



Original Article

Neuroimaging-evident lesional pathology associated with REM sleep behavior disorder



Stuart J. McCarter^{a,b,c}, Maja Tippmann-Peikert^{a,b,c}, David J. Sandness^{a,b,c}, Eoin P. Flanagan^c,
Kejal Kantarci^d, Bradley F. Boeve^{a,b,c}, Michael H. Silber^{a,b,c}, Erik K. St. Louis^{a,b,c,*}

^a Mayo Center for Sleep Medicine, Mayo Clinic and Foundation, Rochester, MN, USA

^b Department of Medicine, Mayo Clinic and Foundation, Rochester, MN, USA

^c Department of Neurology, Mayo Clinic and Foundation, Rochester, MN, USA

^d Department of Radiology, Mayo Clinic and Foundation, Rochester, MN, USA

ARTICLE INFO

Article history:

Received 17 April 2015

Received in revised form 3 July 2015

Accepted 31 July 2015

Available online 14 September 2015

Keywords:

REM sleep behavior disorder

Parasomnia

Brain lesion

Neuroimaging

Outcome

ABSTRACT

Background/Rationale: Rapid eye movement (REM) sleep behavior disorder (RBD) is a potentially injurious parasomnia characterized by dream enactment behavior and polysomnographic REM sleep without atonia (RSWA). Recently, RBD not only has been shown to be strongly associated with synucleinopathy neurodegeneration but has also been rarely reported to be associated with structural lesions involving the brainstem or limbic system. The aim of this study was to describe the clinical, neuroimaging, and outcome characteristics in a case series of patients with lesional RBD.

Methods: This is a retrospective case series from a tertiary care referral center.

Results: A total of 10 patients with lesional RBD were identified. Seven (70%) were men, with an average age of sleep symptom onset of 53.7 ± 17.0 years. Structural pathology evident on neuroimaging included four extraaxial (three meningiomas and one basilar fusiform aneurysm with brainstem compression) and six intraaxial (encephalomalacia, multiple sclerosis, vasculitis, autoimmune limbic encephalitis, and leukodystrophy) lesions. No patient developed parkinsonian features or cognitive impairment suggestive of synucleinopathy over an average of 45.4 ± 35.2 months of follow-up.

Conclusions: RBD is rarely associated with non-synuclein structural lesions affecting the pons, medulla, or limbic system. The spectrum of lesional RBD comprises tumors, aneurysms, leukodystrophy, and autoimmune/inflammatory/demyelinating brain lesions.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a complex and potentially injurious parasomnia involving dream enactment behavior (DEB) that often mirrors terrifying dream content of being attacked or chased, associated with REM sleep without atonia (RWSA) [1–3]. While RBD is a frequent initial sign of synucleinopathy neurodegeneration, several reported RBD cases have been linked to lesional pathology, most commonly disrupting the dorsal pontine tegmentum or limbic system [4–21]. A recent case series of 119 patients with acute cerebral infarcts found that six of 27 patients with brainstem infarcts had RBD (22%) and that only brainstem lesions were independently associated with RBD development [22]. While mechanisms governing control of REM muscle

atonia remain incompletely understood, evidence from studies in the cat, rat, and mouse suggests that glutamatergic neurons in the dorsal pontine sublaterodorsal nucleus (SLD), also known as subcoeruleus, are key in the generation of REM sleep atonia. SLD glutamatergic neurons project to the trigeminal nucleus, ventromedial medulla, and spinal cord, synapsing on GABA_A, GABA_B, and glycinergic neurons in the medullary gigantocellularis nucleus and spinal inhibitory interneurons, resulting in hyperpolarization of trigeminal and spinal cord motoneurons and normal REM sleep atonia [23–25]. The most common structures exhibiting neuropathology or neurodegeneration in RBD patients comprise the SLD, gigantocellular reticular nucleus, dorsal raphe nucleus, and pedunculopontine nucleus [26]. Lesions of the ventromedial medulla, hypothalamus, substantia nigra, and limbic system have also been reported to accompany RBD symptoms [27]. In animals, the size and location of the lesion influence whether DEB involves only simple limb twitches or more complex attack behaviors [28]. Table 1 shows several case reports of RBD associated with brainstem and limbic system lesions that exist in the literature. However, to our knowledge, there has been no previous systematic case series describing common clinical and neuroimaging features of patients with lesional

* Corresponding author. Departments of Medicine and Neurology, Mayo Center for Sleep Medicine, Mayo Clinic College of Medicine, 200 First Street Southwest, Rochester, MN 55905, USA. Tel.: +1 507 266 7456; fax: +1 507 266 7772.

E-mail address: stlouis.erik@mayo.edu (E.K. St. Louis).

¹ Principal Investigator.

Table 1
Previously reported cases of RBD associated with MRI lesions in the literature.

Age/Sex	Lesion Location	Lesion Type/Neuro Diagnosis	Sleep Diagnosis	Outcome	Authors
67/M	Rostral medial pons, left of midline	Ischemic infarct	RBD + cataplexy	90% decrease in RBD and cataplexy symptoms with fluoxetine	Reynolds and Roy [16]
75/F	Left upper pons	Ischemic infarct	RBD	RBD under control with 0.25 mg of clonazepam	Kimura et al. [11]
68/M	Right paramedian pons	Ischemic infarct	RBD	RBD in remission with 0.25 mg of clonazepam	Xi and Luning [20]
79/M	Bilateral cerebellar and pontine white matter lesions	Ischemic infarcts	RBD	Not reported	Peter et al. [13]
40/F	Right pontine tegmentum and right dorsal medulla	Inflammatory/unknown etiology	Overlap parasomnia disorder	RBD and sleepwalking improved with 9 mg of melatonin	Limousin et al. [12]
30/M	Dorsomedial pontine tegmentum	Inflammatory/MS	RBD + narcolepsy	Continued RBD symptoms	Mathis et al. [29]
25/F	Pons	Inflammatory/MS	RBD	Symptoms resolved with adrenocorticotrophic hormone treatment	Plazzi and Montagna [14]
59/M	Left cerebellopontine angle	Neurinoma	RBD	Remission of RBD with tumor resection	Zambelis et al. [21]
30/M	Pontomesencephalic junction at upper/mid pons level	B cell lymphoma	RBD	Chemotherapy improved RBD	Jianhua et al. [30]
81/M	Left medulla	Cavernous hemangioma	RBD	RBD decreased, but persisted with clonazepam	Iranzo and Aparicio [27]
28/M	Pontomesencephalic tegmentum	Post cavernoma resection	RBD + status dissociatus	RBD improved with 2 mg of clonazepam	Provini et al. [15]
22/M	Pontine and mesencephalic tegmentum and mesencephalic tectum	Wilson's disease	RBD	No treatment	Tribi et al. [31]
69/M	Bilateral amygdala and dorsolateral midbrain	Anti-Ma2-associated encephalitis	RBD + narcolepsy	RBD not improved with IVIG and methylprednisolone	Compta et al. [5]
65/M	Bilateral mesial temporal lobes	VGKC Autoantibodies	RBD	Remission of RBD with immunosuppression	Iranzo et al. [10]

Dx = diagnosis, RBD = REM sleep behavior disorder; MS = multiple sclerosis; VGKC = voltage-gated potassium channel.

RBD. We report 10 cases of RBD associated with structural pathology evident on neuroimaging studies.

2. Methods

A diagnosis and text-based search yielded 10 patients having an RBD diagnosis with structural lesional pathology on magnetic resonance imaging (MRI). These 10 patients accounted for 0.67% of RBD cases seen at our center. Three cases were previously reported (Patient #1 [19], Patient #6 [18], and Patient #7 [7]). A chart review was performed to confirm (1) RBD, (2) presence of a neuroimaging lesion in a location known to be associated with RBD, and (3) extraction of relevant clinical and demographic data. Video polysomnographic (PSG) analysis was performed on eight (80%) patients to confirm the presence of RSWA. Since there are no consensus diagnostic criteria for lesional RBD, the suggested criteria of Iranzo and Aparicio was used, including (1) RBD onset temporally associated with a brain lesion; (2) RBD onset coincident with the onset of other symptoms potentially caused by the lesion; (3) lesion location in a brainstem or limbic system area known to regulate REM sleep; (4) lesion disappearance associated with remission or improvement of RBD symptoms; and (5) RBD not better explained by another disorder, such as synucleinopathy, medication use, or withdrawal [27]. This study was approved by the Mayo Clinic Institutional Review Board.

3. Results

Table 2 and Figs 1–7 show individual patient demographic data and symptoms on presentation, radiographic features, and treatment outcomes. Seven patients (70%) were men, with an average age at RBD onset of 53.7 ± 17.0 years. Four (40%) patients were taking antidepressant medications. Of the nine patients with an average follow-up of 45.4 ± 35.2 months (one patient was lost to follow-up), no patient developed parkinsonian features or cognitive impairment suggestive of synucleinopathy. In all patients, except Patient #2, DEB or sleep symptoms began within 1–2 months of neurologic symptom onset, surgical procedure, or identification on MRI imaging. Patient #2 had a longer history of symptoms, probably due to the slowly progressive mass effect associated with an underlying meningioma (Fig. 1). Patient #10 (Fig. 7) presented with seizures, cognitive dysfunction, and DEB consistent with autoimmune limbic encephalitis, which proved to be associated with elevated antibody titers against voltage-gated potassium channels (VGKC), and initial left caudate enhancement as well as later evolution of typical mesiotemporal pathology. The DEB improved with corticosteroids and immunosuppression. The remaining patients had lesions involving brainstem structures known to be associated with REM sleep muscle control, with four (40%) patients having discrete lesions within or neighboring the dorsal pontine tegmentum. Two (20%) patients had complete remission of DEB following surgical resection or radiographic remission of the lesion (Table 2, Figs 1–2). In Patient #8 (Fig. 5), RBD symptoms began following neurosurgical resection of an underlying epidermoid cyst, suggesting that pontine damage resulting from the procedure likely caused RBD.

4. Discussion

To our knowledge, this is one of the largest case series fulfilling the Iranzo/Aparicio criteria of lesional RBD associated with a range of structural pathology evident on neuroimaging, providing further supportive evidence that the pons and medulla, especially the dorsal pontine tegmentum and rostral ventromedial medulla, are responsible for the generation and maintenance of REM sleep muscle atonia [18,23,24,26,32,33], and that more rostral

Table 2
Clinical, demographic, imaging, and outcome data.

ID/Age/ Sex	Neuro Signs and Symptoms	Neuro Diagnosis	DEB Onset in Relation to Neuro Symptoms	DEB Onset in Relation to Imaging	DEB Content	Dream Recall	MRI Findings	Neuro Treatment	RBD Treatment	Outcome	Follow-up
1/51/F	Vertigo, diplopia, gait ataxia, horizontal gaze restriction	Multiple sclerosis	1–2 months after	2 months after imaging	Punching, screaming	None	Demyelinating right dorsal pontine lesion [19]	Rebif	Clonazepam 0.125 mg	RBD remission 45 months after onset w/radiographic remission of lesion	116 months, no RBD
2/68/M	Headaches, left facial paralysis, loss of pin and temperature sensation in V ₁ , V ₂ , V ₃ (Fig. 1)	Meningioma	Unclear	3–4 months before imaging	Punched wife, fell out of bed	Fighting and being chased	Left cerebellopontine angle meningioma with mass effect and upon the brainstem and compression of pons	None	Melatonin 9 mg	“Near complete control of RBD symptoms”	38 months, RBD well controlled
3/62/M	Cognitive difficulty (28/38 on Short Test of Mental Status), shuffling gait, action tremor, personality change (Fig. 2)	Meningioma	Simultaneous onset	1–2 years before imaging	Yelling, punching and kicking, punched wife	Chased or attacked by livestock	Right petroclival meningioma with moderate-marked distortion and displacement of the pons and midbrain to the left	Surgical resection	None	RBD remission with decreased mass effect on pons and midbrain	21 months, no RBD
4/61/F	Headaches, imbalance (Fig. 3)	Meningioma	Simultaneous with increased headaches	20 years after initial imaging	Screaming, thrashing, kicking	Being attacked or fighting intruders	Right cerebellopontine meningioma indenting right pontomedullary junction	None	Clonazepam 0.75 mg + melatonin 9 mg	Fluctuating control of RBD symptoms	88 months, difficult-to-control RBD symptoms
5/74/M	None (Asymptomatic aneurysm noted on MRI) (Fig. 4)	Fusiform basilar aneurysm	No neuro symptoms	Simultaneous onset with imaging	Punches, fallen out of bed, riding bicycle	Playing football, shooting a bow and arrow	Fusiform aneurysm of proximal and mid aspect of basilar artery with involvement of left intradural vertebral artery producing significant mass effect upon ventral and left aspect of the pons	None	Pramipexole 0.5 mg	Still sleep talks, but no thrashing of arms or legs	43 months, no mention of RBD symptoms
6/47/M	Dysarthria, dysphagia, right facial weakness, with right III and IV and bilateral VI, VII, X, and XII cranial neuropathies	Central and peripheral nervous system vasculitis	3 weeks after neuro symptoms	3 weeks after imaging	Pounding, punching, fall out of bed	Being attacked by fire ants, falling through ice	T2 hyperintensity in right pontomedullary junction extending inferiorly to level of medulla [18]	CellCept, Prednisone, Cytoxan	Melatonin 6 mg + buspirone 20 mg	Significant decrease in RBD symptoms	32 months, DEB once per month
7/61/M	Difficulty walking, leg weakness, and bowel and bladder incontinence	Autosomal-dominant, adult-onset leukodystrophy due to lamin B1 gene duplication	Simultaneous with neuro symptoms	2 years before imaging	Scream, flail arms, kick legs, fell out of bed	Being attacked	Bilateral T2-signal hyperintensities in the anterior medulla, middle cerebellar peduncles, dorsal pontine tegmentum, midbrain, and subcortical white matter [7]	None	Melatonin 3 mg	Significant decrease in RBD symptoms	18 months, DEB less than once per week
8/48/M	Gait ataxia, imbalance, cranial nerve VIII palsy (Fig. 5)	Posterior fossa epidermoid cyst	1 month after surgical resection of epidermoid cyst simultaneous with neuro symptoms	3 years before imaging	Punching, kicking, moaning	None	Fluid collection in operative site with flattening of left cerebellar peduncle with subtle brainstem T2 hyperintensity with FLAIR signal change neighboring 4th ventricle	None	Melatonin 3 mg	No follow-up	No follow-up
9/10/F	Headaches (Fig. 6)	Benign nonenhancing focal lesion of undetermined etiology	Unclear	Unclear	Kicking	None	Right nonenhancing dorsal pontine tegmental lesion with subtle mass effect	None	Melatonin 3 mg	No follow-up	17 months, no DEB
10/53/M	Seizures and memory decline (Fig. 7)	Voltage-gated potassium channel autoantibodies (associated with prostate adenocarcinoma)	Simultaneous with neuro symptoms	1 month before imaging	Talking, jerking, grabbing	None	FLAIR hyperintensity in left caudate, hippocampus, and parahippocampal gyrus	IV methylprednisolone, CellCept	None	Improvement in neurologic symptoms, no mention of sleep disturbances	48 months, no mention of RBD symptoms

Age = age at RBD symptom onset; Dx = diagnosis; Sx = symptoms; RBD = REM sleep behavior disorder; RSWA = REM sleep without atonia; DEB = dream enactment behavior; V₁ = ophthalmic nerve, V₂ = maxillary nerve; V₃ = mandibular nerve, Rx = Treatment; mg = milligrams.

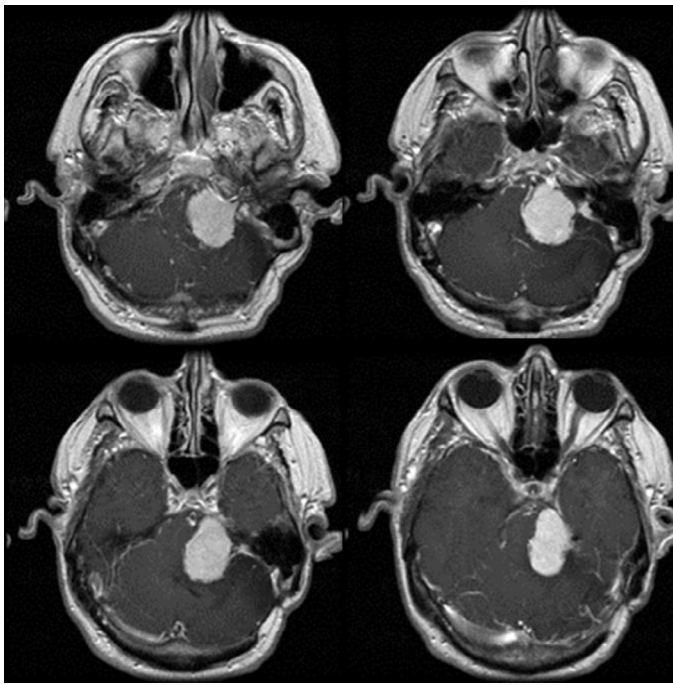


Fig. 1. A 68-year-old man with a left cerebellopontine angle meningioma compressing the pons and medulla, associated with headaches, left facial paresis, and left facial hypesthesia, accompanied by vivid dream enactment behaviors of punching, kicking, and falling out of bed, which remitted following meningioma resection and melatonin treatment (Patient #2 in Table 2).

structures in mesiotemporal limbic and also extralimbic neocortical pathology may also rarely facilitate DEB and (most likely indirectly) provoke dysregulation of REM sleep muscle tone. Two of the cases were cerebellopontine angle meningiomas similar to previous reports of RBD associated with a left cerebellopontine angle neurinoma [21]. Two additional novel structural pathologies not previously described were reported in association with RBD, a patient with a right petroclival meningioma and another with a basilar fusiform aneurysm, both resulting in pontine compression. Similar to a previous report [10], we also identified one patient with VGKC autoimmunity associated with an occult malignancy with improvement of DEB and neurologic symptoms following immunosuppression. We also report a patient who developed RBD postoperatively following removal of an epidermoid cyst, similar to a previous report of brainstem damage related to a surgical procedure inducing RBD [15].

Patient #4 (Fig. 3) did not undergo surgical resection of her right cerebellopontine angle meningioma and continued to have very-difficult-to-control RBD symptoms despite polytherapy with clonazepam and melatonin. However, Patient #2 (Fig. 1) and another previously reported patient having a left cerebellopontine angle mass had excellent response to pharmacologic therapy with 9 mg of melatonin and 1 mg of clonazepam, respectively [21]. Several of the brainstem and cortical lesions reported in our series were not bilateral, suggesting that a unilateral lesion may be sufficient to cause RSWA and RBD symptoms, similar to a previous lesional study showing that unilateral ventral mesopontine junction lesions were sufficient to cause RSWA in cats [28,34]. Given the diversity of different causative pathologies seen in this study and other prior reported cases, location of the lesion and not the underlying disease

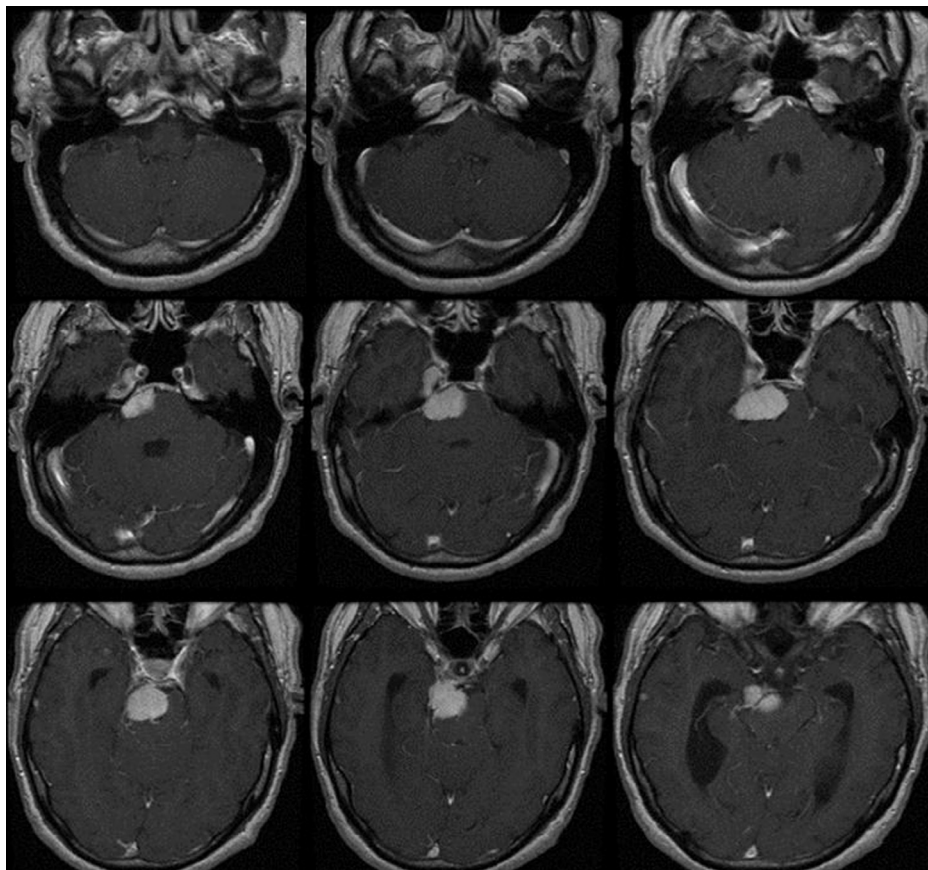


Fig. 2. A 62-year-old man with a right petroclival meningioma compressing the pons and medulla, associated with cognitive impairment and dream enactment behaviors of yelling, kicking, and punching his wife, all of which ceased following surgical resection of the meningioma (Patient #3 in Table 2).

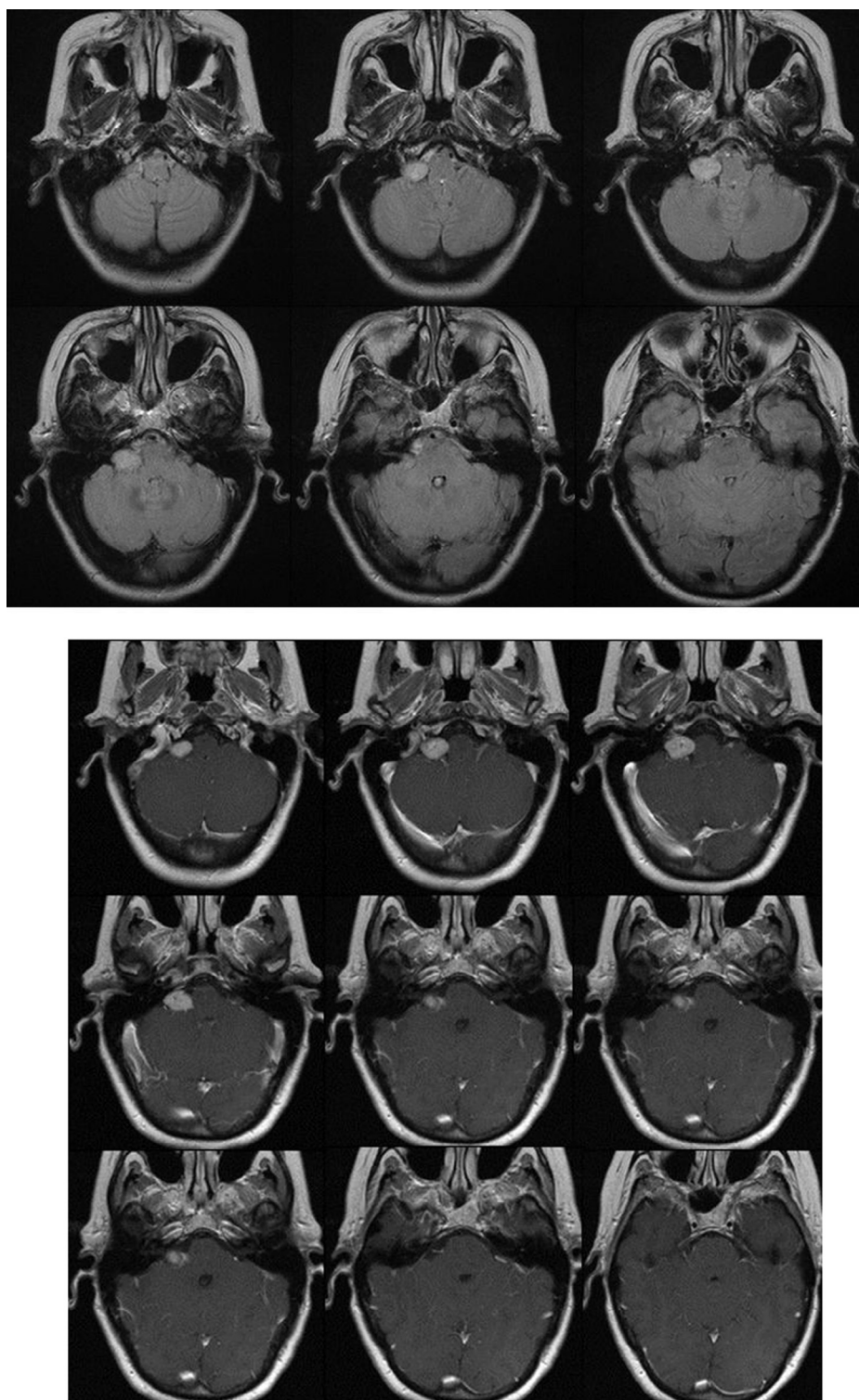


Fig. 3. A 61-year-old woman with a right cerebellopontine angle meningioma compressing the pontomedullary junction, associated with headaches, imbalance, and dream enactment behaviors characterized by screaming, thrashing, and kicking movements, which remained refractory to polytherapy with clonazepam and melatonin (Patient #4 in Table 2).

process (ie, inflammatory, infarct, tumor, surgery, etc.) appears to be the principle factor related to the development of RBD [7,11–14,16,18,19,21,29]. However, Patient #1 (Fig. 1) had complete remission of RBD symptoms with radiographic remission of the lesion, whereas the patient with a vasculitic lesion in the same location (Patient #6 [18]) had continued RBD symptoms despite radiographic remission,

indicating mechanistic difference between disease processes resulting in transient versus permanent damage. Furthermore, dream enactment and dream recall were similar in this series in comparison to that seen in patients with neurodegeneration-associated RBD (i.e., idiopathic RBD, Parkinson's disease [PD]–RBD, multiple system atrophy [MSA]–RBD, dementia with Lewy bodies [DLB]–RBD) again

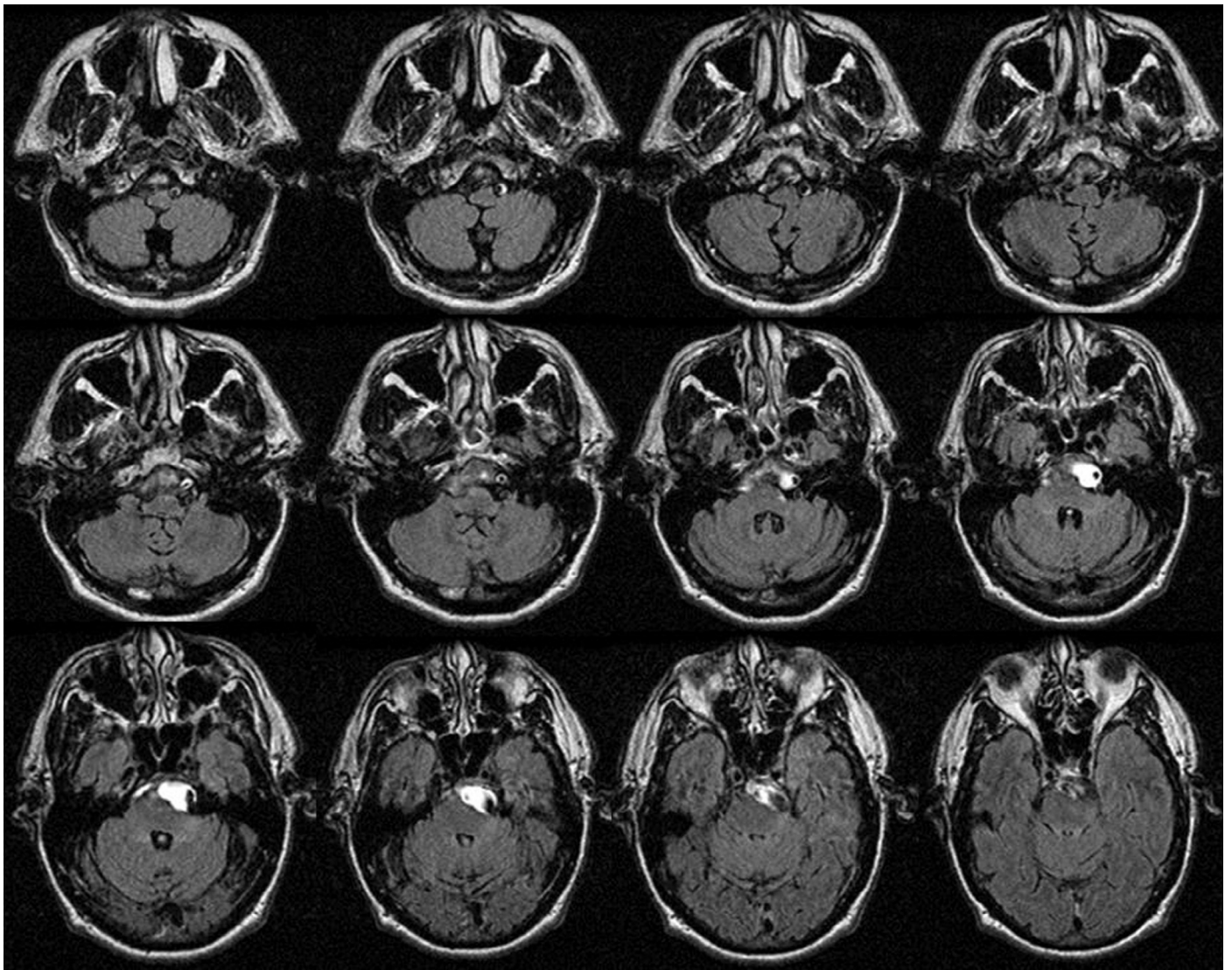


Fig. 4. A 74-year-old man with a large fusiform basilar artery aneurysm, associated with dream enactment behaviors of bicycling movements and falling from bed. Treatment with pramipexole improved the frequency and severity of behaviors, which were reduced to sleep talking only (Patient #5 in Table 2).

suggesting that location of damage was the predominant determination of RBD symptoms [35].

Most of the patients reported in this series had focal neurological deficits apart from RBD which warranted an MRI. However, given the expense of MRI, and the rarity of RBD cases associated with lesions evident on imaging (0.67% of RBD cases seen at our center) in typical RBD patients lacking focal neurological deficits, routine MRI is generally unnecessary.

There are several limitations to this retrospective, single-center study. PSG was not performed on two patients; however, each gave an explicit DEB history, with complete remission of DEB following meningioma resection in one patient (Patient #3). Severe obstructive sleep apnea (OSA) has been reported to mimic symptoms of RBD [36], although Patient #5 (Fig. 4), who did not undergo PSG, had no symptoms or risk factors for OSA. Finally, four patients were taking antidepressant medications, associated with RBD and RSWA [1,2,37,38]. However, two patients (#4 and #8; Figs 3 and 5) were taking selective serotonin reuptake inhibitor (SSRI) medication at stable doses years before DEB onset (which was coincidental with the discovery of meningioma in Patient #4 (Fig. 3) and after surgical resection of epidermoid cyst in Patient #8; Fig. 5), Patient #5 (Fig. 4) had DEB before the

initiation of SSRI therapy, and Patient #6 [18] had persistent DEB despite the cessation of SSRI therapy, indicating that the brain lesion was more likely to be responsible for RBD symptoms than the antidepressant medication. Some of the patients in this study could also have had an alternative underlying neurodegenerative process such as a synucleinopathy that remained covertly present as the primary cause of their RBD. However, several factors mitigate against this possibility: (1) DEB onset with close temporal proximity to other neurological symptoms and visible neuroimaging pathology; (2) a relatively long duration of follow-up in most patients, without any emerging evidence for characteristic overt motor, cognitive, or autonomic neurodegenerative symptoms; and (3) remission of RBD in several cases following lesion resolution or immunosuppressive therapy, suggesting that these patients had lesional RBD. Longitudinal follow-up and eventual autopsy will be necessary to confidently exclude underlying neurodegeneration.

5. Conclusions

Our series supports predominant pontine localization governing REM sleep muscle atonia. In patients with abrupt onset of focal

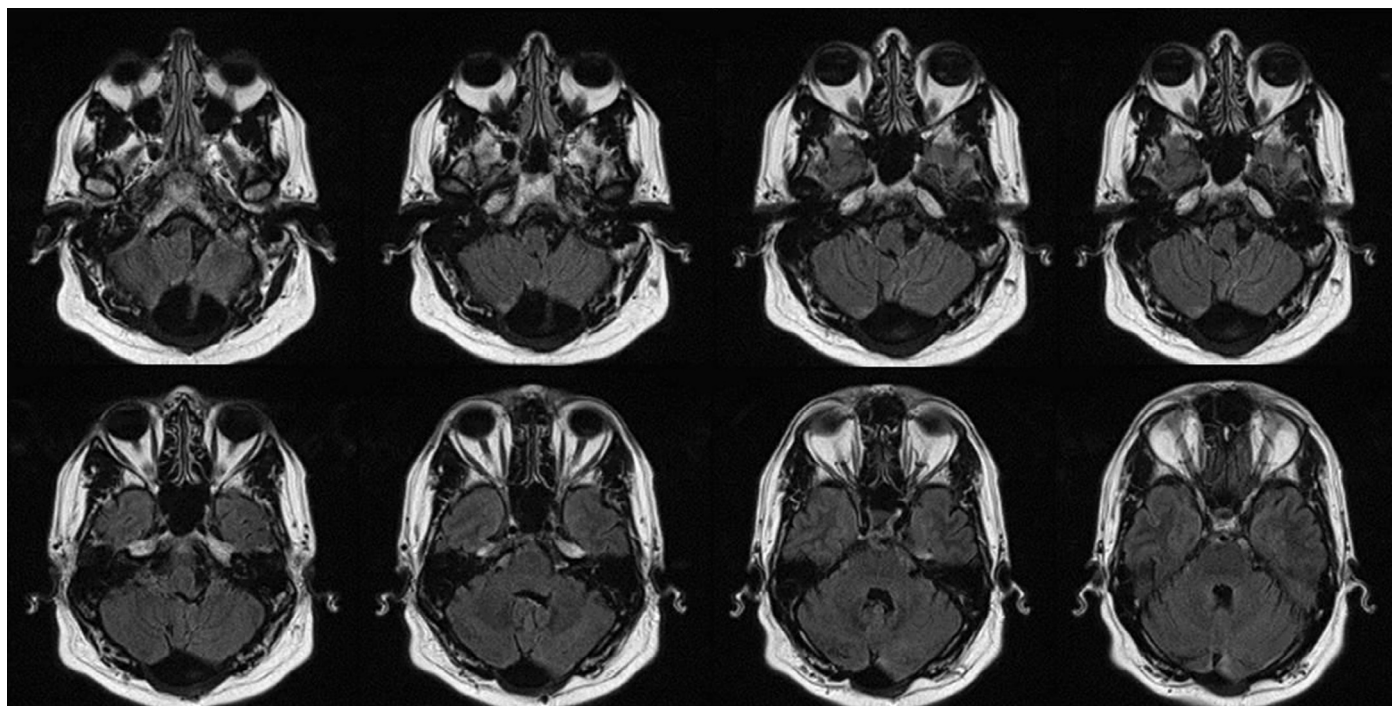


Fig. 5. A 48-year-old male with history of a posterior fossa epidermoid cyst presented with gait ataxia, imbalance, cranial nerve VIII palsy, and a history of punching, kicking, and moaning in his sleep 1 month following the removal of the cyst. MRI revealed a fluid collection in the operative site compressing the left pons and medulla (Patient #8 in Table 2).

neurological symptoms and associated DEB, a brainstem lesion or limbic encephalitis must be considered, as treatment of the underlying condition, such as resection of a tumor, or immunotherapy to decrease inflammation, may improve or resolve DEB and potentially prevent other neurological complications associated with a structural brain lesion. Patients who suffer brainstem injury through infarct or inflammatory processes should also be queried about possible DEB and followed carefully for possible development of RBD so that timely therapy may be initiated to prevent injury. Finally, patients presenting with RBD along with focal neurologic deficits are also recommended to undergo MRI; however, in RBD patients with a normal neurologic exam, MRI is generally not warranted.

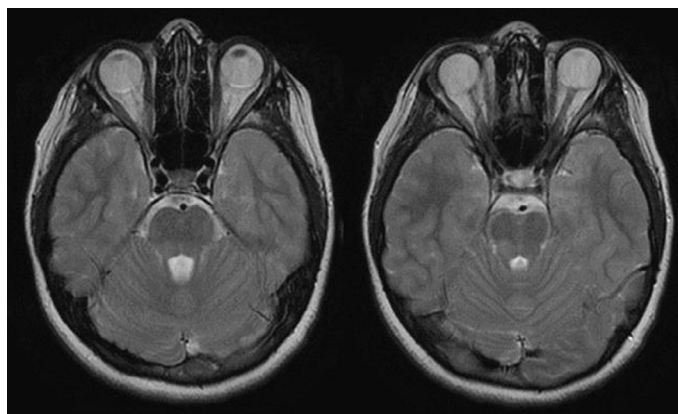


Fig. 6. A 10-year-old girl with an ill-defined ovoid hyperintense FLAIR lesion in the right dorsal pontine tegmentum, associated with headaches and dream enactment behaviors, characterized by kicking and arm movements during polysomnography with REM sleep without atonia (Patient #9 in Table 2).

Conflicts of interest

No off-label medication use.

This project was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through Grant Number 1 UL1 RR024150-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

SJ McCarter, DJ Sandness, M Tippmann-Peikert, and MH Silber report no disclosures.

EK St. Louis reports that he received research support from the Mayo Clinic Center for Translational Science Activities (CTSA), supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH, through Grant Number 1 UL1 RR024150-01.

K Kantarci serves on the data safety monitoring board for Pfizer Inc. and Janssen Alzheimer's Immunotherapy, Takeda Global Research & Development Center, Inc.; she is funded by the NIH [R01AG040042 (PI), P50 AG44170/Project 2 (PI) and R01 AG11378 (Co-I)].

BF Boeve has served as an investigator for a clinical trial sponsored by GE Healthcare. He receives royalties from the publication of a book entitled *Behavioral Neurology of Dementia* (Cambridge Medicine, 2009). He serves on the scientific advisory board of the Tau Consortium. He receives research support from the NIH (U01 AG045390, U54 NS092089, P50 AG016574, U01 AG006786, R01 AG015866, R01 AG032306, R01 AG041797) and the Mangurian Foundation.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2015.07.018>.

EP Flanagan has nothing to disclose.

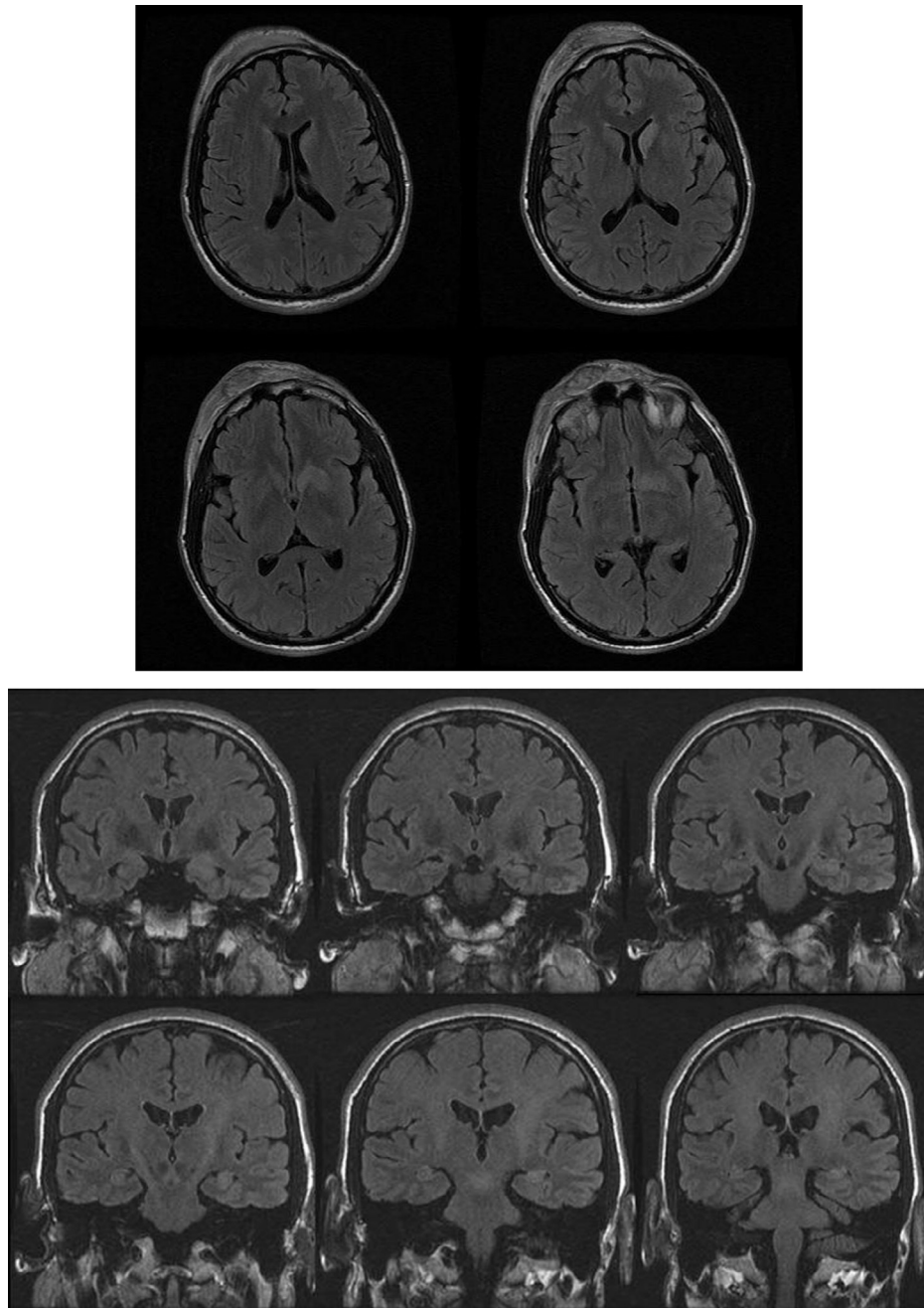


Fig. 7. A 53-year-old man with history of prostate carcinoma presented with seizures, mental status changes, and dream enactment behaviors evolving within 1 month of his other neurological symptoms. Sequential brain MRI initially demonstrated abnormal FLAIR signal hyperintensity in the left caudate, with later development of abnormal FLAIR signal in the hippocampus, and parahippocampal gyrus (Patient #10 in Table 2).

Acknowledgments

This project was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through Grant Number 1 UL1 RR024150-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The authors also gratefully acknowledge Ms. Lori Lynn Reinstrom in the Mayo Clinic Department of Neurology for secretarial assistance with manuscript formatting and submission.

References

- [1] Boeve BF. REM sleep behavior disorder updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci* 2010;1184:15–54.
- [2] McCarter SJ, St Louis EK, Boeve BF. REM sleep behavior disorder and REM sleep without atonia as an early manifestation of degenerative neurological disease. *Curr Neurol Neurosci Rep* 2012;12:182–92.
- [3] McCarter SJ, St Louis EK, Duwell EJ, et al. Diagnostic thresholds for quantitative REM sleep phasic burst duration, phasic and tonic muscle activity, and REM atonia index in REM sleep behavior disorder with and without co-morbid obstructive sleep apnea. *Sleep* 2014;37:1649–62.

- [4] Chen JH, Huang Y, Liu XQ, et al. [Prevalence of REM sleep behavior disorder in patients with brainstem lesions]. *Zhonghua Yi Xue Za Zhi* 2013;93:2942–5.
- [5] Compta Y, Iranzo A, Santamaria J, et al. REM sleep behavior disorder and narcoleptic features in anti-Ma2-associated encephalitis. *Sleep* 2007;30:767–9.
- [6] Cornelius JR, Pittock SJ, McKeon A, et al. Sleep manifestations of voltage-gated potassium channel complex autoimmunity. *Arch Neurol* 2011;68:733–8.
- [7] Flanagan EP, Gavrilova RH, Boeve BF, et al. Adult-onset autosomal dominant leukodystrophy presenting with REM sleep behavior disorder. *Neurology* 2013;80:118–20.
- [8] Gomez-Choco MJ, Iranzo A, Blanco Y, et al. Prevalence of restless legs syndrome and REM sleep behavior disorder in multiple sclerosis. *Mult Scler* 2007;13:805–8.
- [9] Henriques PSA, Pratesi R. Sleep apnea and REM sleep behavior disorder in patients with Chiari malformations. *Arq Neuropsiquiatr* 2008;66:344–9.
- [10] Iranzo A, Graus F, Clover L, et al. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. *Ann Neurol* 2006;59:178–81.
- [11] Kimura K, Tachibana N, Kohyama J, et al. A discrete pontine ischemic lesion could cause REM sleep behavior disorder. *Neurology* 2000;55:894–5.
- [12] Limousin N, Dehais C, Gout O, et al. A brainstem inflammatory lesion causing REM sleep behavior disorder and sleepwalking (parasomnia overlap disorder). *Sleep Med* 2009;10:1059–62.
- [13] Peter A, Hansen ML, Merkl A, et al. REM sleep behavior disorder and excessive startle reaction to visual stimuli in a patient with pontine lesions. *Sleep Med* 2008;9:697–700.
- [14] Plazzi G, Montagna P. Remitting REM sleep behavior disorder as the initial sign of multiple sclerosis. *Sleep Med* 2002;3:437–9.
- [15] Provini F, Vetrugno R, Pastorelli F, et al. Status dissociatus after surgery for tegmental ponto-mesencephalic cavernoma: a state-dependent disorder of motor control during sleep. *Mov Disord* 2004;19:719–23.
- [16] Reynolds TQ, Roy A. Isolated cataplexy and REM sleep behavior disorder after pontine stroke. *J Clin Sleep Med* 2011;7:211–13.
- [17] Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol* 2014;13:575–86.
- [18] St. Louis EK, McCarter SJ, Boeve BF, et al. Lesional REM sleep behavior disorder localizes to the dorsomedial pons. *Neurology* 2014;83:1871–3.
- [19] Tippmann-Peikert M, Boeve BF, Keegan BM. REM sleep behavior disorder initiated by acute brainstem multiple sclerosis. *Neurology* 2006;66:1277–9.
- [20] Xi Z, Luning W. REM sleep behavior disorder in a patient with pontine stroke. *Sleep Med* 2009;10:143–6.
- [21] Zambelis T, Paparrigopoulos T, Soldatos CR. REM sleep behaviour disorder associated with a neurinoma of the left pontocerebellar angle. *J Neurol Neurosurg Psychiatry* 2002;72:821–2.
- [22] Tang WK, Hermann DM, Chen YK, et al. Brainstem infarcts predict REM sleep behavior disorder in acute ischemic stroke. *BMC Neurol* 2014;14:88.
- [23] Brooks PL, Peever JH. Glycinergic and GABA(A)-mediated inhibition of somatic motoneurons does not mediate rapid eye movement sleep motor atonia. *J Neurosci* 2008;28:3535–45.
- [24] Brooks PL, Peever JH. Identification of the transmitter and receptor mechanisms responsible for REM sleep paralysis. *J Neurosci* 2012;32:9785–95.
- [25] Soja PJ, Lopez-Rodriguez F, Morales FR, et al. The postsynaptic inhibitory control of lumbar motoneurons during the atonia of active sleep: effect of strychnine on motoneuron properties. *J Neurosci* 1991;11:2804–11.
- [26] Peever J, Luppi PH, Montplaisir J. Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. *Trends Neurosci* 2014;37:279–88.
- [27] Iranzo A, Aparicio J. A lesson from anatomy: focal brain lesions causing REM sleep behavior disorder. *Sleep Med* 2009;10:9–12.
- [28] Hendricks JC, Morrison AR, Mann GL. Different behaviors during paradoxical sleep without atonia depend on pontine lesion site. *Brain Res* 1982;239:81–105.
- [29] Mathis J, Hess CW, Bassetti C. Isolated mediotegmental lesion causing narcolepsy and rapid eye movement sleep behaviour disorder: a case evidencing a common pathway in narcolepsy and rapid eye movement sleep behaviour disorder. *J Neurol Neurosurg Psychiatry* 2007;78:427–9.
- [30] Jianhua C, Xiuqin L, Quancai C, et al. Rapid eye movement sleep behavior disorder in a patient with brainstem lymphoma. *Intern Med* 2013;52:617–21.
- [31] Tribi GG, Bor-Seng-Shu E, Trindade MC, et al. Wilson's disease presenting as rapid eye movement sleep behavior disorder: a possible window to early treatment. *Arq Neuropsiquiatr* 2014;72:653–8.
- [32] Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain* 2007;130:2770–88.
- [33] Weng FJ, Williams RH, Hawryluk JM, et al. Carbachol excites sublaterodorsal nucleus neurons projecting to the spinal cord. *J Physiol* 2014;592:1601–17.
- [34] Lai YY, Hsieh KC, Nguyen D, et al. Neurotoxic lesions at the ventral mesopontine junction change sleep time and muscle activity during sleep: an animal model of motor disorders in sleep. *Neuroscience* 2008;154:431–43.
- [35] Iranzo A, Santamaria J, Rye DB, et al. Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. *Neurology* 2005;65:247–52.
- [36] Iranzo A, Santamaria J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. *Sleep* 2005;28:203–6.
- [37] Postuma RB, Gagnon JF, Tuineig M, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? *Sleep* 2013;36:1579–85.
- [38] McCarter SJ, St Louis EK, Sandness DJ, et al. Antidepressants increase REM sleep muscle tone in patients with and without REM sleep behavior disorder. *Sleep* 2015;38:907–17.