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Review Article

Overview of Idiopathic REM Sleep Behavior Disorder

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Summary

REM sleep behavior disorder (RBD) is a REM sleep-related parasomnia characterized by action of dream content, which is often an aggressive or terrible nightmare. Because of the self-defense movements and behaviors in dreams, sleep-talking (e.g., yelling and screaming) and violent movements of the arms and legs may injure the patient or bed partner. Idiopathic or isolated RBD that develops after middle age may progress to neurodegenerative diseases, such as Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy, in half of the patients after 10 years. The development of a method that can accurately diagnose RBD by polysomnography may help to identify patients at high short-term risk of developing α-synucleinopathies. Such patients may be enrolled in trials of disease-modifying therapy. Several techniques for the early diagnosis of α-synucleinopathies are under development for clinical use and await application in clinical trials of candidate therapies.

Key Words: REM sleep behavior disorder, Lewy body disease, phenoconversion, MIBG, DAT-SPECT

Introduction

Idiopathic[1] or isolated[2] REM sleep behavior disorder (IRBD) is a parasomnia characterized by complex movements during REM sleep, as if an unpleasant dream experience was demonstrated or acted upon. IRBD can harm the patient or others (i.e., sleep-related injury). For example, almost 90 minutes after falling asleep, the patient talks loudly, screams, exercises, and/or acts. In particular, the patients may raise their hands, kick the futon with their feet, get up, jump out of the bed, jump off, hit the furniture (e.g., chests of drawers) or wall, and fight because they are unable to assess the surrounding situation. In some cases, these actions injure the face (forehead or nose), hands (fists), and legs (shins), leading to serious injuries, such as fractures (REM-related injury). The loud noise produced during IRBD may cause mental burden to the bed partner and cause inconvenience to the neighbors or roommates. In IRBD, the abnormal behavior is characterized by closed eyes and short duration of abnormal behavior, which is easily stopped when the patient awakens. In IRBD, patients rarely walk out of the room, which distinguishes it from non-REM parasomnias. In addition, in IRBD, patients can recall the dream contents immediately after awakening, which may involve a life-threatening situation, discussion, playing a dynamic sport, being cornered by people or

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animals (e.g., tigers, snakes, insects, or dogs), being attacked, falling off a cliff, or frightening situation, such as a child requiring help. Some patients may not clearly remember the dream content. It may not be possible to recall the dream later unless the dream contents are written down immediately after the abnormal behavior or awakening. Dream elements can be centered around life events, such as relationships, anxiety, and success, but the medical history usually does not reveal a history of aggressive or violent behavior in daily life. Patients may present for evaluation due to injuries to the bed partner due to abnormal behavior during sleep or increased frequency of behavior noted by the bed partner[3].

Recent studies revealed that polysomnography (PSG)-confirmed IRBD patients progresses to Parkinson's disease (PD) or dementia with Lewy bodies (DLB) at a rate of 50% or more in about 10 years[4]. A meta-analysis of studies[5] investigating the risk of developing neurodegenerative disease among IRBD patients in 13 countries in 2019 showed a correlation between follow-up duration and progression rate (Table 1). Such patients may be enrolled in trials of disease-modifying therapy. Several techniques for the early diagnosis of α-synucleinopathies are under development for clinical use[6].

Illustrative Case

Case 1.

A 71-year-old female complained of sleep-talking, dreaming, and limb movements for the past 2 years. She yelled during nightmares and her dream content often involved scolding her child. She shared the bedroom with her husband. Since the age of 70 years, the patient showed movements of her hands and feet during nightmares. During such episodes, her husband woke her up. She had excessive sleepiness, often disturbed her family's sleep, had scary dreams, and acted out her dreams. Recently, the patient's husband noticed that she had become slow in making decisions during shopping. On examination, the patient had Japanese version of the RBD Screening Questionnaire (RBDSQ-J) score of 8/13 and Unified Parkinson's disease Rating Scale (UPDRS) part 3 score of 6 points. PSG confirmed the presence of IRBD. At the age of 72 years, the patient's brain MRI did not show evidence of striatal atrophy or abnormal signals, but [^{123}I]FP-CIT SPECT (DAT-SPECT) showed decreased accumulation in the left-dominant striatum. Two months later, the patient's examination clearly showed mild muscle rigidity in the right lower extremity and UPDRS part 3 score of 9, which confirmed the diagnosis of mild PD[7]. Therefore, this was a case of an elderly woman who had the catalyst sleep-talking and abnormal behavior during sleep. As a result of her early treatment, she easily accepted her disease and adjusted to the use of antiparkinsonian drugs without major disruption to her daily life.

Case 2.

This 82-year-old patient presented with loud sleep-talking and repeated fainting and falls. When he was 79-year-old, his family noticed that he could not identify his body odor. He often talked during sleep, which involved yelling. At 80-year-old, he collapsed in the hallway at night while going to the bathroom and developed a bruise. He also had a fall while walking during the daytime followed by momentary loss of consciousness, which resolved after a minute of rest. Since he had three similar episodes in 6 months, he was suspected to have epilepsy by the cardiology department and referred to our department. On examination, his mini-mental status examination (MMSE) score was 25/30, RBDSQ-J score was 8/13, UPDRS part III score was 3, and ECG showed a 1.08 decrease in coefficient of variation of R-R interval (CVR-R). In addition, the active standing test showed a positive result as follows; resting BP of 153/82 mmHg and pulse of 57/min, whereas after standing for 10 minutes, the BP was 84/61 mmHg and pulse was 64/min. PSG confirmed the diagnosis of isolated RBD. During follow up, the patient developed illusions at evening and night, which involved seeing insects on the carpet, seeing animals, and chasing them away when awakening in the toilet at around 2 am, and seeing unnatural things, such as dead people talking to each other. In addition, the patient had several falls on standing up from the sitting position suddenly. Subsequently, the patient developed a resting tremor in his right upper limb. Brain MRI showed hyperintense lesions around the anterior horns of bilateral lateral ventricles, but no putamen atrophy or abnormal signals. The DAT-SPECT scan showed

Table 1 Longitudinal studies of IRBD showing conversion to a defined neurodegenerative syndrome

	Number of patients	Male sex (%)	Mean age at IRBD onset, years (SD)	Mean age at IRBD diagnosis, years (SD)	Mean follow-up time from IRBD diagnosis, years (SD)	Conversion rate (%)	Number of patients with emerging disorders	Number of patients with emerging disorders
Schenck et al. (1996) USA	29	100%	55.4 (8.7)	64.8 (5.8)	6.1 (2.4)	41%	-	PD 11, dementia 1
Schenck et al. (2013) USA	26	100%	57.7 (7.7)	-	16	81%	-	PD 13, DLB 5, dementia 3, MSA 2
Iranzo et al. (2006) Spain	44	89%	62.6 (7.3)	68.9 (6.3)	5.1 (2.7)	45%	-	PD 9, DLB 6, MSA 1, MCI 4
Iranzo et al. (2013) Spain	44	89%	62.6 (7.3)	68.9 (6.3)	10.5	82%	35% at 5 y, 73% at 10 y, 92% at 14 y	PD 16, DLB 14, MSA 1, MCI 5
Iranzo et al. (2014) Spain	174	78%	62.4 (7.8)	68.7 (6.4)	5.1 (3.9)	37%	33.1% at 5 y, 75.7% at 10 y, 90.9% at 14 y	PD 22, DLB 29, MSA 2, MCI 12
Postuma et al. (2009) Canada	93	80.4%	-	65.4 (9.3)	5.2 (median)	28%	17.7% at 5 y, 40.6% at 10 y, 52.4% at 12 y	PD 14, DLB 7, AD 4, MSA 1
Postuma et al. (2015) Canada	89	73%	-	66.9 (9.3)	5.4 (2.9)	46%	30% at 3 y, 47% at 5 y, 66% at 7.5 y	PD 17, DLB 18, dementia 3, MSA 3
Wing et al. (2012) China	91	82%	60.0 (12.7)	65.5 (9.9)	5.6 (3.3)	16%	5% at 3 y, 8% at 5 y, 21% at 7 y, 38% at 9 y	PD 8, DLB 1, AD 8
Youn et al. (2015) South Korea	84	69%	60 (-)	65.5 (6.7)	4.1 (2.1)	21.4%	9% at 3 y, 18% at 5 y, 35% at 6 y	PD 9, DLB 4, AD 3, MSA 1, SCA 1
Postuma et al. (2015) International	279	80%	-	-	-	33%	25% at 3 y, 41% at 5 y	PD 39, DLB 28, dementia 19, MSA 7
Miyamoto et al. (2018) Japan	273	78%	61.1 (9.0)	67.7 (6.6)	3.9 (3.0)	21.7%	11.9% at 3 y, 20.3% at 5 y, 33.2% at 7 y, 51.4% at 10 y	PD 28, DLB 19, unknown CA 1
Postuma et al. (2019) International	1280	82.5%	-	66.3 (8.4)	3.6	28%	10.6% at 2 y, 17.9% at 3 y, 31.3% at 5 y, 51.4% at 8 y, 60.2% at 10 y, 73.5% at 12 y	LBD (Parkinsonism-first 183, dementia-first 153), Probable MSA 16

Abbreviation: AD, Alzheimer's disease; CA, cerebellar ataxia; DLB, dementia with Lewy bodies; IRBD, idiopathic/isolated REM sleep behavior disorder; LBD, Lewy body disease; MCI, mild cognitive impairment; MSA, multiple system atrophy; PD, Parkinson's disease; SCA, spinocerebellar degeneration; y, years.

decreased accumulation from the middle to the tail of bilateral striatum. The patient had been having difficulty with his sense of smell for almost a year and he routinely had fainting and falls. In addition, he sometimes talked during sleep, for which he underwent PSG that confirmed the diagnosis of IRBD. After the

diagnosis, cognitive dysfunction, including hallucinations and delusions, developed, which interfered with his daily life. Therefore, based on the four core features and two indicative biomarkers[8], the patient was diagnosed with probable DLB.

Epidemiology

The prevalence of RBD is estimated to be almost 0.38-7.7% of the general population based on questionnaires and PSG surveys. A prevalence survey to detect probable RBD using the Chinese version of RBD1 Q was conducted among 19,614 people aged ≥ 50 years in Jiading District, Shanghai, China, which showed an estimated prevalence of 4.9% and a relative risk of PD of 2.64 among probable RBD patients[9]. There are few reports of the true RBD prevalence using PSG. In a 1997 survey of the general population of Lausanne, Switzerland who underwent PSG (mean age: 59.0 years), the prevalence rate was 1.06%, with no difference between men and women[10]. A survey of 2,714 general residents (aged 76.0 years on average) in Yuzawa City, Niigata Prefecture reported an estimated prevalence of 1.23%[11]. In Italian study (A total of 1,524 participants were screened), prevalence adjusted by nonparticipants was 3.48% (95% confidence interval, 2.67-4.52) and 1.18% (95% confidence interval, 0.45-1.37) for probable RBD and PSG confirmed definite RBD, respectively[12]. It is presumed that a large number of people do not present to the hospital and the number of diseases among individuals will increase with the aging of population. Therefore, early diagnosis and treatment of IRBD is important.

Pathophysiology

In REM sleep, muscle activity is suppressed. Excitatory neuron that descends from the glutaminergic sublaterodorsal tegmental nucleus (SLD) have glycine or GABAergic projections to the raphe magnus (RMg), which act on ventral gigantocellular (GiV), alfa gigantocellular (GiA), and lateral paragigantocellular (LPGi) reticular nucleus. These projections strengthen the inhibitory mechanism of the ventral medulla oblongata reticular formation, resulting in suppression of spinal cord motoneurons and muscles. In humans, REM on (SLD and locus coeruleus-α: peri-LCα) promotes REM sleep and REM off (ventrolateral part of periaqueductal region) suppresses REM sleep. The grey matter: ventrolateral periaqueductal gray (vlPAG) and lateral pontine tegmentum (LPT) interfere with each other to control REM sleep. IRBD is assumed to involve pathological impairment of muscle suppression during REM sleep[13]. PSG results show occasional active muscle discharges because muscle suppression does not occur in the mentalis and limb electromyograms during REM sleep. These findings, known as REM sleep without atonia (RWA), are included in the diagnostic criterion of IRBD (Fig. 1A, 1B). The severity of RWA can predict the progression to PD among IRBD patients[14].

Pathology

In a case report of RBD, IRBD developed at the age of 64 years and autopsy was performed at the age of 84 years, showing a marked decrease in pigment cells in the substantia nigra and locus coeruleus as well as the appearance of Lewy bodies, which suggested the diagnosis of incidental Lewy body disease (LBD)[15]. Iranzo et al.[16] found that neurodegenerative disease developed in IRBD patients. In addition, 3 autopsy cases showed neuronal disappearance and Lewy bodies (including α-synuclein and Lewy neurons) in the brainstem nucleus that regulates muscle suppression during REM sleep. These findings were consistent with a pathological diagnosis of LBD. Boeve et al.[17] found that among 170 patients with RBD-related neurodegenerative diseases confirmed by PSG, 160 (94%) suffered from α-synucleinopathies and DLB was the most common pathological diagnosis. Conversely, skin biopsy examination in RBD patients showed positive findings of phosphorylated α-synuclein in the neck (C7) and back (Th10), similar to PD patients[18].

Clinical Practice

The remaining interview will proceed with the idea that "we are dominated by the content of our dreams and are moving and talking". In particular, for patients in middle age or older, early detection of IRBD may be based on a questionnaire that has been confirmed to be valid to identify the medical history[19].

1. RBD questionnaires

1) RBDSQ-J[20]

The Japanese version of the RBD Screening Ques-

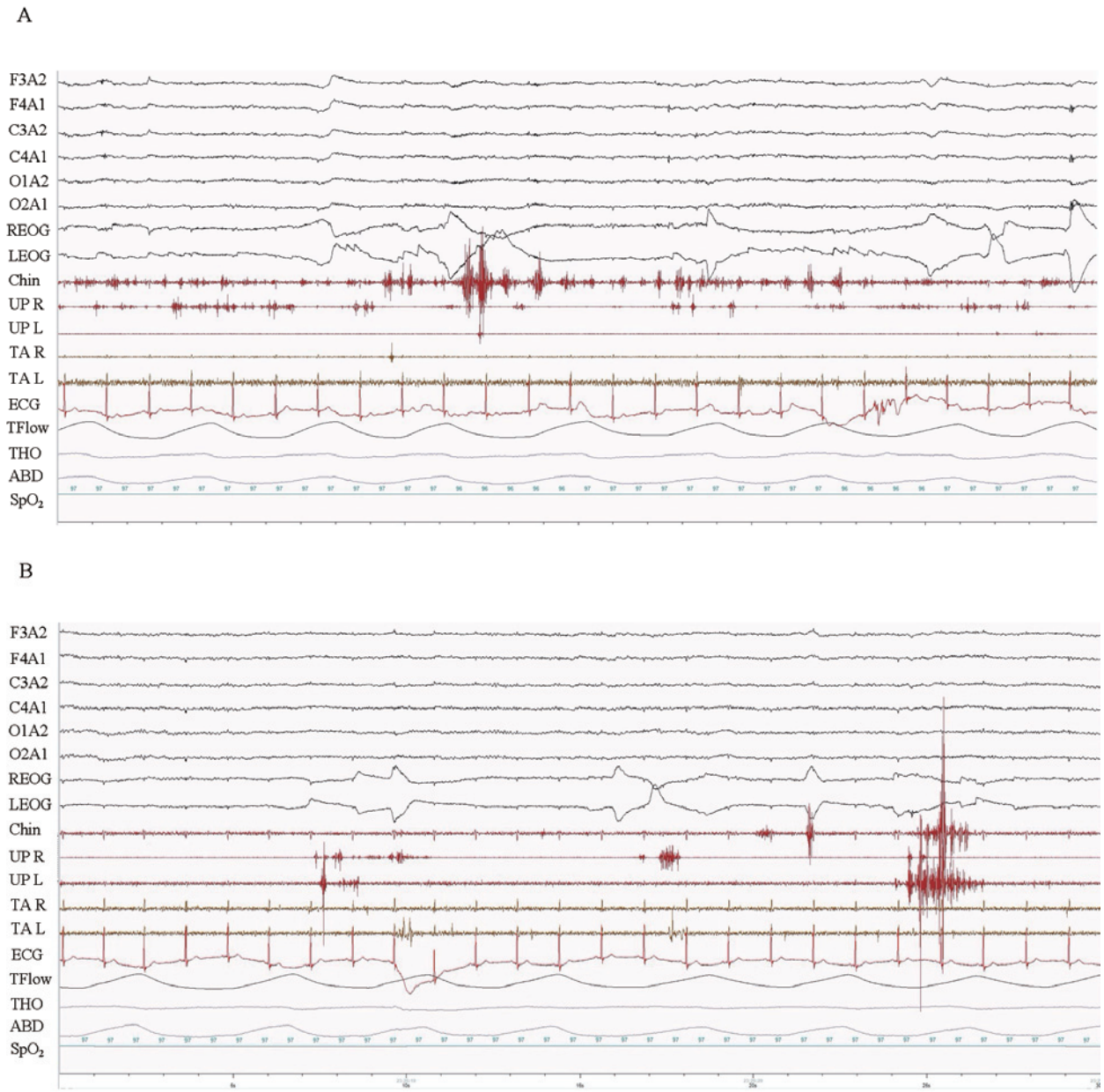

Figure 1 A 30-second epoch from the polysomnography of 76-year-old man referred for evaluation of recurrent violent nighttime awakening. Illustrated here is a typical event that this patient was experiencing. He has complex body movement. There is underlying REM associated muscle atonia in the chin electromyography **(A)** and the left flexor digitrum profudus **(B)**. Channels are as follows: electroencephalogram (F3A2, left frontal; F4A1, right frontal; C3A2, left central, C4A1, right central; O1A2, left occipital; O2A1, right occipital), electro-oculography (REOG, right; LEOG, left), submentalis electromyogram (Chin), limb EMG (UP R, right arm; UP L, left arm; TA R, right tibialis anterior; TA L, left tibialis anterior), electrocardiography channels (ECG); nasal airflow (TFlow); respiratory effort (THO, thoracic; ABD, abdominal), and oxygen saturation (SpO_2).

tionnaire can detect RBD using a cutoff of 5 points or more (total: 0-13 points). Because patients may not be aware of their abnormal behavior at night, interviewing the family members or bed partner improves the diagnostic accuracy of this questionnaire. The interpretation of the questionnaire score should not simply be based on the cutoff value but should also consider non-RBD parasomnias and differential disorders, such as REM sleep-related respiratory disorders, psychiatric disorders, and age-related problems. However, there are reports that the sensitivity is low when investigating the presence or absence of RBD associated with

Table 2 Previous reports of REM sleep behavior disorder

Acute	Etiology
Withdrawal	Alcohol, Meprobamate, Pentazocine, Nitrazepam, Organic solvent, Coccaine
Intoxication	Biperidin, Tricyclic antidepressants, Monoamine oxidase inhibitors, Caffeine
Chronic	
Idiopathic or Isolated	Cryptogenic, A forme fruste of Lewy body disease
Neurodegenerative disorders	Parkinson's disease, Dementia with Lewy bodies, Multiple system atrophy, Spinocerebellar ataxia type 3, Progressive supranuclear palsy, Corticobasal degeneration, Alzheimer's disease, Amyotrophic lateral sclerosis, Fatal familial insomnia
Vascular	Ischemic or hemorrhagic cerebrovascular disease, Subarachnoid hemorrhage, Vasculitis
Tumor	Acoustic neuroma, Pontine neoplasm, Brainstem cavernoma
Autoimmune	Multiple sclerosis, Guillain-Barré syndrome, Autoimmune limbic encephalitis
Drug-induced	Tricyclic antidepressants, Selective serotonin reuptake inhibitors, Serotonin-noradrenaline reuptake inhibitor, Caffeine, Selegiline, Anticholinergic drugs
Others	Narcolepsy, Post-traumatic stress disorder, Normal pressure hydrocephalus, Mitochondrial encephalomyopathy, Tourette's syndrome, Autism, Group A xeroderma pigmentosum

diseases such as PD, and caution is required in the interpretation of questionnaire score.

2) RBD 1Q[21]

"Have you ever been told that you're demonstrating your dream behavior while sleeping (for example, hitting, swinging your arms in the air, or sprinting), or have you ever suspected that yourself? Yes or no?" This question may be used in epidemiological surveys.

2. PSG

According to the Diagnostic Criteria of the International Classification of Sleep Disorders (ICSD-3)[22], voicing or complex movements related to dreaming may occur during REM sleep. Differentiation of IRBD from sleep-related disorders that can cause abnormal behavior at night (e.g., epilepsy and sleep apnea syndrome) is important. Demonstration of RWA without muscle suppression on PSG is an essential finding for the diagnosis (Fig. 1A, B). PSG records cases of persistent or intermittent lack of muscle tone loss or phasic muscle spasms on mentalis or limb EMGs during REM sleep. RWA is defined in the American Academy of Sleep Medicine (AASM) scoring manual[23]. PSG, including video recording, may help to differentiate IRBD from sleep disorders that may cause abnormal behavior at night, such as nocturnal seizures and obstructive sleep apnea syndrome, which have high prevalence in middle-aged and elderly people.

Diagnosis of Neurological Disease (Evaluation of LBD)

RBD is associated with a wide variety of causes[24] (Table 2). In cases where IRBD develops at a young age, possible use of causative drug as well as presence of psychiatric disorders and narcolepsy should be identified. In particular, in cases that develop during middle-age and old age, systematic neurological examination is performed to exclude the possibility of underlying α-synucleinopathies, such as PD, DLB, or multiple system atrophy (MSA). During examination, care should be taken not to miss signs of mild parkinsonism, such as reduced facial expressions, Froment's maneuver, and abnormal posture, walking, or movement. Furthermore, it is necessary to identify hyposmia, constipation, orthostatic hypotension, and cognitive disorders (e.g., vision or pareidolia).

In cases where LBD (PD or DLB) is suspected on the basis of neurological examination, further diagnostic imaging (e.g., cardiac MIBG scintigraphy[25], DAT-SPECT[26], and brain perfusion SPECT)[27] is recommended. It is possible to assess the short-term progression risk among IRBD patients. IRBD patients with early transition to LBD had lower DAT-SPECT values than those with non-transition at baseline and LBD onset. IRBD patients with early transition to LBD have lower DAT-SPECT values than those with no transition at baseline and constitute a high-risk group for the development of LBD. Future studies should accurately

diagnose RBD by PSG, stratify patients with early vs late progression, and evaluate the use of therapeutic agents that can suppress LBD onset.

Treatment

The treatment of RBD focuses on improving sleep symptoms that impair the patient's quality of life and prevent the onset of α-synucleinopathies[28-30]. Sleep symptoms may be improved by the management of the trauma associated with abnormal behavior during sleep and insomnia associated with sleep fragmentation. The bedroom environment should be modified to prevent injuries and accidents associated with IRBD; this includes removal of dangerous objects from the bedroom and encourage awakening of the patient during an episode of abnormal behavior. However, waking a patient in the middle of abnormal behavior may lead to escalation of the behavior, making the situation more dangerous. Therefore, patient should be awakened at the early stage of the behavior, dangerous objects and obstacles should be removed. The patient's behavior should be observed and once the patient becomes calm, they should be awakened. In addition, we recommend that mental and physical stresses should be eliminated because they promote IRBD; heavy alcohol consumption should be avoided. Complications of sleep-related disorders other than RBD, such as severe sleep apnea, may also trigger RBD. In this case, PSG is performed after treatment of the associated sleep disorders and sleep apnea syndrome is treated before RBD treatment.

Few drugs have been found to be effective for IRBD in randomized controlled trials. The effectiveness of clonazepam, yokukansan, and melatonin have been reported. Drug therapy is administered after the aforementioned sleep measures; the frequency and severity of abnormal behavior decreases with treatment. In some cases, the abnormal behavior resolves, whereas in other cases, mild symptoms, such as sleep-talking, persist. These treatments are symptomatic and symptoms recur if treatment is interrupted; therefore, long-term treatment is required. Clonazepam (0.5-2.0 mg)[28-30] is most frequently used and is effective in reducing abnormal behavior during sleep and nightmares in almost 90% of cases. In Japan, yokukansan[28-30] is commonly used and is effective. A single drug should be tried; however, if treatment fails with a single drug, combination therapies may be administered. Often, the abnormal behavior disappears except for sleep-talking.

Pathological modification therapies and neuroprotective therapies are being developed to prevent the onset of α-synucleinopathies. When conducting clinical trials for these therapies, inclusion criteria need to be set and participants should be stratified by the short-term risk of progression to α-synucleinopathies. Clinical trials of drugs should involve objective and reliable evaluation methods. In RBD, dopamine preganglionic nerve function declines over time before the onset of α-synucleinopathies[31,32]. Even in recent reports of DAT-SPECT assessment, the specific binding ratio (SBR) values at baseline varied from those from healthy databases[31,33]. It has been reported that dopaminergic nerve loss progresses with aging even in healthy subjects, but in the case of PD, it progresses rapidly before disease onset and slows down after disease onset[34]. IRBD patients who converted to α-synucleinopathies had reduced baseline DAT-SPECT values[26,32]. In other words, a positive, continuous and temporal standardized comprehensive clinical assessment of RBD, including its biomarkers, is important to evaluate its evolution over time to α-synucleinopathies. These data will contribute to the designing of accurate clinical trials of disease-modifying therapies for latent neurodegenerative diseases in RBD patients.

Disclosure of Disease Prognosis

IRBD symptoms may not be limited to sleep; physicians also need to consider the diagnosis and risk of LBD[35]. Disclosure of the risk of neurodegenerative disease in IRBD is problematic because the time to onset is as long as several decades and there is a lack of disease modifying therapies. The patient should be asked whether they want to know about the future risks and, if so, focus on the risk of developing neurodegenerative disease to prepare the patient for the future, life plan and care plan. The patient should also be provided information regarding participation in trials. Ultimately, disclosure is the choice of patients. However, complete disclosure may lead to unnecessary worry and anxiety among patients. It is difficult to balance the benefits and risks of disclosure, which is especially challenging because risk factors may be corrected be-

fore the onset of the disease and interventions in the early stages of the disease may be most effective. Identifying individuals at risk of α-synucleinopathies will be important for future trials of disease modifying therapies.

Conclusions

RBD patients with onset in middle-aged and elderly age groups constitute a high-risk group with the onset of α-synucleinopathes. Precision medicine[36] in RBD involves the accurate diagnosis by PSG test, identification of the cases with rapid progression, and introduction of therapeutic agents that can suppress the onset of α-synucleinopathies. In recent years, clinical trials of α-synucleinopathies are being prepared and we expect that candidate drugs will come into play in the future.

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