The Pathophysiology and Clinical Relevance of Rapid Eye Movement Sleep Behavior Disorder

Keisuke Suzuki and Koichi Hirata

Key words: rapid eye movement sleep behavior disorder, brain lesions, neurodegenerative diseases

In this issue of Internal Medicine, Chen et al. (1) documented the case of a 30-year-old man who presented with an 11-month history of abnormal nocturnal behavior related to vivid dreams. Brain magnetic resonance images revealed lesions involving the pontomesencephalic junction and the upper pons, and polysomnography (PSG) findings confirmed a diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD). A brainstem biopsy revealed diffuse large B-cell lymphoma. Notably, chemotherapy for lymphoma resulted in the disappearance of the lesions and reduced the frequency of RBD symptoms in the patient.

RBD is a parasomnia characterized by dream-enacting behaviors and a loss of normal muscle atonia during REM sleep. The estimated prevalence of this disorder was reported to be 0.5% in a survey of approximately 4,900 subjects between the ages of 15 and 100 years (2). The dreams of patients with RBD usually include unpleasant and aggressive content, and the patient’s abnormal behavior is typically aggressive and violent, often resulting in serious injury to the patient or their bed partner (3).

Based on the International Classification of Sleep Disorders, second edition (4), the use of PSG is essential for diagnosing RBD. The following criteria should be met: A, the presence of REM sleep without atonia, including excessive amounts of sustained or intermittent elevations of submental electromyographic (EMG) tone or excessive phasic submental or limb EMG twitching; B, abnormal REM sleep behavior based on the patient’s history and/or PSG findings; C, the absence of electroencephalogram (EEG) epileptiform activity during REM sleep; and D, the sleep disturbance is not better explained by medication use or another sleep, medical, neurological, mental or substance use disorder.

In almost 90% of patients with RBD, the administration of clonazepam (0.5 to 1.5 mg) at bedtime is effective. Additionally, melatonin, pramipexole and Yi-Gan San alone or in conjunction with clonazepam may effectively treat RBD.

The anatomic substrate for REM sleep control in humans includes a “REM-off” region, which consists of the ventrolateral part of the periaqueductal gray matter and lateral pontine tegmentum, and a “REM-on” region, which consists of the precoreuleus, sublaterodorsal nucleus, extended portion of the ventrolateral preoptic nucleus, locus coeruleus, laterodorsal tegmental nucleus, pedunculopontine nucleus and raphe nuclei (5). Motor behaviors in patients with RBD may reflect brainstem impairment, while the frightening dreams of RBD may reflect amygdala dysfunction (6).

In humans, RBD can be caused secondarily by brain lesions including the brainstem nuclei, which regulate REM sleep, and the supratentorial structures, including the posterior hypothalamus, anterior thalamus and limbic system, which connect with the brainstem nuclei. Brain tumors, demyelinating plaques, strokes and limbic encephalitis have been reported to cause RBD (6), and narcolepsy is associated with RBD. Several medications can cause RBD, including antidepressants such as tricyclics, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (3).

In 1996, Schenck et al. (7) first reported the delayed emergence of Parkinsonian disorders in 38% of 29 older men initially diagnosed with idiopathic RBD, with a mean interval of 3.7 years after RBD diagnosis and a mean interval of 12.7 years after RBD onset. After an additional 7-year follow-up, the conversion rate from idiopathic RBD to neurodegenerative diseases increased to 65%. Additionally, Iranzo et al. (8) reported that 45% of 44 patients with idiopathic RBD developed neurodegenerative diseases (n=9, Parkinson’s disease (PD); n=6, dementia with Lewy bodies (DLB); n=4, mild cognitive impairment; n=1, multiple system atrophy) at a mean follow-up of 5.1 years and a mean of 11.5 years after RBD onset. Postuma et al. (9) reported that 28% of 93 patients with idiopathic RBD developed neurodegenerative diseases (n=14, PD; n=7, DLB; n=4, Al-
Alzheimer’s disease; n=1, multiple system atrophy) over a mean follow-up of 5.2 years. In that study, the estimated risk of developing neurodegenerative diseases in patients with RBD was 17.7% at five years, 40.6% at 10 years and 52.4% at 12 years.

The Braak staging scheme for PD, which is based on the temporal sequence of α-synuclein pathology, shows that pathological changes primarily arise in the medulla and then ascend to the cortex (1-6 stages) (10). In this staging system, the pathological changes occur in the pontine nuclei regulating REM sleep, including the sublaterodorsal nuclei, before reaching the midbrain, responsible for the motor impairment in PD. Although the descending progression of the degenerative changes from the cortex to the midbrain (top-to-bottom pattern) may be better applied to cases showing cognitive impairment prior to the onset of Parkinsonism, the Braak staging supports a bottom-to-top progression of PD and may better explain how RBD can precede the onset of motor impairment in patients with PD (5).

Intriguingly, idiopathic RBD is reported to possess the observable features of Lewy body diseases such as PD and DLB, including cardiac sympathetic nerve denervation detected on myocardial scintigraphy (11), hyperechogenicity in the substantia nigra on transcranial sonography (12), olfactory dysfunction (13), decreased striatal dopamine transporter binding and cognitive impairment (14). These observations may suggest that RBD is a Lewy body-related disease. Uchiyama et al. (15) reported the autopsy case of an 84-year-old man with a 20-year history of idiopathic RBD that revealed Lewy body pathology with a marked loss of brainstem monoaminergic neurons in the locus coeruleus and substantia nigra.

In conclusion, the early recognition of RBD is important not only for preventing sleep-related injury, but also for enabling the early detection of neurodegenerative diseases through detailed neurological evaluations. Brain imaging is of course essential for excluding brain lesions causing secondary RBD.

Author’s disclosure of potential Conflicts of Interest (COI).
Hirata K: Honoraria, GSK, Fizer, Eisai, Otsuka, Philips, Sanofi-Aventis, Daiichi Sankyo, Novartis and Beringer.

References