunction in the caudate and putamen has been demonstrated by PET studies [2]. Moreover, neurophysiological and functional neuroimaging studies indicate that other brain loci may be involved in the pathophysiology of RLS, including: the sensorimotor cortex, cerebellum, thalamus and the red nuclei and brainstem close to the reticular formation [2]. However, how these different structures may interact in RLS remains unclear. The occurrence of a suprasegmental disinhibition of descending inhibitory pathways has been hypothesized by some authors [1,2].

In our patient, the RLS symptoms were associated with PLM in sleep and while awake, and with disruption of nocturnal sleep architecture (i.e., suppression of REM sleep and marked decrease of total time stage 4). An absence of REM sleep has been observed in patients with pontine lesions, and following cerebral infarction in the

territory of the middle cerebral artery to the right [9]. Discrete pontine lesions have also been associated with the occurrence of PLM. Recently, the role of basal ganglia–brainstem system through the mesopontine tegmentum, together with that of cortico-basal ganglia loop, in the control of motor behaviors, and in the regulation of awake–sleep states has been proposed [5]. The discrete lesion in the right lenticulostriate region documented in our patient might have disrupted this complex loop. In this case the involvement of claustrum and claustric connections is intriguing. The claustrum has reciprocal connections with the motor and sensory areas of the cerebral cortex including the dorsolateral prefrontal cortex, which seems to be involved in attention to pain and visuo-tactile information [3,10]. Additional connections include the nucleus accumbens, which is part of the mesolimbic pathway. Some authors believe that a dysfunction of the central dopaminergic system at this level may play an important pathophysiological role in RLS [2]. Interestingly, autoradiographic studies in animals and humans have detected in the claustrum a high distribution of both opioid receptors, mainly kappa and delta, and serotonin-2A receptors [4]. Opioids have been proven as an effective treatment of both sensory and motor symptoms of RLS, and several drugs that block the synaptic reuptake of serotonin (e.g., fluoxetine) have been associated with RLS [2]. The physiological role of the claustrum in humans remains uncertain. Recently, an involvement of this interconnecting structure in remembering stimuli from muscle positions and in sensorial crossmodal process and emotional aspects of pain has been suggested [3,4]. In our opinion, the purported roles of the claustrum may be relevant for understanding the occurrence of RLS symptoms in this patient.

In conclusion, our report indicates a possible role of specific structures in the right lenticulostriate region in the pathophysiology of RLS and PLM. A lesion in this area (nuclear complex or fiber systems) may exert both an ascending disinhibition on sensorimotor cortex, and a disinhibition of descending inhibitory pathways, resulting in a facilitation of RLS and PLM.

References

- [1] Allen RP, Picchietti D, Hening WA, International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101–19.
- [2] Wetter TC, Eisensehr I, Trenkwalder C. Functional neuroimaging studies in restless legs syndrome. *Sleep Med* 2004;5:401–6.
- [3] Calvert GA, Branner MJ, Bullmore ET, Campbell R, Iversen SD, David AS. Response amplification in sensory-specific cortices during crossmodal binding. *NeuroReport* 1999;10:2619–23.
- [4] Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 2004;127:835–43.
- [5] Takakusaki K, Saitoh K, Harada H, Kashiwayanagi M. Role of basal ganglia–brainstem pathways in the control of motor behaviours. *Neurosci Res* 2004;50:137–51.
- [6] Chung CS, Lee HS, Caplan LR. Caudate infarcts and hemorrhages. In: Bougausslauskys J, Caplan L, editors. *Stroke syndromes*. 2nd ed. Cambridge: Cambridge University Press; 2001. p. 469–78.
- [7] Kapreli E, Athanasopoulos S, Papathanasiou M, Van Hecke P, Strimpakos N, Gouliamos A, et al. Lateralization of brain activity during lower limb joints movement. An fMRI study. *Neuroimage* 2006;32:1709–21.
- [8] Liepert J, Restemeyer C, Kucinski T, Zittel S, Weiller C. Motor strokes: the lesion location determines motor excitability changes. *Stroke* 2005;36:2648–53.
- [9] Korner E, Flooh E, Reinhart B, Wolf R, Ott E, Krenn W, et al. Sleep alterations in ischemic stroke. *Eur Neurol* 1986;25:104–10.
- [10] Tanne-Gariepy J, Boussauod D, Rouiller EM. Projections of the claustrum to the primary motor, premotor, and prefrontal cortices in the macaque monkey. *J Comp Neurol* 2002;454:140–57.