

Idiopathic REM sleep behavior disorder as a long-term predictor of neurodegenerative disorders

Stephany Fulda

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Abstract REM sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behavior and loss of muscle atonia during REM sleep. Idiopathic RBD occurs in the absence of any neurological disease or other possible cause, is male-predominant and its clinical course is generally chronic progressive. Secondary RBD may be related to neurodegenerative disorders such as multiple system atrophy, Parkinson's disease and Lewy body dementia. Recent long-term prospective studies have shown that 30% to 65% of patients with idiopathic RBD will eventually develop a neurodegenerative disorder with the rate of emergence depending on the length of the follow-up period. RBD may therefore be one of the earliest signs of and/or a long-term predictor for neurodegenerative disorders. Because RBD antecedes the development of these disorders by several years or decades, its recognition may enable the delay or prevention of neurodegenerative disorders through the early application of neuroprotective or disease-modifying therapies in the future.

Keywords REM sleep behavior disorder · Parkinson's disease · Multiple system atrophy · Dementia with Lewy bodies · Long-term prediction · Prevention

Abbreviations

AD	Alzheimer's disease
DLB	Dementia with Lewy bodies
EEG	Electroencephalography
EMG	Electromyography

iRBD	Idiopathic REM sleep behavior disorder
MCI	Minimal cognitive impairment
MSA	Multiple system atrophy
NDD	Neurodegenerative disorders
NREM sleep	non REM sleep
REM sleep	Rapid eye movement sleep
RBD	REM sleep behavior disorder
RSWA	REM sleep without atonia
PD	Parkinson's disease
PDD	Parkinson's disease with dementia

Introduction

Human sleep is divided into rapid eye movement (REM) sleep and non REM (NREM) sleep. REM sleep is characterized by the prominent rapid eye movements and active paralysis of all the somatic musculature except the diaphragm to permit breathing. REM sleep behavior disorder (RBD) is a parasomnia where the physiological atonia during REM sleep is absent or greatly diminished and is characterized by dream-enacting behavior associated with nightmares. Motor behavior ranges from vocalizations during REM sleep or simple movements to violent complex and lasting enactment of dream content with significant injury to the patient or a bed partner. The diagnostic criteria for RBD according to the international classification of sleep disorders [1] are given in Table 1 and require a nocturnal polysomnography to document REM sleep without atonia in the presence of dream-enacting behavior.

RBD was first described in 1987 by Schenck, Mahowald and co-workers [2]. It is a male-predominant disorder and usually emerges after the age of 50 years but has also been observed in younger patients [1]. At present, its prevalence

S. Fulda (✉)
Max Planck Institute of Psychiatry,
Kraepelinstraße 2–10,
80804 Munich, Germany
e-mail: fulda@mpipsy.kl.mpg.de

Table 1 Diagnostic criteria of REM sleep behavior disorder (RBD) (taken from [1])

A	REM sleep without atonia: EMG finding of excessive amounts of sustained or intermittent elevation of submental EMG tone or excessive phasic submental or limb EMG twitching.
B	At least one of the following: (1) History of sleep related injurious, potentially injurious, or disruptive behaviors (2) 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 disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

is unknown but estimates range from 0.3 and 0.8% [1]. The onset of RBD can be gradual or rapid but the course is generally chronic and progressive [2]. Complications can include injuries to the patient or a bed partner, which can be life-threatening [3]. Clonazepam, usually in doses of 0.25 to 0.5 mg/night, is efficacious in the majority of patients and is considered first-line treatment but should be used with cautions in patients with dementia, gait disorders or concomitant obstructive sleep apnea [4–6]. Melatonin has also been effective in some patients with RBD [7–9]. Modifying and maintaining a safe sleeping environment should accompany any therapeutic intervention [5].

In the idiopathic form (iRBD), RBD occurs in the absence of any other associated neurological disorder or possible cause. In contrast, RBD may be secondary to neurological diseases particularly multiple system atrophy (MSA), Parkinson's disease (PD) and dementia with Lewy bodies (DLB) (see below). In addition, medication use has been recognized as a precipitating factor, specifically antidepressants and beta-blockers [10–13].

In iRBD no evidence of neurological disease is found, however, in many iRBD patients subclinical abnormalities have been detected such as olfactory deficits [14–19], cognitive dysfunction [20–22], impaired color vision [19], and subtle cortical EEG slowing [21, 23, 24]. Other findings include dysautonomic abnormalities [25–27], reduced cardiac ^{123}I -Metaiodobenzylguanidine scintigraphy [28–31], decreased dopamine transporter imaging [32], and increased substantia nigra echogenicity [33–35]. Follow-up of patients with iRBD shows an increased risk for developing neurodegenerative diseases that strongly depends on the length of the follow-up period. Recent evidence suggests that iRBD is an early sign of a slowly evolving neurodegenerative disorder or a long-term predictor of it. In the following this evidence will be summarized and

presented focusing on the prevalence and features of RBD in neurodegenerative disorders, the emergence of neurodegenerative disorders in long-term follow-up studies of patients with iRBD and baseline differences between iRBD patients who developed a neurodegenerative disease and those who remained disease free.

REM sleep behavior disorder in neurodegenerative diseases

RBD is frequently encountered in neurodegenerative disorders, particularly in MSA, PD and DLB (Table 2). The majority of patients with MSA will also have RBD with reported prevalences of 80% to 100% [10, 36–38]. Indeed, RBD is currently considered a red flag for the diagnosis of MSA [39]. Interestingly, the strong male predominance encountered in the idiopathic form and in RBD associated with PD and DLB is less evident in MSA where only 33% to 61% of the patients are male [36, 38, 40]. Concerning the onset of RBD in relation to the occurrence of MSA, studies with retrospective estimates have shown that in 16% to 54% of MSA patients RBD preceded the onset of MSA [10, 36, 38, 40, 41]. In one of the studies RBD preceded MSA by a mean of 7 years (1 to 38 years) in 52% of the patients [10], in another [41], RBD occurred 4 years (1 to 11 years) earlier in 36% of MSA patients and in a third [36], RBD preceded MSA by 1 to 19 years in 44% of the patients.

The prevalence of RBD in PD lies between 30% and 41% [42–45]. Between 65% to 75% of PD patients with RBD are male [38, 44]. RBD occurs both in idiopathic PD and PD secondary to genetic mutations [46] and in PD patients that are untreated or treated with dopaminergic substances [10]. RBD is more common in the rigid-akinetic subtype of PD than in the tremoric subtype [47, 48]. Nondemented patients with PD and RBD are more likely to show EEG slowing during wakefulness [49] and poorer cognitive function [50] but RBD in PD patients has also been linked to longer duration of PD [41, 44]. RBD in PD is not associated with age, disease severity, depression, or sleep architecture [10]. RBD preceded PD in 18% to 25% of patients [38, 41, 48], on average between 3 (1 to 30 years) [41] and 4 years [48]. However, in patients with *Parkin* mutations, RBD develops after PD onset [46] and RBD rarely precedes PD onset in patients with early onset PD (< 50 years) [48]. Interestingly, it seems that in patients with iRBD who subsequently developed PD, the onset of PD is later (~72 years) than reported for PD patients (~62 years) [51].

The prevalence of RBD in DLB is not as well established and available studies showed prevalences between 40% [52] and 72% [53] again with a male predominance [10]. RBD preceded the onset of cognitive complaints and dementia in

Table 2 REM sleep behavior disorder (RBD) in neurodegenerative disorders

	Prevalence of RBD	RBD preceded onset of neurodegenerative disorder		References
		in % of patients	time interval	
Multiple system atrophy	80–100%	16–54%	4–7 years	[10, 36–38, 40, 41]
Parkinson’s disease	30–41%	18–25%	3–4 years	[38, 41–45, 48]
Dementia with Lewy bodies	40–72%	71–100%	6–10 years	[10, 41, 52–56]

the vast majority of patients (71 to 100%) [10, 41, 54, 55] and the onset of cognitive decline followed on average 6 [54], 9 [55] or 10 years [56] later. Current consensus criteria for DLB consider RBD as a suggestive feature of this disease [57] and it is thought that the clinical combination of dementia and RBD very likely indicates underlying Lewy body disease, i.e. DLB and PD with dementia (PDD) [10].

All three disorders—MSA, PD, and DLB - are characterized by intraneural deposition of α -synuclein and therefore it has been speculated that the RBD may be linked to synuclein pathology [52]. RBD has also been observed in cases with pure autonomic failure [58, 59]. Until recently, RBD has been considered comparatively rare in tauopathies, however, newer studies have reported a RBD or REM sleep without atonia (RSWA) also in progressive supranuclear palsy (27%) [60] and Alzheimer’s disease (7% RBD, 29% RSWA) [61]. However, RBD has not been observed in pallidopontonigral degeneration [62]. Also, so far no case of RBD in a patient with Pick’s disease has been reported [63]. RBD has also been associated to autoimmune mechanisms as REM sleep without atonia is frequently found in narco-

lepsy [64–67], another rare sleep disorder with a possible autoimmune background. Similarly, RBD has been observed in 5 of 6 patients with nonparaneoplastic limbic encephalitis associated with antibodies to voltage-gated potassium channels [68]. Interestingly, symptoms of RBD coincided with the onset of the disorder and in 3 of the patients immunosuppression resulted in a resolution of RBD in parallel with the remission of the limbic syndrome [68].

In summary, at present the available evidence shows that RBD is a common feature of synucleinopathies, especially MSA, DLB, and PD. Nevertheless, among these disorders RBD is distinctly more prevalent in MSA, maybe because brainstem cell loss is widespread and severe in this disorder. Retrospective assessment indicates that RBD frequently precedes the onset of these disorders but this seems to be most pronounced in DLB probably reflecting the differences in clinical course and progression in these disorders. RBD has also been observed in tauopathies and disorders with a neuroimmunological background, however, at the moment the association with synucleinopathies outweighs that with any other.

Table 3 New onset of neurodegenerative disorders in prospective follow-up studies of patients with idiopathic REM sleep behavior disorder

Study	Subjects	Follow-up time	Prevalence	Time since	
				RBD onset	RBD diagnosis
Schenck et al. 1996 [77]	29 patients \geq 50 y with iRBD	~13 y	38% ($n = 11$) PD [8 definite PD, 2 probable PD, 1 possible PD]	~13 y	~4 y
Schenck et al. 2003 [78]		~20 y	65% ($n = 17$ of 26) [13 PD, 1 PDD, 2 DLB, 1 AD]	~13 y (3–29)	
Iranzo et al. 2006 [51]	44 patients with iRBD	~5 y (2–15 y)	45% ($n = 20$) [7 PD, 2 PDD, 6 DLB, 1 MSA, 4 MCI]	~12 y	~4 y
Iranzo et al. 2008 [80]		~7 y	64% ($n = 28$) [6PD, 4 PDD, 8 DLB, 1 MSA, 9 MCI]		
Postuma et al. 2009 [81]	93 patients with iRBD	~5 y	30% ($n = 26$) [14 PD, 7 DLB, 4 AD, 1 MSA]	~12 y	
Tippman-Peikert et al. 2006 [79]	23 patients with iRBD	~11 y	65% ($n = 15$) [1 PD, 3 DLB, 1 dementia, 10 reported symptoms highly suggestive of a parkinsonian or dementing disorder]		

AD Alzheimer’s disease; DLB dementia with Lewy bodies; iRBD idiopathic REM sleep behavior disorder; MCI minimal cognitive impairment; MSA multiple system atrophy; PD Parkinson’s disease; PDD Parkinson’s disease dementia; y years

RBD as a long-term predictor for neurodegenerative disorders

There are several case studies reporting the new onset of neurodegenerative disorders years to decades after the onset of RBD. This has been documented for Parkinson's disease [69], Lewy body disorder [70–73], multiple system atrophy [72], and shy drager syndrome [74] and periods of 2 to 50 years [75]. Interestingly, in two of these cases Lewy body disease was only discovered at autopsy [70, 76].

In systematic long-term prospective studies the percentage of patients with iRBD who will eventually develop a neurodegenerative disorder ranges from 30% to 65% strongly depending on the length of the follow-up period (Table 3). Schenck and co-workers were the first to report that during a follow-up time of 13 years 38% of a group of 29 male iRBD patients above 50 years of age developed PD [77]. In a subsequent follow-up 7 years later, 65% had

developed a neurodegenerative disorder [78]. Similar results were reported for 23 patients with iRBD of which 65% developed a neurodegenerative disorder during an average follow-up time of 11 years [79]. In an even larger case series of 44 consecutive iRBD patients, 45% developed PD, DLB, MSA or minimal cognitive impairment (MCI) after an average follow-up time of 5 years [51] and 64% after 7 years [80]. In the largest case series to date, 26 of 93 patients (30%) with iRBD developed neurodegenerative disorders after an average follow-up time of 5 years [81]. In the same study [81], the authors conducted a formal survival analysis and estimated the risk for the development of neurodegenerative disorders as 18% for a 5 year period, 41% for a 10-year period, and 52% for a 12-year period. Summarizing these four case series, across average follow-up periods of 5 to 20 years 86 of 189 patients (46%) with iRBD developed a neurodegenerative disorder. The average time between the onset of RBD and the onset of the neurodegenerative disorder was 12 years and for the 76 patients with a

Table 4 Possible predictors for the development of neurodegenerative disorders in RBD: Baseline differences between iRBD patients who developed neurodegenerative disorders and iRBD patients who remained disease free

Study	Subjects	Follow-up time	Measured function/Main findings
Schenck et al. 1996 [77]	29 male patients \geq 50 y with iRBD of which 11 developed PD	~13 y	<i>Sleep, tonic and phasic chin EMG during REM sleep:</i> Patients with PD had increased REM sleep and periodic leg movements at baseline. No difference in tonic or phasic EMG during REM, other sleep parameters.
Iranzo et al. 2011 [24]	23 iRBD of which 10 developed MCI 10 healthy controls	2.4 \pm 1.6 y	<i>Quantitative EEG (wake, REM sleep):</i> Compared to healthy controls both RBD groups showed slowing of EEG during wakefulness and REM sleep. No significant difference between RBD with and without MCI but trend towards greater EEG slowing during wakefulness.
Iranzo et al. 2010 [86]	43 iRBD of which 8 developed NDD ^a 18 and 143 healthy controls	~2.5 y	<i>¹²³I-FP-CIT striatal binding, substantia nigra hyperechogenicity:</i> 27 (63%) had reduced ¹²³ I-FP-CIT striatal binding (40%) and/or substantia nigra hyperechogenicity (36%). All 8 with MCI had reduced ¹²³ I-FP-CIT uptake or substantia nigra hyperechogenicity at baseline; 30% (8–27) of those with abnormal imaging at baseline developed NDD). None of the 15 iRBD patients with normal neuroimaging developed NDD.
Postuma et al. 2010 [85]	26 iRBD with development of NDD 26 matched iRBDD without NDD ^b	~7 y	<i>Sleep, tonic and phasic chin EMG during REM sleep:</i> Patients with NDD had increased percentage of tonic submental EMG activity at baseline (more severe loss of REM atonia) and increased stage 1 sleep. No difference for phasic submental EMG or other sleep parameters.
Postuma et al. 2011 [87]	62 iRBD of which 21 developed NDD ^c	~5 y	<i>Olfaction, color vision testing:</i> Patients who developed NDD had more severe abnormalities of olfaction and color vision at baseline
Postuma et al. 2010 [27]	42 iRBD of which 21 developed NDD ^d	~7 y	<i>Cardiac autonomic function:</i> No difference between patient groups for any measure of cardiac autonomic function

AD Alzheimer's disease; DLB dementia with Lewy bodies; iRBD idiopathic REM sleep behavior disorder; MCI minimal cognitive impairment; MSA multiple system atrophy; NDD neurodegenerative disorder; PD Parkinson's disease; PDD Parkinson's disease dementia; y years

^a 5 PD, 2 DLB, 1 MSA; ^b 12 PD, 1 MSA, 7 DLB, 6 dementia; ^c 16 PDD, 4 PD, 1 dementia; ^d 11 PD, 1 MSA, 5 DLB, 4AD

definite diagnosis the new onset disorder was Parkinson's disease in 39 (51%), Lewy body disease in 20 (26%), minimal cognitive impairment in 9 (12%), Alzheimer's disease in 5 (7%), MSA in 2 (3%) and dementia in 1 patient (Table 2).

Long-term studies in iRBD patients have shown that over time excessive phasic and tonic muscle activity during REM sleep increases [82], cognitive functioning declines [83], and nigrostriatal presynaptic dopaminergic function possible decreases [84] compatible with a general neurodegenerative process.

Possible predictors for the future development of neurodegenerative disorders in patients with iRBD have emerged from studies that compared baseline measurement of iRBD patients with subsequent neurodegenerative disorders to disease-free iRBD patients (Table 4). Distinguishing characteristics in these studies were an increase in REM sleep [77] or stage 1 sleep [85], increased tonic submental EMG activity [85], increased striatal dopamine dysfunction or substantia nigra hyperechogenicity [86], more severe abnormalities of olfaction and color vision [87] and a tendency towards more pronounced EEG slowing during wakefulness [24] (Table 3). Interestingly, cardiac autonomic function which differs between RBD and healthy controls [25, 26], did not distinguish between RBD patients with subsequent neurodegenerative disorders and disease free patients, suggesting that autonomic dysfunction in RBD may be independent from associated PD or LBD [27]. Currently, these promising studies await independent replication. For the future it is hoped that the timely identification of iRBD patients who will develop a neurodegenerative disorder provides a window of opportunity for prevention or early treatment of these disorders.

Summary and outlook

RBD is relatively rare sleep disorder with a male predominance that is characterized by dream-enactment and loss of REM sleep atonia. Secondary RBD is frequently encountered in neurodegenerative disorders and in particular in synucleinopathies such as MSA, DLB, and PD. Retrospective assessment of the onset of RBD in these disorders suggests that RBD precedes the onset of these synucleinopathies in a significant proportion by several years to decades. This is confirmed by prospective long-term studies of patients with iRBD, free of neurological disorders at the time of the diagnosis or RBD. These studies showed that up to 60% of patients with iRBD will subsequently develop a neurodegenerative disorder, most frequently PD and DLB. Again, the time span between the onset of RBD and the onset of the subsequent neurodegenerative disorder was around a decade with increasing conversion rates across longer the follow-up periods. First

studies have also explored possible predictors for the development of subsequent neurodegenerative diseases in iRBD patients, but more research is needed in this area.

RBD can be seen as a long-term predictor for the development of neurodegenerative disorders. Most likely it is one of the earliest signs of these disorders. Indeed, for some of these disorders such as PD, it is now apparent that the preclinical phase can extend to 20 years or longer before the motor manifestations [88, 89] and among the symptoms that precede PD by 10 to 20 years are constipation, anemia, and anxiety disorders [89]. Possible predictors for the development of neurodegenerative disorders in patients with iRBD include increased REM or stage 1 sleep, increased submental EMG activity during REM sleep, striatal dopamine dysfunction and substantia nigra hyperechogenicity, more severe abnormalities of olfaction and color vision and EEG slowing during wakefulness. Nocturnal polysomnography, imaging of dopamine metabolism, transcranial sonography, olfactory and color testing and daytime EEG may therefore be clinical tools to identify RBD patients at an increased risk for future neurodegenerative disorders. Because RBD precedes the development of neurodegenerative disorders by years to decades, its timely recognition in patients may offer a window of opportunity where the early application of neuroprotective or disease modifying therapies is hoped to delay or prevent the onset of neurodegenerative disorders.

Conflict of interest statement There is no conflict of interest

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