Rapid eye movement sleep behaviour disorder symptomatic of a brain stem cavernoma

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SUMMARY
A 75-year-old man complained of excessive daytime sleepiness (EDS), difficulty falling asleep and nocturnal agitation during sleep. Restless legs syndrome (RLS) was diagnosed and treated. Because of persistent EDS, snoring and nycturia, a nocturnal polysomnography (PSG) was performed. PSG showed high sleep fragmentation related to a moderate to severe obstructive sleep apnea syndrome. Continuous positive airway pressure treatment (CPAP) was proposed. Because of the persistence of abnormal nocturnal behaviours, characterized by screaming, punching and falling out of bed, a video-PSG with CPAP treatment was performed. The recording showed typical chin electromyography (EMG) activity increase associated with violent movements during rapid eye movement (REM) sleep, suggesting REM sleep behaviour disorders (RBD). Clinical neurological examination found no parkinsonian syndrome, no dysautonomic sign and no neurological focal sign. Dopamine transporter imaging [123I-FP-CIT single photon emission computed tomography (SPECT)] did not find any presynaptic dopaminergic pathways degeneration. Brain magnetic resonance imaging showed a vascular lesion suggestive of cavernoma located in the pons. The present case illustrates the complexity of sleep disturbance diagnosis with a possible entanglement of aetiologies responsible for nocturnal agitation, and confirms that an isolated pons cavernoma should be considered among the rare causes of RBD.

CASE REPORT
A 75-year-old man was referred to his general practitioner because of excessive daytime sleepiness (EDS), difficulty falling asleep and nocturnal agitation during sleep for several years. His medical history consisted of lung cancer treated by surgery 6 years previously. His weight was within normal range.

He reported uncomfortable sensations in the legs that were relieved by movement. Symptoms typically begin and worsen when at rest, and occur notably in the evening. The patient mentioned familiar history of similar symptoms. Restless legs syndrome (RLS) was diagnosed and treated first by clonazepam, with poor tolerance, and then by pramipexole (0.7 mg/day) without clear efficacy. Because of a low ferritin level (15.7 ng/mL), iron supplementation was prescribed, which led to partial improvement. Because of EDS, snoring and nycturia, nocturnal polysomnography (PSG) was performed, using a conventional montage combining electroencephalography (EEG), electro-oculography (EOG), oronasal airflow by thermistor and nasal pressure measurements, thoraco-abdominal belts, electromyography (EMG) of chin and tibialis anterior muscles, electrocardiography (ECG), pulse oximetry and position captors. Sleep analysis demonstrated high fragmentation (microarousal index = 31/h) related to a moderate to severe obstructive sleep apnea syndrome (apnea–hypopnea index = 29/h). In addition, frequent periodic limb movements (105/h) were recorded. No typical chin EMG activity increase during rapid eye movement (REM) sleep was reported specifically. Thus a diagnosis of obstructive sleep apnea syndrome was made, and continuous positive airway pressure treatment (CPAP) was proposed.

Despite these treatments, nocturnal agitation and EDS (Epworth Sleepiness Scale: 12/24) remained troublesome and the patient was referred to a neurological clinic. Apart...
from RLS, the patient described abnormal nocturnal behaviours, characterized by screaming, punching or kicking his spouse and sometimes falling out of his bed. These behaviours were associated with vivid dreams that he could describe to his spouse. His dreams had frightening and zoological content. This description was highly suggestive of REM sleep behaviour disorders. The rest of the neurological examination did not reveal any parkinsonian syndrome, dysautonomic sign or neurological focal sign. The patient did not complain of any cognitive impairment and did not show depressive symptoms. In addition, orientated questions did not reveal any sign evocative of premotor Parkinson’s disease, such as hyposmia, fatigue, anxiety, apathy or constipation.

He was referred to a sleep specialist and a second PSG was performed, using a conventional montage as described previously, with CPAP treatment, pneumotachograph and video recording. The patient was fully informed and signed a written consent for video use in teaching, scientific conferences and medical publication. No ethical committee permission was requested, because our work involved only one clinical observation. PSG showed poor sleep efficiency (76%), numerous microarousals (74/h), periodic limb movements (105/h) and persistence of respiratory events (30/h), despite CPAP. Typical chin EMG activity increase associated with violent movements (kicking, boxing, etc.) during REM sleep was observed, providing confirmation of REM sleep behaviour disorders (RBD) (Fig. 1 and Video S1). Brain magnetic resonance imaging (MRI) was performed with T1 weighted images with and without contrast, gradient echo T2 weighted images, fluid attenuation inversion recovery (FLAIR) and diffusion sequences. MRI showed only a vascular lesion suggestive of cavernoma in the midline lower pons level next to the junction between pons and medulla (Fig. 2). No medullary MRI was performed in the absence of associated neurological symptoms or familial history of cavernomas. A single photon emission computed tomography (SPECT) using 123I-FP-CIT [dopamine transporter (DAT) scan*] did not find any sign of nigrostriatal dopaminergic pathway degeneration (Fig 3).

Overall, this patient presented the association of RLS, RBD and sleep apnea syndrome. Iron supplementation associated with pregabalin (150 mg/day) brought complete relief of RLS symptoms. Modification of CPAP settings was proposed and allowed a decrease in EDS and a partial improvement of RBD. Treatment with melatonin for RBD was begun but did not prove to be completely effective. Surgical removal of this cavernoma located in the brain stem between pons and medulla was never considered because of the neurological risk of surgery and because, as medical treatment was at least partially efficient, no self-injury (nor harm to others) could be observed. Since then, the patient has been regularly followed-up to detect clinical evolution and adjust treatment.

**DISCUSSION**

This case report illustrates the complexity of sleep disturbance mechanisms in the same subject, making diagnosis and treatment difficult. Indeed, our patient suffered from a combination of three frequent sleep disorders (Bresnitz et al., 1994; Kang et al., 2013; Ohayon et al., 2012): obstructive sleep apnea syndrome, RLS with periodic limb movements and RBD. To finally reach a complete diagnosis, several clinical and technical approaches were needed to provide a complete picture of the disease and adequate management of his symptoms.

In this particular case, we suspect the pons cavernoma of playing a role in the RBD mechanism. As the patient (and his spouse) did not describe a precise and acute onset of

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Figure 1. Polysomnography: typical chin electromyograph (EMG) activity increase during rapid eye movement (REM) sleep (red pointer). Fp2, C4, T4, O2, Fz, Cz, Pz: electroencephalograph (EEG) tracks; EOG (R) and EOG (L): right and left electro-oculogram tracks; chin: chin EMG track; EMG Limb (R) and (L): right and left limb EMG tracks; NAS: nasal air pressure track; THERM: thermal sensor track.
symptoms, we assume that repeated microbleeds in the cavernoma led gradually to the emergence of symptoms. Indeed, the patient had violent dream-enacting behaviours, with self-injury and injury to his spouse during nocturnal sleep, associated on PSG recording with the absence of physiological REM sleep atonia, which satisfied the diagnostic criteria for RBD [American Academy of Sleep Medicine (AASM), 2005]. RBD may be idiopathic but, in most cases, involves men aged more than 50 years, and is associated with neurodegenerative diseases, particularly with synucleinopathies [Parkinson’s disease, multiple system atrophy (MSA) and dementia with Lewy bodies] (Iranzo et al., 2013; Mahowald and Schenck, 2013). RBD may also be induced by drugs (especially antidepressant treatment) or may be associated with narcolepsy–cataplexy (Tippmann-Peikert et al., 2006). Some cases have rarely been observed in various acquired neurological conditions involving the brain stem (Table 1). Indeed, ischaemic lesions, localized in the left upper pons (Kimura et al., 2000) or in the right pontine tegmental (Xi and Luning, 2009) and demyelinating lesions in the dorsal pontine tegmentum (Tippmann-Peikert et al., 2006), have been reported to be associated with RBD. Other
conditions, such as Guillain–Barré syndrome, may also be associated with RBD (Thomas et al., 2007). To our knowledge, the present report is the first RBD case associated with a lower pons cavernoma. Notably, Provini et al. (2004) reported the development of RBD in a patient following resection of a tegmental ponto-mesencephalic cavernoma. These symptomatic cases of RBD provide arguments in favour of Boeve et al.’s (2007) theory about neural networks involved in human RBD pathophysiology. They hypothesize that brain structures and networks involved in REM sleep tone control in humans are analogous to those described in animal models (cats and rats). Thanks to animal studies, current views on REM sleep generation indicate that REM-on region is represented by the sublaterodorsal (SLD) nucleus and the precoeruleus region (PC). These nuclei, localized medial to the locus coeruleus at the lower/mid-level of the pons, exert a tonic excitatory effect on neurones of the magnocellular reticular formation in the ventromedial medulla that suppresses spinal motor neurone activity via the ventrolateral reticulospinal tract during REM sleep. Lesions of the PC region can reproduce REM sleep without atonia accompanied by motor behaviours in a cat (Siegel, 2006), and lesions of the SLD nucleus lead to disinhibition of spinal motoneurones, resulting in increased EMG tone during REM sleep in a rat (Lu et al., 2006). Several case reports, including ours, of brain stem lesions in humans causing RBD, argue for the crucial role of PC and SLD in REM atonia.

Our observation suggests that, even when isolated, RBD justifies brain MRI exploration in order to rule out a vascular or inflammatory lesion (Kimura et al., 2000; Provini et al., 2004; Tippmann-Peikert et al., 2006; Xi and Luning, 2009). Brain MRI more or less combined with123I-FP-CIT SPECT is also of interest for the diagnosis of neurodegenerative disorders such as MSA or PD even at the premotor phase of the disease, as suggested by long-term follow-up of subjects suffering from ‘idiopathic’ RBD (Siegel, 2006). RBD should be considered as an alerting symptom of synucleinopathies or of focal brain stem lesions. In our patient the DAT scan was normal, which supports the imputability of pons cavernoma in his RBD. However, only long-term follow-up of this patient will ensure that he will not develop associated neurodegenerative disease in the future (Iranzo et al., 2011).

**CONCLUSION**

RBD diagnosis may be difficult because of associated sleep disorders such as RLS, PLM and sleep apnea syndrome

<table>
<thead>
<tr>
<th>References (Publication year)</th>
<th>Lesion type</th>
<th>Lesion location</th>
<th>Associated neurological symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimura et al. (2000)</td>
<td>Ischaemia</td>
<td>Left upper pons</td>
<td>Episodes of transient dizziness and weakness in the right upper and lower extremities</td>
</tr>
<tr>
<td>Plazzi and Montagna (2002)</td>
<td>Multiple sclerosis</td>
<td>Pons</td>
<td>None</td>
</tr>
<tr>
<td>Zambelis et al. (2002)</td>
<td>Neurinoma</td>
<td>Left ponto cerebellar angle</td>
<td>Left side deafness</td>
</tr>
<tr>
<td>Tippmann-Debepeikert et al. (2006)</td>
<td>Multiple sclerosis</td>
<td>Median dorsal pons</td>
<td>Acute vertigo, ataxia, diplopia, dysarthria, bifacial weakness</td>
</tr>
<tr>
<td>Mathis et al. (2007)</td>
<td>Inflammatory lesion</td>
<td>Dorsomedial pontine tegmentum</td>
<td>Diplopia, horizontal nystagmus, vestibular syndrome, narcolepsy (sleep attacks, cataplexy like episodes, hypnagogic and hypnopompic hallucinations, sleep onset rapid eye movement on multiple sleep latency test)</td>
</tr>
<tr>
<td>Gómez-Choco et al. (2007)</td>
<td>Multiple sclerosis</td>
<td>Pons</td>
<td>Not available</td>
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<tr>
<td>Iranzo and Aparicio (2009)</td>
<td>Acute haemorrhage (cavernous haemangiom)</td>
<td>Left medulla</td>
<td>Wallenberg syndrome</td>
</tr>
<tr>
<td>Henriques-Filho and Pratesi (2008)</td>
<td>Arnold-Chiari malformation</td>
<td>Medulla and lower portion of the pons</td>
<td>Periodic limb movement during sleep</td>
</tr>
<tr>
<td>Xi and Luning. (2009)</td>
<td>Lacunar ischaemic infarct</td>
<td>Right paramedian pons</td>
<td>None</td>
</tr>
<tr>
<td>Limousin et al. (2009)</td>
<td>Post-inflammatory lesions</td>
<td>Right pontine tegmentum and right dorsal medulla</td>
<td>Internuclear ophthalmpoplegia, cerebellar ataxia</td>
</tr>
<tr>
<td>Reynolds and Roy (2011)</td>
<td>Encephalomalacia</td>
<td>Rostral medial pons, left of mid-line</td>
<td>Cataplexy</td>
</tr>
<tr>
<td>Jianhua et al. (2013)</td>
<td>Large B cell brain stem lymphoma</td>
<td>Ponto-mesencephalic junction and upper/mid pons level</td>
<td>Headache, ptosis, diplopia (right third nerve palsy), bilateral Babinski sign</td>
</tr>
<tr>
<td>Tang et al. (2014)</td>
<td>Ischaemic infarcts</td>
<td>Various brain stem locations (mainly pons)</td>
<td>Not available</td>
</tr>
</tbody>
</table>
(SAS). Complete PSG recording, including video, is a crucial exploration. RBD has to be considered as a focal neurological symptom that requires MRI and/or 123I-FP-CIT SPECT in order to detect brain stem lesions and/or early signs of synucleinopathies such as MS and PD.

REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Video S1. Rapid eye movement sleep behaviour disorder.