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Original

Background Factors in the Interpretation of the Results of REM Sleep Behavior Disorder Screening Questionnaire-Japanese Version

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Summary

Polysomnography (PSG) is necessary for the diagnosis of REM sleep behavior disorder (RBD) according to the diagnostic criteria of the International Classification of Sleep Disorders, 2nd edition. We administered the REM sleep behavior disorder screening questionnaire-Japanese version (RBDSQ-J) to patients admitted to the hospital for PSG due to suspected sleep disorders and evaluated the background factors in patients with suspected RBD. We analyzed data from 261 out of 269 consecutive patients who were administered the RBDSQ-J and underwent PSG. Probable RBD was defined as a total RBDSQ-J score of ≥ 5. Sixty-six of the 261 patients (25.3%) had a total RBDSQ-J score of ≥ 5. Among the 66 patients, 10 (15.2%) had idiopathic or isolated RBD, 1 (1.5%) had secondary RBD with multiple system atrophy, and 55 (83.3%) did not have RBD. Among patients aged 50 years or older, all patients (n = 11) had RBD, whereas among those aged less than 50 years, none had RBD. The background factor in patients with false positive results was mainly obstructive sleep apnea syndrome (OSAS), whereas among young patients, the factors other than OSAS included narcolepsy, migraine, psychological disorders (such as PTSD, depression, or schizophrenia), and complications of central neurological disorders (such as sequelae of brainstem infarction or limbic encephalitis). RBDSQ-J is useful to screen for idiopathic/isolated RBD-associated synucleinopathies among middle-aged and elderly people aged ≥ 50 years, but among young patients and those with positive result of RBDSQ-J, various background factors may be present and the results should be interpreted with caution.

Key Words: REM sleep behavior disorder, RBDSQ, pseudo-RBD, polysomnography, RBD symptomology

Introduction

REM sleep behavior disorder (RBD) includes enactment of complex movements in dreams due to the loss of normal muscle suppression during REM sleep that are associated with an increased risk of self-injury and

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平成　　年　　月　　日
名前　　年齢　　歳　男・女

下記のいずれかに○をつけてから、回答をお願いします。
1. 自分自身だけで記入した。　2. 家族あるいはベットパートナーと相談して記入した。

RBD スクリーニング問診票

質問	答え
1. とてもはっきりした夢をときどき見る。	はい ・ いいえ
2. 攻撃的だったり、動きが盛りだくさんだったりする夢をよく見る。	はい ・ いいえ
3. 夢を見ているときに、夢の中と同じ動作をすることが多い。	はい ・ いいえ
4. 寝ている時にうでや足を動かしていることがある。	はい ・ いいえ
5. 寝ている時にうでや足を動かすので、隣で寝ている人にケガを負わせたり、自分がケガをしたりすることもある。	はい ・ いいえ
6. 夢を見ているときに以下のできごとが以前にあったり、今もある。	
6.1 誰かとしゃべる、大声でどなる、大声でののしる、大声で笑う。	はい ・ いいえ
6.2 うでと足を突如動かす/ けんかをしているように。	はい ・ いいえ
6.3 寝ている間に、身振りや複雑な動作をする。(例:手を振る、挨拶をする、何かを手で追い払う、ベッドから落ちる)	はい ・ いいえ
6.4 ベッドの周りの物を落とす。(例:電気スタンド、本、メガネ)	はい ・ いいえ
7. 寝ている時に自分の動作で目が覚めることがある。	はい ・ いいえ
8. 目が覚めた後、夢の内容をだいたい覚えている。	はい ・ いいえ
9. 眠りがよく妨げられる。	はい ・ いいえ
10. 以下のいずれかの神経系の病気を、以前患っていた、または現在患ってますか。(例:脳卒中、頭部外傷、パーキンソン病、むずむず脚症候群、ナルコレプシー、うつ病、てんかん、脳の炎症性疾患)	はい ・ いいえ

－RBDSQ-J－

Figure 1
REM sleep behavior disorder screening questionnaire-Japanese version (RBDSQ-J) [4]

other harm. Idiopathic or isolated RBD (IRBD) develops after the age of 50 years and is a precursor to neurodegenerative diseases, such as Parkinson's disease (PD), Lewy body dementia (DLB), and multiple system atrophy (MSA)[1]. Polysomnography (PSG) is essential to confirm the diagnosis of RBD based on the second edition of the International Classification of Sleep Disorders (ICSD-2)[2]. The REM sleep behavior disorder screening questionnaire (RBDSQ) is a self-administered compulsory two-choice questionnaire developed by Stiasny-Kolster et al.[3] for RBD screening. A score is marked for each answer of "yes" to the questions and the total is calculated by adding the scores of questions. We developed a Japanese version of RBDSQ (RBDSQ-J) (Fig. 1) with the permission of the original authors, verified its reliability and validity, and used it to screen patients aged ≥ 50 years for IRBD. We previously reported high sensitivity, specificity, and reli-

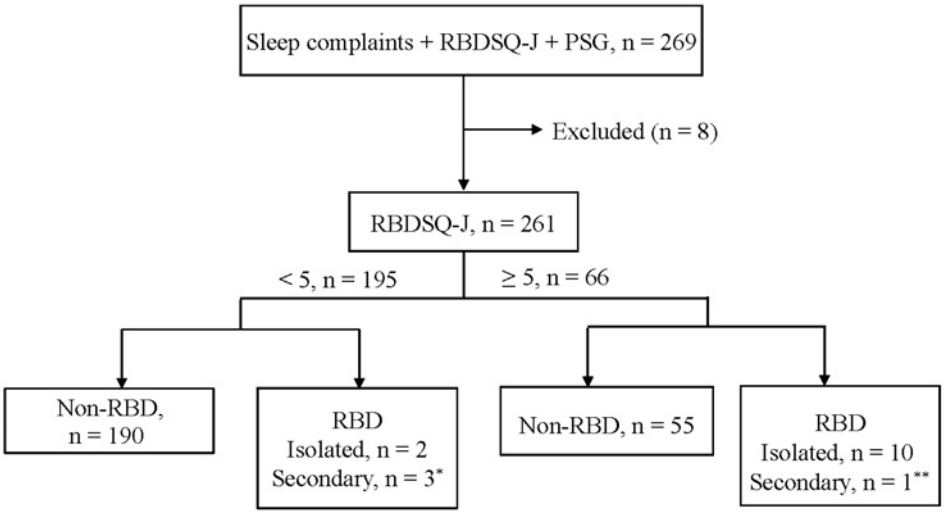

Figure 2

Flow chart of RBDSQ-J administered to 269 consecutive individuals.

We analyzed data from 261 of 269 consecutive patients with suspected sleep disorders who underwent RBDSQ-J and polysomnography. Suspected RBD was defined as a total RBDSQ-J score of ≥ 5. Sixty-six of 261 patients (25.3%) had a total score of ≥ 5. Of the 66 patients with RBDSQ-J score ≥ 5, 11 had IRBD. Two patients with score < 5 had IRBD.

*Parkinson's disease, n = 1; multiple system atrophy, n = 1; mild cognitive impairment, n = 1. **multiple system atrophy, n = 1.

Abbreviations: RBDSQ-J, REM sleep behavior disorder screening questionnaire-Japanese version; IRBD, idiopathic REM sleep behavior disorder.

ability of RBDSQ-J[4]. In the present study, we used RBDSQ-J to screen for RBD among patients who visited the sleep center. We retrospectively investigated the cases with probable RBD-with sleep-related diseases other than RBD that were confirmed by PSG.

Participants and Methods

Of the 269 consecutive patients who underwent both RBDSQ-J (Fig. 1) and PSG at the Center of Sleep Medicine, Dokkyo Medical University with suspected sleep disorders between May 2009 and April 2010, we retrospectively analyzed the data from 261 patients (178 males and 83 females; mean ± standard deviation: 49.4 ± 17.1), excluding 3 children younger than 15 years old and 5 undiagnosed patients (Fig. 2). RBDSQ-J was completed by the patients at the first outpatient visit and RBDSQ-J score of ≥ 5 was defined as probable RBD (pRBD)[3,4]. The diagnosis of sleep-related diseases was confirmed in accordance with the ICSD-2 diagnostic criteria[2]. Based on the PSG findings, sleep-related disorders were classified into groups according to the major items of ICSD-2, namely insomnia, sleep-related breathing disorders, hypersomnias of central origin, circadian rhythm sleep disorders, parasomnias and sleep-related movement disorders groups. We also investigated the backgrounds in each group.

This study was conducted from 2009 to 2010 and based on the Dokkyo Medical University Research Ethics at that time. We made efforts to protect the personal information of participants, including personal attributes and questionnaire answers.

Results

Based on a RBDSQ-J score of ≥ 5, pRBD was diagnosed in 66 of 261 cases (25.3%), of which PSG confirmed RBD in 11 (23.4%) patients: 10 with isolated RBD and 1 with RBD secondary to multiple system atrophy. Conversely, among patients with RBDSQ-J score of ≥ 5, 55 (83.3%) did not have RBD on PSG (non-RBD). Among 195 patients with RBDSQ-J score < 5, PSG confirmed RBD in 5 cases (2.6%): 2 with isolated RBD and 3 with secondary RBD (1 with PD, 1 with MSA, and 1 with mild cognitive impairment). The remaining 190 patients (97.4%) did not have RBD (Fig. 2).

Probable RBD was defined as a total RBDSQ-J score of ≥ 5. Sixty-six of the 261 patients (25.3%) had a total RBDSQ-J score of ≥ 5 points. Among 66 patients, 10 (15.2%) had idiopathic or isolated RBD, 1 (1.5%) had sec-

Table 1 Background factors from the perspective of ICSD-2 for RBDSQ-J ≥ 5

	RBDSQ-J score ≥ 5, n (%)
Total, n = 261	66 (25.3)
Parasomnias, n = 16	**11 (68.8)**
Idiopathic or isolated RBD, n = 12	**10 (83.3)**
Secondary RBD, n = 4	**1 (25.0)**
Insomnia, n = 12	3 (25.0) *
Insomnia due to mental disorder, n = 3	2 (66.7)
Unspecified nonorganic insomnia, n = 6	0 (0)
Inadequate sleep hygiene, n = 3	1 (33.3)
Sleep-related breathing disorder, n = 179	35 (19.6)
OSAS, n = 177	35 (19.8)
CSAS, n = 2	0 (0)
Hypersomnia of central origin, n = 35	11 (31.4) *
Narcolepsy with cataplexy, n = 5	2 (40.0)
Narcolepsy without cataplexy, n = 8	2 (25.0)
Narcolepsy due to medical condition, n = 1	0 (0)
Idiopathic hypersomnia, n = 12	4 (33.3)
Insufficient sleep syndrome, n = 7	3 (42.9)
Nonorganic hypersomnia, n = 2	0 (0)
Sleep related movement disorder, n = 13	5 (38.5) *
Restless legs syndrome, n = 10	5 (50.0)
Periodic limb movement disorder, n = 3	0 (0)
Normal variant, n = 6	1 (16.7) *
Snoring, n = 6	1 (16.7)

CSAS, central sleep apnea syndromes; OSAS, obstructive sleep apnea syndromes; RBD, REM sleep behavior disorder; RBDSQ-J, REM sleep behavior screening questionnaire-Japanese version. *, false positive results.

ondary RBD with multiple system atrophy, and 55 (83.3%) had false positive results. The background factors from the perspective of ICSD-2 for RBDSQ-J ≥ 5 in patients with false positive results (n = 55) were insomnia (n = 3), sleep-related breathing disorder (n = 35), hypersomnias of central origin (n = 11), sleep-related movement disorder (n = 5), and normal variant (n = 1) (Table 1).

Among patients younger than and older than 50 years, the RBDSQ-J score was ≥ 5 in 35 (13.4%) and 31 (11.9%) patients, respectively (Table 2). None of the 35 patients with RBDSQ-J score of ≥ 5 and age < 50 years had RBD. These 35 patients had insomnia (n = 3; inadequate sleep hygiene or unspecified nonorganic insomnia), sleep-related breathing disorder (n = 19; OSAS), hypersomnias of central origin (n = 10; narcolepsy, idiopathic hypersomnia, or insufficient sleep syndrome), sleep-related movement disorder (n = 2; restless legs syndrome), or normal variant (n = 1; snoring).

Among the 31 patients with RBDSQ-J score of ≥ 5 and age ≥ 50 years, 11 had RBD and 20 did not have RBD; these 20 non-RBD patients had insomnia (n=1: insomnia due to mental disorder), sleep related breathing disorders (n=16: OSAS), or sleep-related movement disorder (n=3: restless legs syndrome).

The background factors other than sleep-related disorders among patients with RBDSQ-J score ≥ 5 are presented in Table 3. Two cases of migraine and one case each of MSA, neuromyelitis optica spectrum disorders (NMOSD), post-traumatic stress disorder (PTSD), depression, fibromyalgia, schizophrenia, sequelae of brainstem infarction, and sequelae of limbic encephalitis were included as background factors in the sleep-related breathing disorders group. In addition, one case each of migraine and hyperthyroidism were included as background factors in the sleep-related movement disorders group (Table 3).

The parasomnia group had significantly higher RBDSQ-J score than the other five groups (i.e., insomnia, sleep related breathing disorder, hypersomnias of central origin, sleep-related movement disorder, and normal variant groups) (Fig. 3).

Table 2 Differences among age groups of patients with RBDSQ-J score ≥ 5

	RBDSQ-J score ≥ 5, n (%)	
	< 50 years	≥ 50 years
Total, n = 261	35 (13.4)	31 (11.9)
Parasomnias, n = 16	**0 (0)**	**11 (68.8)**
Idiopathic or isolated RBD, n = 12	**0 (0)**	**10 (83.3)**
Secondary RBD, n = 4	**0 (0)**	**1 (25.5)**
Insomnia, n = 12	3 (25.0)	1 (8.3)
Insomnia due to mental disorder, n = 3	0 (0)	1 (33.3)
Unspecified nonorganic insomnia, n = 6	1 (0)	0 (0)
Inadequate sleep hygiene, n = 3	2 (66.7)	0 (0)
Sleep-related breathing disorder, n = 179	19 (10.6)	16 (8.9)
OSAS, n = 177	19 (10.7)	16 (9.0)
CSAS, n = 2	0 (0)	0 (0)
Hypersomnia of central origin, n = 35	10 (28.6)	0 (0)
Narcolepsy with cataplexy, n = 5	2 (40.0)	0 (0)
Narcolepsy without cataplexy, n = 8	2 (25.0)	0 (0)
Narcolepsy due to medical condition, n = 1	0 (0)	0 (0)
Idiopathic hypersomnia, n = 12	4 (33.3)	0 (0)
Insufficient sleep syndrome, n = 7	2 (28.6)	0 (0)
Nonorganic hypersomnia, n = 2	0 (0)	0 (0)
Sleep-related movement disorder, n = 13	2 (15.4)	3 (23.1)
Restless legs syndrome, n = 10	2 (20.0)	3 (30.0)
Periodic limb movement disorder, n = 3	0 (0)	0 (0)
Normal variant, n = 6	1 (16.7)	0 (0)
Snoring, n = 6	1 (16.7)	0 (0)

CSAS, central sleep apnea syndromes; OSAS, obstructive sleep apnea syndromes; RBD, REM sleep behavior disorder; RBDSQ-J, REM sleep behavior screening questionnaire-Japanese version.

Table 3 Background factors other than sleep-related disorders of patients with RBDSQ-J score ≥ 5

Migraine	3
Multiple system atrophy	1
Neuromyelitis optica spectrum disorders	1
Post-traumatic stress disorder	1
Depression	1
Fibromyalgia	1
Schizophrenia	1
Sequelae of brain stem infarction	1
Sequelae of limbic encephalitis	1
Hyperthyroidism	1

Discussion

According to the International Classification of Sleep Disorders (ICSD-1)[5], the definitive diagnosis of RBD was based on clinical signs only, without the need of PSG. The PSG findings of RBD include preservation of REM sleep without atonia and confirmation of no epileptic discharges during REM sleep. In 2015, the diagnostic criteria was revised in ICSD-3. PSG is also indispensable for the diagnosis of sleep disorders other than RBD, including hypersomnia (e.g., OSAS and narcolepsy) and periodic limb movement disorder[2]. However, only a limited number of facilities in Japan are equipped to perform PSG and not all medical institutions can definitively diagnose RBD. Accurate patient screening is essential before referral of patients to medical centers specializing in sleep disorders. Therefore, RBDSQ, which was developed in Germany to screen for RBD, was completed through a predetermined process based on the creation process of the Japanese version of Pittsburgh Sleep Quality Index[6]; in addition, the reliability and validity of RBDSQ-J were verified[4]. In the present study, the optimal cut-off values of the sensitivity and specificity for OSAS in patients aged ≥ 50 years who entered the stable treatment phase of the disease-controlled disease control

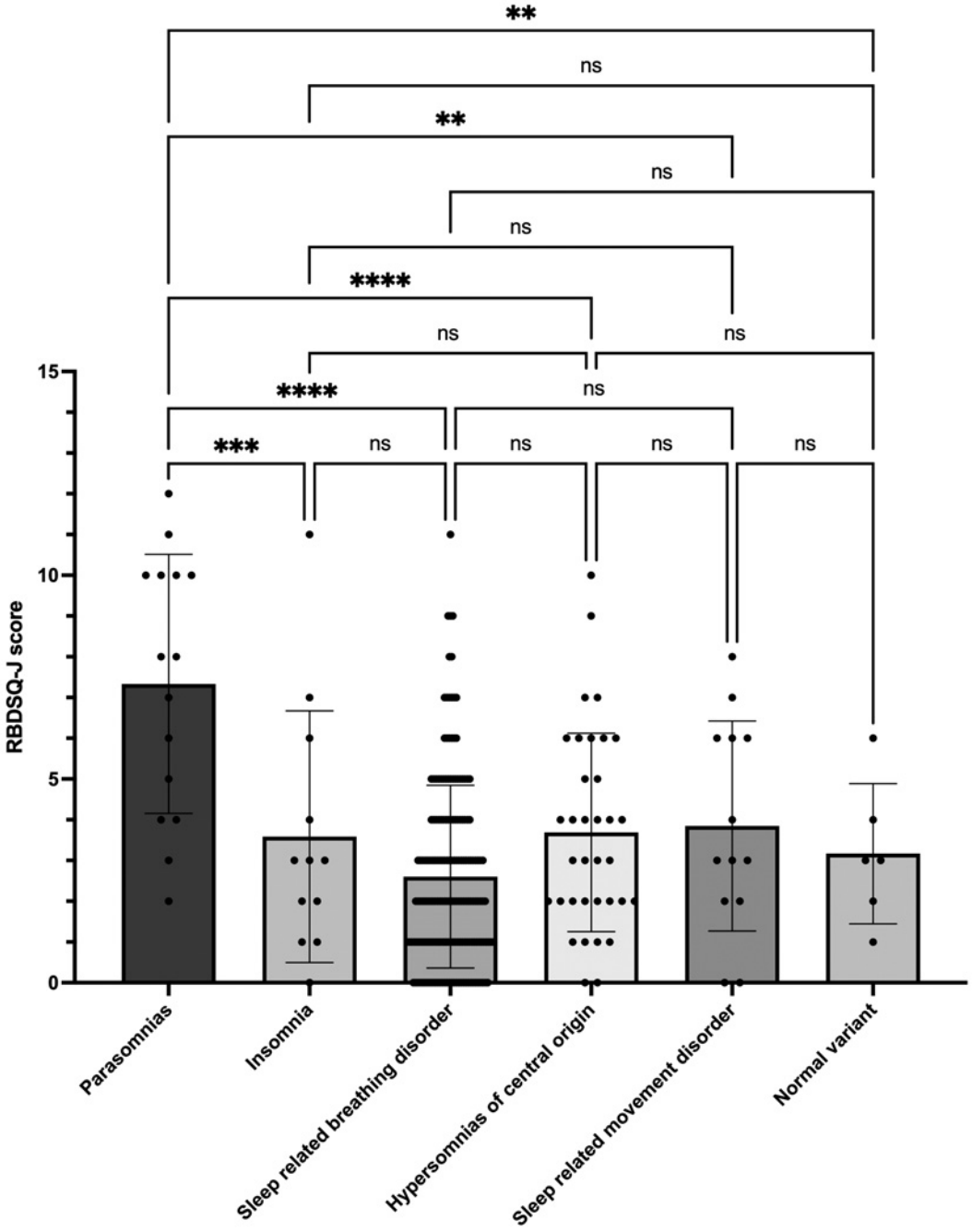

Figure 3

Comparison of six groups of RBDSQ-J scores

RBDSQ-J, REM sleep behavior disorder screening questionnaire-Japanese version.

, 0.0009; *, < 0.0001; **, 0.0019; **, 0.0046

were integer values, as reported by the original author. IRBD should be differentiated from pseudo-RBD[7,8], PTSD[9-11], sleep-related dissociative disorder[2], narcolepsy[2], and secondary RBD due to neurodegenerative diseases (e.g., PD, DLB, and MSA)[2,12].

Among 55 out of 66 patients (83.3%), the RBDSQ-J score was ≥ 5 but RBD was not found on PSG; among these patients. The background factor from ICSD-2 was mainly OSAS. OSAS may mimic the symptoms of RBD; patients with mild OSAS have REM sleep instability due to sleep apnea and patients with severe OSAS have apnea-induced arousal[7].

In this study, all patients aged 50 years and older (n = 11) had RBD, whereas none of the patients aged less

than 50 years had RBD. Among younger patients (aged < 50 years) with probable RBD, the factors other than OSAS included narcolepsy, migraine, psychological disorders, such as PTSD, depression, or schizophrenia, and complications of central neurological disorders, such as sequelae of brainstem infarction, and limbic encephalitis. Typical RBD occurs at age 50 years or above and has a strong association with neurodegenerative diseases, particularly synucleinopathies, such as PD, DLB and MSA. In contrast, RBD in younger adults (aged under 50 years) is relatively rare and has different demographic characteristics from RBD in the elderly population[15]. In younger RBD patients, secondary RBD due to neurodegenerative disease is much less common compared to elderly RBD[15], whereas other causes of secondary RBD are common, including antidepressant medication use (antidepressants induce motor activity during REM sleep)[15], narcolepsy (decreased input of hypocretinergic innervation from hypothalamus to the limbic system and brainstem nuclei that regulate REM sleep muscle tone)[15], parasomnia overlap syndrome (coexistence of RBD with a NREM parasomnia)[15], autoimmune or inflammatory diseases (may be associated with non-synuclein structural lesions affecting the pons, medulla, or limbic system.)[14,16], brainstem lesion (causing direct injury to the brainstem regions involved in REM sleep control)[15], PTSD (disruptive nocturnal behaviors and nightmares following traumatic events)[15], and depression (complex dysregulation in the locus coeruleus-noradrenergic system and hence disruption of the normal REM sleep inhibition of muscle activity resulting in RWA)[15]. Dream-enacting behavior (DEB), as evaluated by RBDSQ-J, was commonly observed in narcolepsy patients[17]. In addition, migraine patients with DEB also had high scores on the Migraine Disability Assessment and Pittsburgh Sleep Quality Index[18]. DEB was associated with impaired sleep and severe headache-related disability in migraine patients, and may reflect brainstem dysfunction and increased brain excitability in migraine patients. In such patients, it is necessary to pay attention to the interpretation of pRBD in RBDSQ-J. In this study, there were no patients aged under 50 years with RBDSQ-J score ≥ 5 points with a definitive diagnosis of RBD. However, it is necessary to consider that young people may have a different cause of RBD from neurodegenerative diseases and other background factors may cause dream enactment behavior.

In the present study, two IRBD patients had RBDSQ-J score < 5. The first patient was a 60-year-old man who presented with snoring, falls out of bed, and dreams of being chased. The PSG showed RBD comorbid with moderate sleep apnea and continuous positive airway pressure (CPAP) therapy was advised to improve his symptoms. The patient's snoring was more problematic than the RBD symptoms because of the annoyance to the bed partner; therefore, the RBDSQ underestimated the patient's symptoms. The other patient was an 80-year-old man who had no subjective symptoms but his family noticed that his behavior during sleep correlated with his dream contents, which was confirmed by PSG. In other words, RBDSQ-J is a self-administered questionnaire, which may underestimate the score if information from the bed partners is not available. In cases where information cannot be obtained from the bed partner for items 3-6 (Fig. 1), the score may be underestimated and some items should be interpreted with caution.

The limitation of this study was that the participants were enrolled from a sleep center and this population may differ from the general population[19], which may cause bias. The diagnostic value of the RBDSQ strongly depends on the clinical setting and may be influenced by the individual's awareness on RBD[20]. The strength of this study was that RBDSQ-J and PSG were performed on participants with a wide age range and the results could be verified.

In conclusion, RBDSQ-J is useful to screen for idiopathic/isolated RBD, which may be associated with synucleinopathies among middle-aged and elderly people aged ≥ 50 years. However, among young patients, a positive result of RBDSQ-J may be associated with various background factors; therefore, the results should be interpreted with caution.

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