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CASE REPORTS

REM sleep behavior disorder with predominant nightmares in a patient with ischemic pontine lesions

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Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia typically associated with synucleinopathy and evolving to neurodegenerative disorders. RBD is caused by impairment of brainstem nuclei controlling REM sleep muscle atonia. Rarely, focal lesions of the brainstem can cause secondary RBD. We present the case of a 74-year-old patient, previously evaluated at age 70 years for insomnia and periodic limb movements during sleep, who then rapidly developed unpleasant dreams with minor motor behavior, affecting his sleep quality. Polysomnography recorded REM sleep without atonia and motor behaviors in REM sleep. Ischemic lesions in the pons were detected by magnetic resonance imaging. Clinical, biological, and instrumental biomarkers of neurodegeneration were repeatedly negative at 2 years' follow-up. Although rare, a lesional cause of RBD must be considered in cases of atypical presentation and without evidence of neurodegeneration. The complaint of unpleasant dreams suggests a possible role of brainstem nuclei controlling REM sleep atonia in affecting oneiric content.

Keywords: lesional REM sleep behavior disorder, REM sleep without atonia, pons lesion

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INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM sleep parasomnia presenting with abnormal motor behaviors usually congruous with the oneiric content and associated with loss of the physiological REM sleep muscle atonia. RBD is strongly associated with neurodegenerative disorders in the spectrum of synucleinopathies (ie, Parkinson disease, dementia with Lewy bodies, and multiple system atrophy), and isolated RBD has the highest positive predictive value for impending neurodegeneration due to an underlying synucleinopathy.[1] Neuropathological studies and animal models suggested that RBD is caused by impairment of brainstem nuclei controlling REM sleep muscle tone (mainly tegmental nuclei of the dorsomedial pons).[2] Rarely, RBD has been described associated with focal lesions of the brainstem.[3]

REPORT OF CASE

A 70-year-old man was initially referred complaining of discomfort in his lower limbs at bedtime and during the night associated with insomnia and fragmented sleep. He had a history of heavy smoking habit, arterial hypertension (treated with losartan, lercanidipine, and doxazosin), and dyslipidemia (treated with ezetimibe). Neurological examination was normal. Video-polysomnography (v-PSG) documented reduced sleep efficiency (64%) and periodic limb movement (PLM) during sleep with a PLM index of 24 events/h; muscle atonia during REM sleep was normal (REM sleep atonia index [RAI], 0.932).[4] Pramipexole up to 0.36 mg and melatonin 5 mg at bedtime were prescribed with partial benefit on limb discomfort and sleep quality.

At age 74 the patient suddenly developed unpleasant and terrifying dreams (eg, fighting with burglars, being trapped by a fire), impairing his sleep quality, which dramatically worsened. His wife witnessed sleep-talking, coherent with the oneiric content (usually with elements of menace or violence), but no major motor events. He denied constipation, hyposmia, and any symptoms of autonomic dysfunction. Neurologic examination and neuropsychological tests were unremarkable. About 6 months later, follow-up v-PSG documented a 60-second episode in REM sleep with the patient swinging his trunk and semi-purposefully moving his upper limbs. Compared with the previous v-PSG, tonic and phasic activities in REM sleep were mildly increased on chin-electromyography (EMG), with a substantial increase in phasic muscle activity on bilateral extensor digitorum in the upper limbs. REM sleep without atonia was borderline on chin-EMG (RAI = 0.876), and pathological if chin and extensor digitorum–EMG were combined according to the SINBAR (Sleep Innsbruck Barcelona) criteria (REM sleep without atonia 75%) (**Table 1**).[4,5] PLM index was 11 events/h; apnea-hypopnea index was 3 events/h. About 9 months after the onset of unpleasant dreams, brain magnetic resonance imaging (MRI) showed 2 millimetric T2-hyperintense lesions in the rostral pontine tegmentum (1 medial and 1 on the left) (**Figure 1**), without signs of restriction in diffusion-weighted imaging, suggestive of previous ischemic lesions. Dopamine

Table 1—Comparison between v-PSGs.

	v-PSG at 70	v-PSG at 74	v-PSG at 76	Cutoff Values
Apnea-hypopnea index (events/h of TST)	0.6	3.0	1.6	> 5 events/h
PLM index (events/h of TST)	**24**	11.1	1.3	> 15 events/h
RAI on chin-EMG	0.932	**0.876**	0.918	> 0.9 normal 0.8–0.9 borderline < 0.8 pathological
SINBAR				
Phasic activity on chin-EMG (% of REM sleep 3-s mini-epochs)	13%	**26**%	**19**%	> 16.3% pathological
Any activity on chin-EMG (% of REM sleep 3-s mini-epochs)	16%	**31**%	**23**%	> 18% pathological
Any activity on chin-EMG or phasic activity on ED-EMG (% of REM sleep 3-s mini-epochs)	27%	**63**%	**53**%	> 32% pathological
Any activity on chin-EMG or phasic activity on ED-EMG (% of REM sleep 30-s epochs)	23%	**75**%	**63**%	> 27% pathological
Any activity on chin-EMG or phasic activity on AT-EMG (% of REM sleep 3-second mini-epochs)	33%	**48**%	38%	> 46.4% pathological
Ongoing medications	Losartan, lercanidipine, doxazosin, ezetimibe	Losartan, lercanidipine, doxazosin, ezetimibe, pramipexole, melatonin	Losartan, lercanidipine, doxazosin, ezetimibe, clonazepam, melatonin	

Evolution of muscle activity during REM sleep between the 3 v-PSGs, quantified according to automated RAI[4] and to manual SINBAR criteria[5] (altered values in bold). AT = anterior tibialis; ED = extensor digitorum; EMG = electromyography; PLM = periodic limb movement, v-PSG = video-polysomnography, RAI = REM sleep atonia index, REM = rapid eye movement, SINBAR = Sleep Innsbruck Barcelona, TST = total sleep time.

transporter–single photon emission computed tomography (DAT-SPECT) showed normal tracer uptake in the nigrostriatal dopaminergic pathway. Indirect immunofluorescence on skin biopsy was negative for intraneuronal phosphorylated alpha-synuclein. Pramipexole was discontinued for lack of efficacy on these new symptoms. The patient was treated with clonazepam up to 1 mg and melatonin increased up to 9 mg at night, with a poor control of disturbing nightmares at follow-up. Other medications remained unmodified.

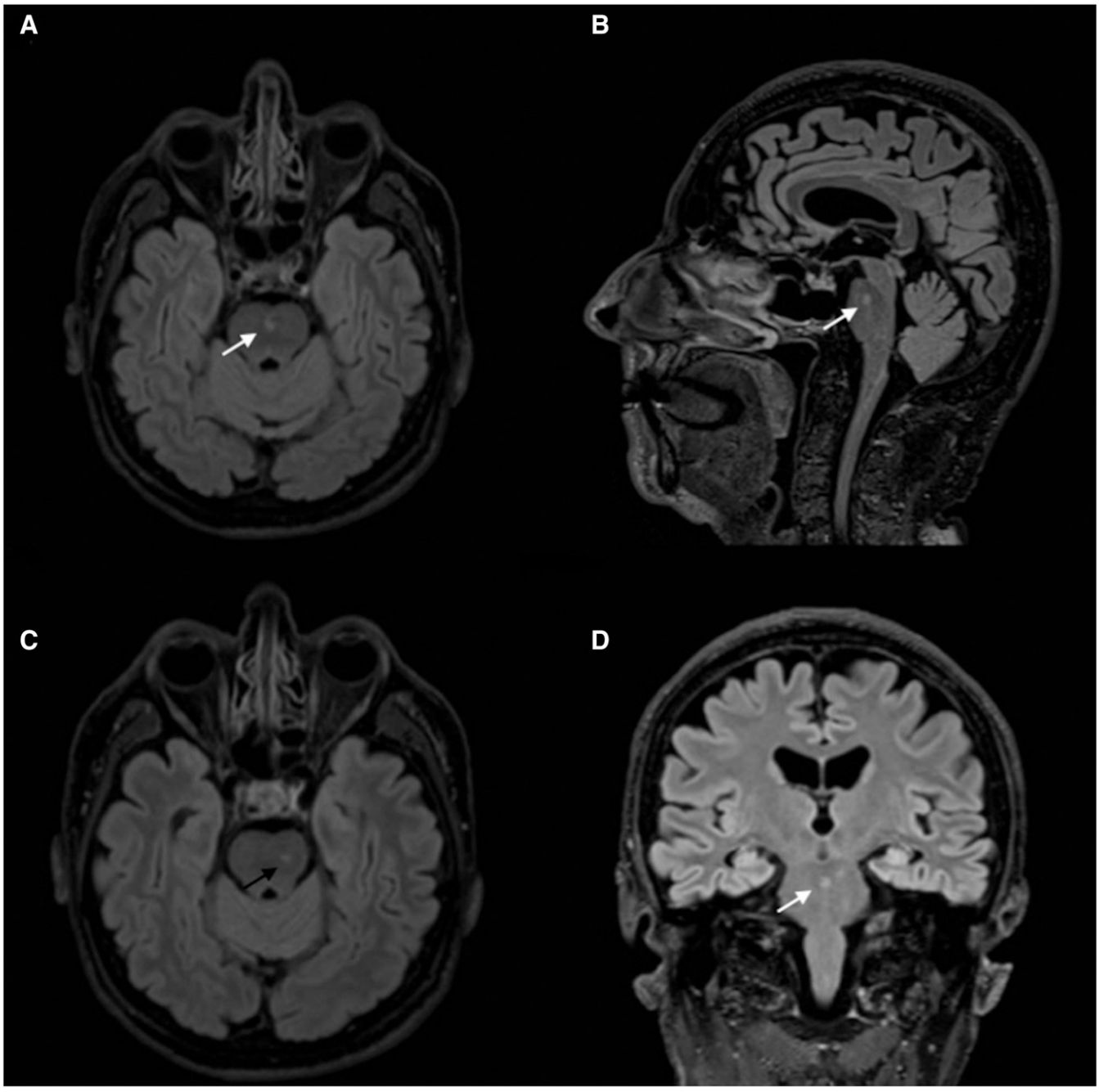
At age 76 years, the patient's symptoms and neurological examination were unchanged. Repeated neuropsychological tests, DAT-SPECT, and skin biopsy continued to be normal. Real-time quaking-induced conversion (RT-QuIC) performed on cerebrospinal fluid[6] showed negative results for alpha-synuclein. Screening for additional cerebrospinal fluid markers of neurodegeneration (tau, phosphorylated tau, and beta-amyloid) was also negative. A third v-PSG recorded a motor event in REM sleep similar to the one recorded at age 74 years, associated with promptly reported oneiric content (he was arguing with his wife). REM sleep without atonia persisted altered but, compared with the previous v-PSG, was mildly improved according to both SINBAR criteria and RAI (**Table 1**).

DISCUSSION

We present a case of RBD associated with pontine ischemic lesions. It is not possible to associate the timing of RBD onset with the appearance of the lesions (as proposed criteria for lesional RBD),[7] because brain MRI was performed several months after the onset of symptoms and no previous brain imaging was available for a comparison. The relatively short follow-up time does not allow us to rule out a synucleinopathy. However, neurodegenerative etiology of RBD appears unlikely, given repeated negativity of neurological examination, neuropsychological tests, DAT-SPECT, skin biopsy, and cerebrospinal fluid–RT-QuIC for alpha-synuclein.[6,8] Periodic limb movements during sleep were more likely idiopathic rather than related to the lesion, considering they preceded the acute onset of RBD by at least 4 years. Periodic limb movements during sleep faded in the second and third v-PSG when RBD was documented, probably efficaciously treated with pramipexole and clonazepam.

Conversely, the patient's complaint of sudden occurrence of nightmares since he was 74, affecting his quality of sleep, clinically marked the probable time course of ischemic pons damage

Figure 1—Brain MRI.



T2-FLAIR sequences of brain MRI showing hyperintense lesions in medial rostral pontine tegmentum (white arrow in A, B, D) and in left rostral pontine tegmentum (black arrow in C). MRI = magnetic resonance imaging.

associated with acute symptom onset. Accordingly, after the onset of RBD symptoms, the second and third v-PSG disclosed minor motor behaviors and moderately increased muscle activity during REM sleep, without a worsening over time, as reported instead for isolated RBD.[8] Different from typical RBD, no major motor behaviors were reported.

The incomplete loss of physiological REM sleep atonia could rely on the minimal dimensions and position of both lesions, as they are located more rostrally and ventrally than the dorsal pontine nuclei primarily involved in the control of REM sleep atonia and damaged in RBD.[2] The medial lesion appears in the rostral extremity of the raphe nucleus. Rarely, REM sleep atonia is reported partially preserved in other patients with lesional RBD. Similar to our case, a woman with T2-hyperintensity in the pontine and mesencephalic tegmentum and mesencephalic tectum (due to Wilson's disease) complained of vivid dreams, nightmares with sleep-talking, and v-PSG–documented minor motor events with mildly increased muscle tone in REM sleep.[9]

Disturbing dreams with violent and threatening themes are known to be frequent in RBD.[10] The reason is still debated: oneiric

content could change due to a more extensive subtle neurodegeneration involving higher functions or the limbic circuit,[11] or it could depend on a memory bias (violent dreams are more likely to be remembered than other dreams, because the first are more likely to be violently acted and thus to awaken the patient). However, these hypotheses cannot explain unpleasant dreams in an RBD due to brainstem lesions and without major motor behaviors. In this case, instead, disturbing dreams can be interpreted according to the hypothesis of Blumberg and Plumeau: damage in pontine areas controlling REM sleep atonia increases muscular twitches and provokes an enhanced sensory feedback from moving limbs that, in turn, influences oneiric content at the cortical level.[12]

On a more practical level, as shown by our case, brain MRI should be performed in the work-up of isolated RBD, at least when there are clues for suspecting the chance of a causative lesion. Some red flags should be considered: acute/subacute onset of the complaint, young age (unless in the context of narcolepsy), major cerebrovascular risk factors, other conditions potentially affecting the central nervous system (eg, malignancies, inflammatory disorders), associated focal neurological signs pointing to diencephalic or brainstem damage (absent in the presented case),[3,7] or absence of other additional motor and nonmotor symptoms suggestive of neurodegeneration.[1] Moreover, patients with RBD can rarely show disturbing nightmares predominant over the more typical symptoms of dream enactment. A v-PSG could be considered in the diagnostic work-up of patients with adult-onset nightmares (especially with a violent content, characteristic of RBD) and only mild motor behaviors during sleep.

ABBREVIATIONS

EMG, electromyography
MRI, magnetic resonance imaging
PLM, periodic limb movement
RAI, rapid eye movement sleep atonia index
RBD, rapid eye movement sleep behavior disorder
REM, rapid eye movement
v-PSG, video-polysomnography

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DISCLOSURE STATEMENT

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