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Original Article

REM sleep behavior disorder in 703 sleep-disorder patients: The importance of eliciting a comprehensive sleep history

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ABSTRACT

Objectives: The aim of our study was to evaluate the frequency of REM sleep behavior disorder (RBD) in a mixed sleep laboratory population and to assess potential associations. Moreover, we investigated referral diagnoses of patients subsequently diagnosed with RBD and assessed the frequency of incidental RBD.
Methods: Charts and polysomnographic reports of 703 consecutive patients comprising the full spectrum of ICSD-2 sleep disorders [501 males, 202 females; mean age, 51.0 ± 14.1 years (range: 10–82 years)] were carefully reviewed. The vast majority of patients were adults (98.7%). Patients were categorized into those with and without RBD. For associations, all concomitant sleep and neurological diagnoses and medications were evaluated.
Results: Thirty-four patients (4.8%) were diagnosed with RBD (27 men; 7 women, mean age, 57.7 ± 12.3 years). RBD was idiopathic in 11 patients (1.6%; 9 men) and symptomatic in 23 patients (3.3%; 18 men) secondary to Parkinsonian syndromes ($n = 11$), use of antidepressants ($n = 7$), narcolepsy with cataplexy ($n = 4$), and pontine infarction ($n = 1$). Six out of 34 patients were referred for suspected RBD, 20 reported RBD symptoms only on specific questioning, and 8 patients had no history of RBD but showed typical RBD behavioral manifestations in the video-polysomnography. Logistic regression analysis revealed significant associations between RBD and the presence of Parkinsonian syndromes (odds ratio [OR] 16.8, 95%CI: 6.4–44.1; $P < 0.001$), narcolepsy with cataplexy (OR 10.7, 95%CI: 2.9–40.2; $P < 0.001$), SSRI use (OR 3.9, 95%CI: 1.6–9.8; $P = 0.003$), and age (OR 1.5/10-year increase, 95%CI: 1.0–2.0; $P = 0.039$).
Conclusion: In this population of 703 consecutive sleep-disorder patients, RBD was uncommon. Its etiology was predominantly symptomatic. The majority of RBD patients reported RBD symptoms on specific questioning only, underlining the importance of eliciting a comprehensive sleep history for the diagnosis of RBD.

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1. Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by apparent dream-enacting behaviors and loss of normal REM sleep muscle atonia [1].

While the International Classification of Sleep Disorders (ICSD)-1 revised criteria [2] allowed diagnosis of RBD on the basis of history, polysomnography has become obligatory according to the ICSD-2 criteria [3] for the diagnosis of RBD.

The prevalence of RBD is assumed to be approximately 0.5% (with a male preponderance) in the general population [4,5]. RBD is much more common in patients with Parkinson's disease (PD), Lewy body dementia (DLB) or multiple system atrophy (MSA) [6–9], and it has been shown to precede the clinical onset of these disorders for years [10,11].

The prevalence of RBD in a full-spectrum sleep-disorder population has not been assessed so far. It is unknown if milder cases of RBD are frequently underdiagnosed due to the demanding diagnostic requirements (a detailed specific history, a careful analysis of polysomnography with regard to muscle tone and video, as well as the use of an extended EMG montage with more EMG channels than the chin EMG alone [12]) and due to the challenging differential diagnosis (e.g., epilepsy, sleep apnea, or other parasomnias).

The present study was performed to examine the frequency of RBD based on history and polysomnographic data in a sample of consecutive patients referred to our Sleep Disorders Unit for polysomnography (PSG) and to assess potential associations with other

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medical conditions and medications. Moreover, we investigated referral diagnoses of patients subsequently diagnosed with RBD and assessed the frequency of incidental RBD.

2. Methods

2.1. Data collection

All consecutive PSG reports obtained at the Sleep Disorders Unit, Department of Neurology, Innsbruck Medical University, between March 2003 and December 2004 were reviewed for this study. In patients who underwent more than one PSG during the study period (e.g., for nasal CPAP titration), the first examination was included. From a total of 817 PSG reports, 114 were excluded due to repeated examinations. From the remaining 703 PSG reports and patients' histories the following information was extracted: reasons for admission to the sleep laboratory, sleep diagnoses, neurological comorbidities, and all medications. Psychiatric comorbidities were not assessed. The Innsbruck sleep laboratory is a tertiary sleep-disorder referral center serving a population of about 2 million mostly from western Austria and South Tyrol (Northern Italy). It is the only academic facility for diagnosis and treatment of sleep disorders in the abovementioned area. Patients represent the full spectrum of sleep disorders. *Sleep diagnoses* were stratified according to ICSD-2 main categories into insomnias, sleep-related breathing disorders, hypersomnias/excessive daytime sleepiness, parasomnias, and sleep-related movement disorders. Main categories were further subcategorized according to ICSD-2.

RBD was originally diagnosed in all patients according to ICSD-1 rev. criteria [2] but all patients had polysomnographic confirmation as now required by the ICSD-2 criteria [3]. For a diagnosis of idiopathic RBD, the absence of cognitive and motor complaints and a normal neurological examination were required. Moreover, a temporal relation with other etiologies and medications known to cause RBD had to be excluded.

Neurological comorbidities were stratified into cerebrovascular diseases, CNS infectious diseases, craniocerebral trauma, dementia, epilepsy, Parkinson syndromes, headache syndromes, neuroimmunological diseases, neurooncological diseases, and spinal cord, peripheral nerve and muscle disorders. *Medication* taken at the time of polysomnographic evaluation was recorded for all patients and grouped into antihypertensives, central nervous system (CNS) active drugs, anticoagulants and platelet aggregation inhibitors, lipid lowering drugs, thyroid medication, analgetics and antidiabetic medication. CNS active drugs were subdivided into antidepressants, stimulants and wake-enhancing drugs, dopaminergic drugs, hypnotics and sleep enhancing substances, neuroleptics, anticonvulsants, and cholinesterase inhibitors. Antidepressants were further specified as selective serotonin reuptake inhibitors, tricyclic antidepressants, trazodone, norepinephrine and serotonin selective antagonists, norepinephrine reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and others.

2.2. Polysomnographic recordings

All patients underwent nocturnal 8-h PSG for 2 or 3 consecutive nights. PSG was performed with a digital polygraph (Brainlab 3.30, Schwarzer Inc., Munich, Germany). A standard montage was used including C3, C4, O1, O2, A1, and A2 electrodes, vertical and horizontal electrooculography and electromyography of mental, submental and both tibialis anterior muscles. Cardiorespiratory variables included electrocardiography, nasal and buccal airflow (thermocouple), nasal pressure cannula, tracheal microphone, thoracic and abdominal respiratory effort, and transcutaneous oxygen saturation. Sleep stages were scored according to Rechtschaffen and Kales with the allowance to score REM sleep despite persistence of tonic or phasic EMG activity [12].

2.3. Statistics

Statistical analyses were performed using the SPSS statistical analysis program (SPSS 15.0, Chicago, IL, USA). Data are reported as means ± standard deviation or frequencies (percentages), as applicable. Data were tested for normal distribution using the Shapiro–Wilks test. To compare frequencies, the Fisher's exact test was used to assess differences between patients with and without RBD. To compare age between both groups, Mann–Whitney-*U* test was applied. Linear logistic regression analysis (Wald backward procedure) was performed to evaluate potential associations. Selection of covariates was based on variables of univariate statistical analysis reaching a significant P-value < 0.05.

3. Results

3.1. Characteristics of the study population

In this study, 703 patients [501 males (71%); mean age, 51.0 ± 14.1 years (range 10–82)] were included. The vast majority of patients were adults (98.7%). Reasons for admission to overnight PSG were suspected sleep-related breathing disorders with or without *n*CPAP titration ($n = 407$, 57.9%), evaluation of insomnia ($n = 115$, 16.4%), excessive daytime sleepiness ($n = 90$, 12.8%), suspected sleep-related movement disorders ($n = 50$, 7.1%), and clinically suspected parasomnia ($n = 40$, 5.7%). Typical parasomnia behavioral manifestations were observed in 15 out of 40 patients (37.5%) during polysomnography. Neurological comorbidity was present in 234 (33.3%) patients. One hundred patients (14.2%) had a spinal cord, peripheral nerve or muscle disease; 42 (6.0%) cerebrovascular diseases; 29 (4.1%) headache syndromes; 28 (4.0%) epilepsy; 26 (3.7%) Parkinson syndromes (22 PD, 3 MSA, 1 LBD); 11 (1.7%) neurooncological diseases; 7 (1.0%) neuroimmunological diseases; and 5 (0.7%) dementia. Twenty patients (2.8%) had a history of craniocerebral trauma and 5 (0.7%) a history of a CNS infectious disease. Sleep diagnoses are given in Table 1. Medication is given in Table 3.

3.2. RBD

Thirty-four patients of the whole study sample were diagnosed with RBD (4.8%; 27 men, 7 women; mean age, 57.7 ± 12.3 years). RBD was symptomatic in 23 patients (3.3%; 18 men, 5 women; mean age, 59.3 ± 13.7 years) and occurred in the context of PD ($n = 8$), use of SSRIs ($n = 5$), narcolepsy with cataplexy ($n = 4$), use of venlafaxine ($n = 2$), MSA ($n = 2$), LBD ($n = 1$), and pontine infarction ($n = 1$). RBD was idiopathic in 11 patients (1.6%; 9 men, 2 women; mean age, 54.2 ± 8.6 years).

3.3. Reasons for referral to the sleep laboratory in patients with RBD

Only a minority of patients was referred for suspected RBD ($n = 6$; 3 PD, 1 MSA, 1 SSRI, 1 idiopathic), whereas the majority was referred for suspected sleep-related breathing disorder (12), excessive daytime sleepiness (7), insomnia ($n = 5$), and sleep-related movement disorders ($n = 4$). Twenty of these 34 patients reported RBD symptoms only on specific questioning. Eight patients had no history of RBD but showed typical RBD behavioral manifestations in the video-polysomnography.

Table 1
Final diagnoses of the study collective adapted to ICSD-2 criteria.

ICSD-2 Diagnoses	Frequency	
	Main category *N* (%*)	Subcategory *N* (%*)
Insomnia	110 (15.6)	
Sleep-related breathing disorder	477 67.9)	
Hypersomnia	34 (4.8)	
Narcolepsy with cataplexy		21 (3)
Narcolepsy without cataplexy		3 (0.4)
Behaviorally induced insufficient sleep syndrome		7 (1.0)
Idiopathic hypersomnia		3 (0.4)
Circadian rhythm disorder	4 (0.6)	
Parasomnia	49 (7)	
Disorders of arousal (from non-REM sleep)		10 (1.4)
REM parasomnias		38 (5.6)#
Other parasomnias (catathrenia)		1 (0.1)
Sleep-related movement disorder	167 (23.8)	
Restless legs syndrome		123 (17.5)
Periodic limb movement disorder		14 (2.0)
Sleep related bruxism		29 (4.1)
Sleep related rhythmic movement disorders		5 (0.7)
Sleep related leg cramps		1 (0.1)

* Percentages are fractions of the whole study population with a given diagnosis. Note that more than one diagnosis was possible per individual patient.
# Thirty-four out of 38 patients with REM parasomnias were patients with REM sleep behavior disorder.

3.4. Comparison between patients with and without RBD

Frequencies of PSG diagnoses, neurological comorbidity as well as concomitant medication are given in Tables 2 and 3. A significant association between RBD and the age at examination, the presence of any neurological comorbidity, Parkinson syndromes, narcolepsy, use of SSRIs, levodopa, dopamine agonists, and cholinesterase inhibitors were shown. There was no association with gender, any other sleep diagnosis, neurological comorbidity (except narcolepsy and Parkinsonian syndromes), or medication. Logistic regression analysis showed a significant association between RBD and Parkinsonian syndromes (OR 16.8, 95% CI 6.4–44.1; $P < 0.001$), narcolepsy with cataplexy (OR 10.7, 95% CI 2.9 – 40.2; $P < 0.001$), SSRI use (OR 3.9, 95% CI 1.6–9.8; $P = 0.003$), and age at time of examination (OR 1.5/10-year increase, 95% CI 1.0 – 2.0; $P = 0.039$). The intake of dopaminergic drugs, cholinesterase inhibitors and the presence of any other neurological comorbidity did not enter the equation ($P > 0.05$).

4. Discussion

This is the first study to investigate the frequency of PSG confirmed RBD in a large sleep-disorder population of 703 patients and to examine referral diagnoses of patients subsequently diagnosed with RBD. In the whole study sample, the frequency of RBD was 4.8%, and its etiology was predominantly symptomatic. Idiopathic RBD was uncommon even in this full-spectrum sleep-disorder population, and only a minority of patients subsequently diagnosed with RBD was referred for suspected RBD.

Previous studies investigating the prevalence of RBD have been performed in the general population [4,5], in patients with various neurodegenerative diseases [6–9], as well as in patients with narcolepsy [13,14]. In the general population, RBD frequency was shown to be approximately 0.5% [4,5]. Since most of these data were based on patients' history, they can only give an approximation of the true frequency because the final diagnosis of RBD requires polysomnographic confirmation. In narcolepsy, its prevalence varied widely between 5% (PSG-based study) [13] and 41% (questionnaire-based study) [14]. Questionnaire-based studies in RBD, however, have been reported to underestimate the prevalence of RBD, since mild RBD can be missed without PSG [15]. In contrast to the findings in narcolepsy, the polysomnographically confirmed prevalence of RBD in Parkinson disease was found to be 33–40% [6,7]. Even in severe RBD, violent episodes represent

Table 2
Sleep and neurological diagnoses of patients with and without RBD.

	RBD 34 (4.8%)		No RBD 669 (95.2%)		*P*-value#
	N	%	*n*	%	
Demographic variables					
Age, mean ± SD	57.7 ± 12.3		50.6 ± 14.1		0.006
Men	27	79.4	474	70.9	n.s.
Sleep diagnoses*					
Insomnia	9	26.5	101	15.1	n.s.
Sleep related breathing disorders	20	58.8	457	68.3	n.s.
Hypersomnias/excessive daytime sleepiness	4	11.8	30	4.5	n.s.
Narcolepsy	4	11.8	20	3	0.024
Non-REM parasomnias	1	2.9	9	1.3	n.s.
Sleep related movement disorders	10	29.4	157	23.5	n.s.
Neurological diagnoses except sleep diagnoses	17	50	217	32.4	0.04
Cerebrovascular diseases	2	5.9	40	6	n.s.
CNS infectious diseases	0	0	5	0.7	n.s.
Craniocerebral trauma	0	0	20	3	n.s.
Dementia	1	2.9	5	0.7	n.s.
Epilepsy	0	0	28	4.2	n.s.
Headache syndromes	0	0	29	4.3	n.s.
Neuroimmunological diseases	0	0	7	1	n.s.
Neurooncological diseases	0	0	11	1.6	n.s.
Parkinsonian syndromes	11	32.4	15	2.2	<0.001
Spinal cord, peripheral nerve and muscle disorders	7	20.6	93	13.9	n.s.

Numbers given are absolutes with percentages in parenthesis. Percentages refer to patients with and without RBD, as applicable. Note that percentages of diagnoses and medications add up to more than 100 % because individual patients could have more than one diagnosis (also in main categories) and be on various medications. *P*-values are obtained from Mann-Whitney-*U* test or Fisher's exact test, as applicable.
* Note that subcategories of diagnoses or medications are only listed if significant differences were shown between patients with and without RBD.
# Calculated *P*-values were not corrected for multiple comparisons.

Table 3
Concomitant medication of the whole study collective.

Medication*	Whole study collective (*n* = 703)		RBD 34 (4.8 %)		No RBD 669 (95.2%)		*P*-value#
	n	%	*n*	%	*n*	%	
Antihypertensive drugs	226	32.1	13	38.2	213	31.8	n.s.
CNS active substances	223	31.7	21	61.8	202	30.2	<0.001
Antidepressants	110	15.6	10	29.4	100	14.9	0.048
SSRI	64	9.1	9	26.5	55	8.2	0.002
Hypnotics	81	11.5	7	20.6	74	11.1	n.s.
Levodopa	41	5.8	11	32.4	30	4.5	<0.001
Dopamine agonists	38	5.4	12	35.3	26	3.9	<0.001
Anticonvulsants	48	6.8	2	5.9	46	6.9	n.s.
Neuroleptics	19	2.7	1	2.9	18	2.7	n.s.
Stimulants/wake enhancing drugs	12	1,7	2	5.9	10	1.5	n.s.
Cholinesterase inhibitors	2	0.3	2	5.9	0	0	0.002
Anticoagulants/Platelet aggregation inhibitors	147	20.9	10	29.4	137	20.5	n.s.
Lipid-lowering drugs	115	16.4	5	14.7	110	16.4	n.s.
Thyroid medication	75	10.7	5	14.7	70	10.5	n.s.
Analgetics	52	7.4	2	5.9	50	7.5	n.s.
Antidiabetic drugs	34	4.8	2	5.9	32	4.8	n.s.

Numbers given are absolutes with percentages in parenthesis. Percentages refer to patients with and without RBD, as applicable. Note that percentages of diagnoses and medications add up to more than 100 % because individual patients could have more than one diagnosis (also in main categories) and be on various medications. *P*-values are obtained from Mann-Whitney-*U* test or Fisher's exact test, as applicable.

* Note that subcategories of diagnoses or medications are only listed if significant differences were shown between patients with and without RBD.

\# Calculated *P*-values were not corrected for multiple comparisons.

only a small fraction of motor events [16]. On the other hand, confounding RBD with seizures or sleep-related breathing disorders cannot be ruled out by questionnaire only. Therefore, one of the main strengths of our study is that polysomnographic registration was performed in all patients. Nevertheless, a potential referral bias cannot be excluded.

In this collective, the etiology of RBD was predominantly symptomatic. About 45–65% of patients initially diagnosed as idiopathic RBD have been reported to eventually develop a Parkinson syndrome after a mean interval of 11.5–20 years from the onset of RBD [10,11]. Some authors have recently questioned whether the idiopathic form of RBD even exists [17] given the abnormal slowing of the waking EEG [18], the existence of neuropsychological deficits [17,19,20], olfactory dysfunction [21–23], autonomic dysregulation [24,25] and subtle motor deficits [26].

Another interesting aspect is that only a minority of patients was referred due to their RBD symptoms. The majority only reported RBD on specific questioning of the patient and his/her spouse, underlining the need for eliciting a comprehensive sleep history to avoid missing milder forms of RBD. This is especially important since RBD often precedes neurodegenerative disorders for years [10,11]. Recently, the first screening questionnaire for RBD was validated [27]. The administration of such a questionnaire might further increase the detection rate of RBD and should therefore be recommended for clinical practice. Another important aspect is the input of the bed partner or the patient's caregiver, which should be considered mandatory in screening for RBD.

Main associations of RBD in our patient group were Parkinson syndromes, narcolepsy and SSRI intake. These findings are in accordance with the literature [6–9,13,14,28]. We could not find a significant association between tricyclic antidepressants or mirtazapine and RBD. But symptomatic RBD due to mirtazapine has been described only in patients with PD [29]. The small number of patients taking these medications in our study may explain that no association was demonstrable.

RBD secondary to treatment with the beta-blocker bisoprolol has been reported in 2 patients [30]. We found no significant difference in the frequency of beta-blocker intake between patients with and without RBD in our comparatively large sample. Recently, a comorbidity of RBD and epilepsy has been reported in 12.5% of 80 epilepsy patients [31]. In our group, 28 patients had epilepsy; however, none of them had RBD. Differences in the type of epilepsy, age, and gender might potentially explain the difference between these results.

For each 10-year increase in age, RBD was on average 1.5-fold more frequent than in the previous decade. This finding is similar to that in a very recently published study showing a 10-year risk of developing a neurodegenerative disease of 41% [32].

Idiopathic RBD affects men more frequently than women [1]. Our study did not reveal a significant gender difference. This could be explained by the referral pattern to the sleep laboratory. More than half of the patients were referred due to suspected sleep-related breathing disorder – a male predominant disorder [33]. In fact, the sex distribution in the RBD group as a whole (80% men) was similar to that reported in the literature [34].

Movement disorders are a main clinical and research focus of the Department of Neurology of Innsbruck Medical University. This partly explains the relatively high frequency of various Parkinson syndromes in our sample. Moreover, our study can only give associations between RBD and medication use. Causal relationships cannot be established since medications could not be withdrawn for control examinations due to ethical reasons.

In summary, this study showed that idiopathic RBD is uncommon even in this full-spectrum sleep-disorder population. Only a minority of patients consulted due to RBD, whereas the majority was diagnosed with RBD only after specific questioning of the patients and their spouses underlining the need for eliciting a comprehensive sleep history. Because of the risk for injury, including life-threatening injury to patient and his/her spouse [35], and also because of the considerably increased risk for the future emergence of a parkinsonian disorder in middle-age and older adults [32], it is especially important for sleep physicians to educate general physicians and nurses in as many ways possible (lectures, seminars, publications, etc.) about RBD and its presenting symptoms.

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