Rapid Eye Movement Sleep Behavior Disorder

This sleep disorder is a strong predictor for the development of synucleinopathies, including Parkinson's disease, multiple system atrophy, and dementia with Lewy bodies.

By Ahmad Alsibai, MD and Jill M. Giordano Farmer, DO

Few medical disorders have been used as a defense in murder trials; rapid eye movement (REM) sleep behavior disorder (RBD) has. A fascinating parasomnia of REM sleep, RBD relieves patients of the muscle paralysis (atonia) that is a cardinal feature of REM sleep in adults. Motor activity and behavior reflecting dream enactment ensues, often in a violent manner that can lead to injuries.[1,2] A 1996 article in *The New York Times* titled "When Can Killers Claim Sleep Walking as a Legal Defense?" exposed the extremes of RBD. Although the article may have been a bit alarmist, and the RBD defense has not become common as feared, RBD has gained notoriety as a herald of neurodegenerative disorders, which is far more ominous.

Clinical Presentation and Diagnosis

In addition to injury to self or sleep partners and disrupted sleep, it is of great clinical significance that RBD is a strong predictor for synucleinopathies (eg, multiple system atrophy, dementia with Lewy bodies, and Parkinson's disease [PD]).[2-6] People with RBD may dream they are being chased by other people or animals and react by shouting, screaming, crying, kicking, choking, or even jumping out of bed.[5,6] Diagnosis is made with polysomnography that shows lack of atonia with related motor behaviors during REM sleep.[1] Patients with idiopathic RBD (iRBD) are likely to have history of head injury or pesticide exposure (similar to PD) and depression. In these patients, however, depression may be an early sign of a neurodegenerative disorder. Low level of education, smoking, and ischemic heart disease are also associated with iRBD. A family history of dream-enacting behavior is common in patients with iRBD, even without family history of dementia or PD.

Pathophysiology

In 1959, Michel Jouvet showed cats require an intact pontine tegmentum for REM sleep and that REM sleep atonia is due to inhibiting motor centers in the medulla oblongata. Cats with locus coeruleus lesions had motor behavior patterns suggestive of dreams of attack and defense.[7] In humans, REM sleep behavior disorder was first described by Carlos Schenck and Mark Mahowald.[5,8] Neurons in the subcoeruleus nucleus (SubC)—a reticular nucleus in the pons near the mesopontine junction—are activated during REM sleep. Most of these neurons are glutamatergic, although some GABA-ergic neurons have also been implicated.[9] Activated SubC neurons recruit GABA-ergic and glycinergic neurons in the ventromedial medulla and spinal cord that project to inhibit motor neurons and produce REM sleep atonia.[9] Pharmacologic activation of SubC neurons causes REM-sleep atonia; SubC lesions or degeneration prevent or reduce REM-sleep atonia allowing motor activity.[9]

Association With Asynucleinopathies

Although patients with RBD may have no other neurologic signs suggesting neurodegenerative disorders, subtle clues may be found on neurologic examination, including subtly reduced motor abilities, mild cognitive impairment, hyposmia, reduced color vision, or autonomic dysfunction. Typical latency between onset of iRBD and a synucleinopathy is 11 to 16 years but can be much longer, especially as the onset of most synucleinopathies is after age 50.[3,10] This offers a window of opportunity to observe symptom development and perhaps intervene earlier. As the concept of a prodromal phase for neurodegenerative diagnoses gains ground, the potential for testing patients with iRBD with biomarkers for synucleinopathies is an area of debate, focusing primarily on what to do with any information gained. As yet, treatment is symptomatic only, raising the question of what patients and physicians would do when there are no symptoms to treat. More research is needed to determine the best patient-centered and cost-effective approach to early diagnosis. In the meantime, early diagnosis may be useful in identifying individuals for clinical trials. A multicenter study followed 1,280 patients with polysomnographically confirmed iRBD for up to 19 years (mean 3.6 years) and showed rate of annual conversion to synucleinopathy of 6.25%,

suggesting that over 70% of patients with iRBD would develop a neurodegenerative disease over a 12-year period.[4]

Treatment

Treatment includes making the sleep environment safe and optimizing sleep practices.[12-14] Cognitive-behavioral therapy, including imaging rescripting (IR) and imaginal exposure (IE) has shown some benefit.[13] Melatonin and clonazepam have limited efficacy and safety; clonazepam may be more effective,[16] but melatonin has a preferable side-effect profile.[12-14] Some medications, including mirtazapine, antidepressants, tramadol, and beta blockers worsen RBD and should be avoided or discontinued whenever possible.[5]

Conclusion

As research focuses on identifying prodromal phases of neurodegenerative conditions, RBD consistently shows sensitivity for predicting them. Although this may seem nightmarish for patients at the moment, as disease modifying therapies are developed, early detection of RBD and synucleinopathies may be the stuff of dreams. ■

1. Portet F, Touchon J. REM Sleep behavioral disorder. *Revue neurologique*. 2002;158(11):1049–1056.

2. St. Louis EK, Boeve BF. REM sleep behavior disorder: diagnosis, clinical implications, and future directions. *Mayo Clinic Proc*. 2019; 92(11):1723-1736.

3. Boot BP. Comprehensive treatment of dementia with Lewy bodies. *Alzheimers Res Ther*. 2015 May 29;7(1):45.

4. Arnaldi D, Antelmi E, St Louis EK, Postuma RB, Arnulf I. Idiopathic REM sleep behavior disorder and neurodegenerative risk: to tell or not to tell to the patient? How to minimize the risk? *Sleep Med Rev*. 2017;36:82-95.

5. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*. 2019;142(3):744-759.

6. St Louis EK, Boeve AR, Boeve BF. REM sleep behavior disorder in Parkinson's disease and other synucleinopathies. *Movement Dis*. 2017;32:645-658.

7. American Academy of Sleep Medicine. *Michel Jouvet: Sleep Research Pioneer (1925-2017)*. https://aasm.org/michel-jouvet-sleep-research-pioneer-1925-2017/. Published October 4, 2017. Accessed March 6, 2019.

8. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep*. 1986;9(2):293–308.

9. Fraigne JJ, Torontali ZA, Snow MB, Peever JH. REM sleep at its core - circuits, neurotransmitters, and pathophysiology. *Front Neurol*. 2015;(6):123.

10. Boeve BF, Silber MH, Ferman TJ, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med*. 2013;14(8):754-762.

11. Kunze A, Lancee J, Morina N, Kindt M, Arntz A. Efficacy and mechanisms of imagery rescripting and imaginal exposure for nightmares: study protocol for a randomized controlled trial. *Trials*. 2016;17:469.

12. McCarter SJ, Boswell CL, St Louis EK, et al. Treatment outcomes in REM sleep behavior disorder. *Sleep Med*. 2013;14(3):237-242.

13. McKeith IG, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89(1):88–100.

14. Aurora RN, Zak RS, Maganti RK, et al. Best practice guide for the treatment for REM sleep behavior disorder (RBD). *J Clin Sleep Med*. 2010;6(1):85–95.

Ahmad Alsibai, MD
Neurology Resident PGY IV
Drexel University College of Medicine
Hahnemann University Hospital
Philadelphia, PA

Jill M. Giordano Farmer, DO
Assistant Professor and Director
Parkinson's Disease & Movement Disorder Program
Drexel University College of Medicine
Hahnemann University Hospital
Philadelphia, PA