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Screening Methods for REM Sleep Behavior Disorder

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1. Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behavior and vivid, action-filled or unpleasant dreams and presents a risk for self-injury and harm to others (e.g., a bed partner) due to abnormal REM sleep during which control of muscle tone is lacking. Polysomnography is required to establish the diagnosis and represents the diagnostic gold standard for revealing loss of REM-related muscle atonia with excessive sustained or intermittent elevation of submental EMG tone or excessive phasic submental or limb EMG twitching. Idiopathic RBD (iRBD) has a male preponderance and usually emerges after the age of 50 and has a known association with neurodegenerative diseases, in particular the α -synucleinopathies such as Parkinson's disease (PD), dementia with Lewy body disease and multiple system atrophy (Schenck & Mahowald, 2002). Even more important, evidence is growing that iRBD precedes parkinsonism by years or even decades, and that iRBD might present an early stage in the development of neurodegenerative disorders (Schenck et al., 1996). Thus, to identify clinical RBD as early as possible appears to be useful for early diagnosis, a clinical trial with a potentially neuroprotective substance, and also for epidemiological studies. To meet the need for an easily applicable diagnostic screening tool, Stiasny-Kolster et al. developed and validated a specific screening scale for assessment of RBD, the RBD screening questionnaire (RBDSQ) (Stiasny-Kolster et al., 2007). Subsequently we developed a Japanese version of the RBDSQ (RBDSQ-J) after obtaining approval from the patent owner and investigated its validity and reliability (Miyamoto et al., 2009). We found that detection of RBD using the RBDSQ-J would be useful in the stepwise diagnostic process. We will discuss screening methods for RBD and describe RBD screening questionnaires, including the RBDSQ-J.

2. Prevalence of REM sleep behavior disorder

The overall prevalence of RBD remains largely unknown. A large telephone survey using the Sleep-EVAL system for assessing violent behaviors during sleep in the general

population (4972 individuals aged 15-100 years) in the United Kingdom suggested an estimated prevalence of RBD of about 0.5% (Ohayon et al., 1997). A study of 1034 elderly subjects aged 70 years or above in the Hong Kong area found an estimated prevalence of polysomnography (PSG)-confirmed RBD of 0.38% (Chiu et al., 2000). There is a male predominance (87%) with primarily men over the age of 50 being affected (Schenck & Mahowald, 2002). Boeve summarized the demographics and clinical phenomenology of RBD (Table 1) (Boeve, 2010a).

Male gender predilection

Age of onset typically 40-70 years (range 15-80 years)

Abnormal vocalizations -orating, yelling, swearing, screaming

Abnormal motor behavior- limb flailing, punching, kicking, lurching out of bed

Altered dream mentation - typically involves a chasing/attacking theme with insects, animals or other humans being the aggressors and the patient being the defender

Exhibited behaviors mirror dream content

Behaviors tend to occur in the latter half of the sleep period

Table 1. Demographics and clinical phenomenology of RBD (Modified from Boeve, 2010a)

3. Diagnosis for REM sleep behavior disorder

Until recently, the diagnosis of RBD was based on clinical manifestations, namely the presence of limb or body movements associated with dream mentation and at least one of the following: (1) harmful or potentially harmful sleep behaviors during sleep; (2) dreams that appear to be acted out; and (3) sleep behaviors that disrupt sleep continuity. Polysomnographic observations of patients were not necessary for diagnosis according to the International Classification of Sleep Disorders-1 (ICSD-1).

Eisensehr et al. and Gagnon et al. pointed out the limitations of these criteria because one half of the cases of RBD with PD would have been undetected based clinical interviews alone (Eisensehr et al., 2001; Gagnon et al., 2002). RBD-like features can occur with other sleep conditions such as obstructive sleep apnea syndrome (OSAS), sleepwalking, night terrors, and sleep-related seizures (see below 4). In the second version of the ICSD (ICSD-2), PSG findings were required to establish the diagnosis. The first essential criterion is the presence of REM sleep without atonia. The second criterion is the presence of either sleep-related injurious or disruptive behaviors revealed by history or abnormal REM sleep behaviors documented during PSG recording. Time-synchronized video recording is essential for helping to establish the diagnosis of RBD during PSG. The last two criteria are exclusion criteria, which are the absence of epileptiform activity during sleep and the presence of other sleep disorders or medical or neurological disorders that could better explain the sleep disturbance. The diagnostic criteria are listed in Table 2.

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- A. Presence of REM sleep without atonia: EMG finding of excessive amounts of sustained or intermittent elevation of submental EMG tone or excessive phasic submental or (upper or lower) limb EMG twitching.
 - B. At least one of the following is present:
 - i. Sleep related injurious, potentially injurious, or disruptive behaviors by history
 - ii. Abnormal REM sleep behaviors documented during polysomnographic monitoring
 - C. Absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep related seizure disorder.
 - D. The sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.
-

Table 2. Diagnostic criteria for REM sleep behavior disorder in ICSD-2

4. Differential diagnosis of REM sleep behavior disorder

RBD is a relatively rare condition and is largely unknown to most physicians (see above 2), therefore it is often misdiagnosed and mistreated.

The differential diagnosis of recurrent dream enactment behavior includes NREM parasomnia, nocturnal panic attacks, nocturnal seizures, nightmares, nocturnal wandering associated with dementia, and OSAS (Boeve, 2010a). A complaint of nocturnal disruptive behaviors is the major clinical feature of several other conditions, such as primary and secondary disorders of arousal, dreaming, and panic disorders (Table 3).

Primary disorders of arousal (from NREM sleep) Confusional arousals Sleepwalking Sleep terrors Secondary arousal disorders Obstructive sleep apnea syndrome (pseudo RBD) Sleep-related epilepsy Psychiatric diseases Sleep-related dissociative disorder Panic disorder Posttraumatic stress syndrome

Table 3. Differential diagnosis of RBD

Primary arousal disorders from NREM sleep include confusional arousals, sleepwalking, and sleep terrors. In contrast to RBD, sleepwalking and sleep terrors are more frequent in children and rarely appear *de novo* in middle-aged or elderly individuals. They are also characterized by confusion and retrograde amnesia upon awakening at the time of nocturnal episodes; these phenomena are not seen in patients with RBD. In general, RBD involves attempted enactment of altered dreams and rapid awakening from an episode that usually occurs two or more

hours after sleep onset. In contrast, sleepwalking and sleep terror episodes often emerge within two hours after sleep onset, are not usually associated with rapid alertness, and are rarely associated with dreaming in children. Adults can have associated dreaming, but it is usually more fragmentary and more limited than RBD dreams.

Severe OSAS and nocturnal epilepsy may mimic the symptoms of RBD. Patients with severe OSAS may present with unpleasant dreams and dream-enacting behaviors (Iranzo & Santamaria, 2005). Continuous positive airway pressure (CPAP) therapy can eliminate abnormal nocturnal behaviors. Sleep-related seizures usually present with repetitive stereotypical behaviors.

When a diagnostic clarification is necessary, particularly when the risk for injury is high, the behaviors occur at any time of the night, other features suggesting an evolving neurodegenerative are present, or loud snoring and observed apnea suggestive of OSA are present, PSG with simultaneous video monitoring is warranted (Boeve, 2010a).

5. The need for screening and screening methods for RBD

PSG is clearly necessary for establishing the diagnosis of RBD, but the procedure requires appropriate monitoring equipment, including time synchronized video recordings, specially trained technologists, bed availability in a sleep laboratory, and clinicians who can interpret the data. The procedure is costly, especially for patients with limited insurance coverage.

Subjects must be willing and able to sleep in a sleep laboratory and undergo monitoring. Some patients with coexisting neurologic disorders are too cognitively or physically impaired to tolerate and undergo an adequate study, are too uncooperative to permit all of the monitoring equipment to remain in place, are at risk for falls during the night, or are institutionalized. RBD cannot be accurately assessed in the home. Due to the limited number of sleep disorder centers in many countries, PSG is not possible even when clearly medically warranted. As it is impractical to perform PSG in large numbers of subjects in epidemiologic studies of sleep disorders, the availability of a simple, short, reliable, and accurate measure to screen for the presence of various sleep disorders would be highly valuable (Boeve, 2010a).

A recent study suggested that a clinical interview by expert clinicians could provide good sensitivity (100%) and specificity (99.6%) in diagnosing RBD in non-PD patients (Eisensehr et al, 2001). The interobserver reliability of ICSD-R criteria for RBD was also found to be substantial (Bologna, Genova, Parma and Pisa Universities group for the study of REM sleep Behaviour Disorder (RBD) in Parkinson's Disease, 2003). Nevertheless, conducting a useful clinical interview may require considerable expertise, training, time and resources. In addition, waiting times might be long for and access limited to clinical and PSG assessments in some medical settings. Hence, an easily applicable questionnaire may be considered as a supplemental assessment tool in clinical practice to provide a quick and accurate appraisal of RBD symptoms in order to prioritize assessment and intervention.

We describe RBD screening questionnaires such as the Mayo Sleep Questionnaire (MSQ), RBDSQ (English/German version and Japanese version) and RBDQ-HK.

5.1 Mayo sleep questionnaire

RBD is a parasomnia that can develop in otherwise neurologically-normal adults as well as in those with a neurodegenerative disease. Confirmation of RBD requires PSG. A simple screening measure for RBD is desirable for clinical and research purposes. Boeve et al.

developed the Mayo Sleep Questionnaire (MSQ), a 16-item measure to screen for the presence of RBD, periodic legs movement disorder (PLMD), restless legs syndrome (RLS), sleepwalking, OSAS and sleep-related leg cramps (Boeve, 2010a; Boeve et al., 2002a, 2002b, 2010b, 2011). The data presented herein refer to the primary question on RBD (Question 1); if the primary question is answered affirmatively, subquestions are asked (subquestions 1b-e) as shown in Table 4.

1. Have you ever seen the patient appear to “act out his/her dreams” while sleeping?

(punched or flailed arms in the air, shouted or screamed).

If yes,

- (a) How many months or years has this been going on? (data on this subquestion were not analyzed in this analysis)
 - (b) Has the patient ever been injured from these behaviors (bruises, cuts, broken bones)?
 - (c) Has a bed partner ever been injured from these behaviors (bruises, blows, pulled hair)?
 - (d) Has the patient told you about dreams of being chased, attacked or that involve defending himself/herself?
 - (e) If the patient woke up and told you about a dream, did the details of the dream match the movements made while sleeping?
-

Table 4. Primary question on RBD in the Mayo Sleep Questionnaire (MSQ)
(from the website: <http://www.mayoclinic.org/pdfs/MSQ-copyrightfinal.pdf>.)

Among the community-dwelling elderly, the MSQ has high sensitivity (100%) and specificity (95%) for diagnosis of RBD and was particularly specific for RBD in the absence of an OSA feature (Boeve, 2010b).

Boeve et al. also assessed the validity of the MSQ by comparing the responses of patients' bed partners with the findings (REM sleep without atonia) on PSG. The study subjects were 176 individuals (150 males; median age 71 years (range 39-90)) with the following clinical diagnoses: normal (n=8), mild cognitive impairment (n=44), Alzheimer's disease (n=23), dementia with Lewy bodies (n=74), and other dementia and/or parkinsonian syndromes (n=27). Sensitivity and specificity for question 1 on the MSQ for PSG-proven RBD were 98% and 74%, respectively. They concluded that the MSQ has adequate sensitivity and specificity for the diagnosis of RBD among aged subjects with cognitive impairment and/or parkinsonism (Boeve et al, 2011).

5.2 RBDSQ

Stiasny-Kolster et al. in 2007 developed the original German/English RBD Screening Questionnaire (RBDSQ) (Stiasny-Kolster et al., 2007). The RBDSQ is a 10-item patient self-rating instrument that assesses sleep behavior with short questions that have to be answered by either “yes” or “no” by the patient. Since patients do not always have a long-time companion, the bed partner's input was encouraged but not required. Items 1 to 4 address the frequency and content of dreams and their relationship to nocturnal movements and

behavior. Item 5 asks about self-injuries and injuries of the bed partner. Item 6 consists of four subitems that assess nocturnal motor behavior more specifically, e.g., questions about nocturnal vocalization, sudden limb movements, complex movements, or items around the bed that fell down. Items 7 and 8 deal with nocturnal awakenings. Item 9 focuses on disturbed sleep in general and item 10 on the presence of any neurological disorder. The maximum total score for the RBDSQ is 13 points. The RBDSQ was applied to 54 RBD patients (mean age 53.7 years, range 19-79) who had been clinically diagnosed with iRBD (n=19), narcolepsy (n=33), early PD (n=2)) and 160 patients without RBD (age 50.8 years, range 20-83) who had been diagnosed as having RLS (n=73), narcolepsy (n=27), OSAS (n=21), hypersomnia (n=10), PLMD (n=8), insomnia (n=4), sleepwalking (n=4), epilepsy (n=3), nightmares (n=1), sleep bruxism (n=1), or depression. (n=1). Also studied were 133 healthy subjects (mean age 46.9 years, range 20-72). Using a cut-off value of five points on the RBDSQ as a discriminatory variable, the questionnaire revealed a sensitivity of 96% and a specificity of 56%, correctly diagnosing 66% of subjects with sleep disorders. They mentioned that the lower specificity might be due to the fact that most of their control patients had sleep disturbances or neurological disorders that are known to be associated with periodic leg movements, e.g., RLS, PLMD, narcolepsy, and OSAS. This selection bias predisposed to positive answers for items that are related either to limb movements such as items 4, 5, 6.2, and 7 or to the presence of sleep and/or neurologic disorders such as for items 9 and 10, leading to higher RBDSQ total scores and thus to a lower specificity. Considering its high sensitivity, the RBDSQ represents an adequate tool to detect subjects with RBD. In subjects without additional neurologic or sleep disorders, the specificity was high, but in patients with either neurologic diseases or sleep disorders, the specificity is poorer but acceptable. The authors demonstrated the RBDSQ might be applied within a stepwise diagnostic process (questionnaire, interview, PSG).

5.3 RBDSQ-J

We developed a Japanese version of the RBDSQ (RBDSQ-J) after obtaining approval from the patent owner and investigated its validity and reliability (Miyamoto et al., 2009). The RBDSQ-J was administered to 52 consecutive patients with iRBD diagnosed according to criteria in the ICSD-2 (mean age 66.4 years; 36 males, 16 females), 55 consecutive OSAS patients who had responded well to CPAP therapy (mean age 63.1 years; 44 males, 11 females) after a diagnosis of RBD was ruled out by history and PSG and 65 apparently healthy subjects (mean age 64.6 years; 37 males, 28 females).

The mean RBDSQ-J scores for the iRBD group, the OSAS group and the healthy subjects were 7.5, 1.9, and 1.6 points, respectively. Sensitivity and specificity using a cut-off of 4.5 were high in differentiating the iRBD group from healthy subjects or the OSAS group. An RBDSQ-J score cut-off of 5.0 was considered useful for differentiating the iRBD group from the healthy subjects or the OSAS group. Cronbach's alpha for the entire RBDSQ-J was 0.866. The RBDSQ-J score had no correlation with the duration of RBD (mean disease duration in the iRBD group from symptom onset was 4.6 years, range 0.2 to 18 years). Answers to some items varied or had lower sensitivity. For example, for items 5, 6.2, and 6.3 a bed partner would be needed to provide answers, and the situations referred to in items 6.4 and 8 were often obscure. In evaluation of reliability, items that enlarged the kappa coefficient were 1, 2, 5 and 6.1 for iRBD. It can be proposed that future evaluations should use weighted scores

for RBDSQ-J items, which may improve the accuracy of the questionnaire. The RBDSQ-J has high sensitivity, specificity, and reliability and would be applicable as a screening method for iRBD in an elderly Japanese population. Early-onset patients (≤ 50 years) were reported to have significantly more past and present psychiatric diagnoses and antidepressant usage than late-onset patients (>50 years) (Teman et al., 2009). It may be necessary to validate the RBDSQ-J in early-onset patients.

Nomura et al. evaluated the usefulness of the RBDSQ-J among patients with PD (Nomura et al., 2011). A total score of 6 points on the RBDSQ-J represented the best cut-off value for detecting RBD. This cut-off value for RBD secondary to PD was approximately 1 point higher than that reported for iRBD in studies performed by Stiasny-Kolster et al. and Miyamoto et al. However, the cut-off value with the RBDSQ-J for PD patients would become equal to the above-indicated value for iRBD patients if item 10 were removed. Nomura et al. showed that the RBDSQ-J may be useful for detecting RBD among a PD population regardless of the RBD symptoms. In addition, positivity for item 6.1 might represent a key criterion for analyzing populations with non-violent RBD.

5.4 RBDQ-HK

The existing RBD questionnaires may overlook the prevalence, frequency and severity of the clinical symptoms. There remains an obstacle for physicians to quantitatively observe and monitor treatment progress in clinical settings without the availability of timely PSG. Screening instruments for diagnosis of RBD are limited and there are none for quantifying the severity of the disease. Li et al. developed and validated a 13-item self-reported RBD questionnaire for diagnostic and monitoring purposes (Li et al., 2010). The patient always answered and the bed partner sometimes also answered in addition to the patient. Items 1-5 (Q1-Q5) were pertinent to patients' dreams and nightmares and the last eight items (Q6-Q13) elicited information on the typical behavioral consequences as a result of patients' dream enactments. Each item assesses two scales: lifetime occurrence and recent 1-yr frequency (5 point scale: 3 times or above per week; 1-2 times per week; once or a few times per month; once or few times per year; none). Scores are weighted in 7/13 questions according to the clinical importance of the behavioral manifestations of RBD. Scores range from 0-100. In a study to validate the instrument, 107 PSG-confirmed RBD patients (mean age 62.5 y) with the diagnosis of cryptogenic RBD, symptomatic RBD (PD, dementia, PD with dementia, narcolepsy), RBD-like disorder) and 107 controls (mean age 55.3 y) participated. The best RBDQ-HK cut-off score for RBD detection was 18-19, with 82% sensitivity, 87% specificity, and 86% positive predictive value; there was high test-retest reliability. Among the RBD cases, the scores of RBDQ-HK based on patients' self-reports were slightly lower compared to those provided by both patients and their relatives (e.g., bed partner)[self-report: 40.56(21.26) vs. self and relatives: 54.89(17.34), $p=0.05$]. The RBDQ-HK can be completed by patients with or without other informants such as a bed partner. However, abnormal nocturnal behaviors can go unnoticed in some RBD cases (e.g., when there is no assault or injury to self or bed partner), making the sensitivity of the RBDQ-HK different between those living and sleeping on their own and those living and sleeping with others. Hence, input on RBDQ-HK from relatives of patients is encouraged as it may enhance accuracy of the diagnosis and provide a better appraisal of treatment progress.

6. Conclusion

We have described screening methods for RBD as well as some of the available RBD screening questionnaires. All of the questionnaires had high sensitivity in screening for RBD, but lower specificity. There were some problems and limitations related to these instruments. These validation studies were mainly performed in middle aged and elderly subjects. Therefore, validation of RBD screening questionnaires should be done in younger people. In the case of self-reported questionnaires, information from a bed partner is useful in achieving higher sensitivity and specificity for the instrument. Boeve suggested that the MSQ likely to be more appropriate for use in those with cognitive impairment/dementia since the responses are provided by bed partners (Boeve, 2010a). In any of the instruments that might be applied but are unable or unwilling to undergo PSG, or who have little or no apparent REM sleep during PSG, then a diagnosis of probable RBD would be justified (Boeve, 2010a). OSAS may represent a confounding factor in the clinical diagnosis of RBD (Comella et al., 2002). To differentiate RBD from OSAS, simultaneously screening for OSAS by pulse oxymetry may be useful. It is impractical to frequently perform PSG and the availability of PSG is often limited. Therefore, it is important to evaluate and follow up the severity of RBD through instruments such as RBDQ-HK. It is also necessary to develop a severity index for RBD. Tachibana recently developed an RBD severity index (RBDSI) in Japanese (Tachibana, 2009).

In conclusion, RBD questionnaires may be applied within a stepwise diagnostic process (questionnaire, interview, polysomnography) for RBD (Table 5).

1st step	Screening	Questionnaire
2nd step	Interview	Sleep specialist, Neurologist
3rd step	Final diagnosis	Video PSG

Table 5. Diagnostic process for RBD

7. APPENDIX

RBD Screening Questionnaire (RBDSQ-J) (from Miyamoto T, et al., 2009) (RBD スクリーニング問診票)

English (Japanese)	Questions (質問)	Answer (答え)	
1.	I sometimes have very vivid dreams. とてもはっきりした夢をととき見る。	Yes (はい)	No (いいえ)
2.	My dreams frequently have an aggressive or action-packed contents. 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。	Yes (はい)	No (いいえ)
3.	The dream contents mostly match my nocturnal behavior. 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。	Yes (はい)	No (いいえ)
4.	I know that my arms or legs move when I sleep. 寝ている時にうでや足を動かしていることがある。	Yes (はい)	No (いいえ)
5.	It thereby happened that I (almost) hurt my bed partner or myself. 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、自分がケガをしったりすることもある。	Yes (はい)	No (いいえ)

6. I have or had the following phenomena during my dreams. 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- speaking, shouting, sweating, laughing, loudly 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。	Yes (はい)	No (いいえ)
6.2- sudden limb movements, "fights" うでと足を突如動かす/ けんかをしているように。	Yes (はい)	No (いいえ)
6.3- gesture, complex movements, that are useless during sleep, e.g. to wave, to salute, to frighten mosquitoes, falls off the bed 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)	Yes (はい)	No (いいえ)
6.4 - things that fell down around the bed, e.g. bedside lamp, book glasses. ベッドの周りの物を落とす。(例:電気スタンド、本、メガネ)	Yes (はい)	No (いいえ)
7. It happens that my movements awake me. 寝ている時に自分の動作で目が覚めることがある。	Yes (はい)	No (いいえ)
8. After awakening I mostly remember the content of my dreams well. 目が覚めた後、夢の内容をだいたい覚えている。	Yes (はい)	No (いいえ)
9. My sleep is frequently disturbed. 眠りがよく妨げられる。	Yes (はい)	No (いいえ)
10. I have/had a disease of the nervous system (e.g. stroke, head trauma, parkinsonism, RLS, narcolepsy, depression, epilepsy, inflammatory disease of the brain), which? 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)	Yes (はい)	No (いいえ)

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For progress to be maintained in a clinical field like sleep medicine, unimpeded, unrestricted access to data and the advances in clinical practice should be available. The reason why this book is exciting is that it breaks down the barriers to dissemination of information, providing scientists, physicians, researchers and interested individuals with a valuable insight into the latest diverse developments within the study of sleep disorders. This book is a collection of chapters, which can be viewed as independent units dealing with different aspects and issues connected to sleep disorders, having in common that they reflect leading edge ideas, reflections and observations. The authors take into account the medical and social aspects of sleep-related disorders, concentrating on different focus groups, from adults to pregnant women, adolescents, children and professional workers.

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