REM sleep behaviour disorder in Parkinson's disease (Review)

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Abstract. Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia defined by simple or complex abnormal movements occurring in REM state, instead of the physiological muscular atonia. RBD may be idiopathic, or secondary as in the case of Parkinson's disease (PD). Several studies have confirmed that idiopathic RBD may precede with several years the onset of the specific motor characteristics of PD. The high prevalence of RBD in PD (19-70%) may be explained by several common pathophysiological pathways, mainly related to the dopaminergic cell loss. RBD is also associated with several comorbidities, including cognitive impairment, hallucinations, dysautonomia, or daytime sleepiness. The gold standard investigation for the diagnosis and assessment of RBD is video polysomnography, but in clinical practice, the use of clinical scales and questionnaires is reasonable for the screening of this complex parasomnia. Management options include ensuring a safe environment for the patient and pharmacological treatment, incuding clonazepam, melatonin or certain antiparkinsonian drugs.

Contents

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) belongs to the parasomnia subcategory of sleep disorders. It has the following main features: Abnormal behaviors (movements, gestures, vocalization), nightmares, and loss of normal skeletal atonia during REM stage. The movements that can occur instead of REM muscular atonia may be simple (muscular twitches) or complex (kicking, fighting), the latter being dangerous for the patient and for the bed partner in some cases. Dreams are usually intense, disagreeable, frightening and the abnormal motor behavior occurs as a response to the contents of the dreams (1).

Parkinson's disease (PD), a common neurodegenerative disorder, is characterized by specific motor features and various non-motor symptoms, including sleep disturbances. Sleep complains are common among PD patients (estimated prevalence: 40 to 98% of PD patients) and have important negative consequences on quality of life (2).

The aim of this review was to investigate the main clinical and pathophysiological aspects of RBD, in order to offer updated and practical information for the clinical practitioner regarding this sleep disorder, which is commonly identified in PD patients. The epidemiology, pathophysiology, clinical correlations, evaluation and management of RBD are further detailed.

According to a meta-analysis including eight studies, the estimated prevalence of RBD in the PD population varies between 19 to 70% (3). The co-occurrence of RBD and PD is important given the fact that RBD symptoms may precede with several years the onset of the motor features of PD. Therefore, idiopathic RBD is considered a pre-motor biomarker in PD (4). The estimated risk of developing neurodegenerative disorders in patients with idiopathic RBD increases from 35% at 5 years to 73% at 10 years and to 92% at 14 years (5). In a study including 100 PD patients, De Cock *et al* reported 22% of cases in which RBD preceded PD, 23% of cases in which the parkinsonism and RBD developed simultaneously, while in the rest of the cases (55%), RBD occured years after manifest parkinsonism (1).

2. Pathophysiology

The amygdala and the subcoeruleus nucleus are the main structures known to modulate the physiological sleep atonia during REM sleep (6). These nuclei send inhibitory inputs to the cells of the spinal anterior horns, resulting in loss of skeletal muscular tone (7,8). The reduction of signal intensity in the locus coeruleus/subcoeruleus has been revealed to be correlated with the loss of physiological atonia during sleep in PD patients with RBD (6).

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A diminished gray matter volume was found in several brain regions, such as the left posterior cingulated gyrus and hippocampus (9).

The amount of dopaminergic loss observed in RBD is less defined than in manifest parkinsonism (10). Reduced thalamic volume on voxel-based morphometry was observed in PD patients with RBD (11). Pathological hyperecogenity of the substantia nigra was suggested in both idiopathic RBD and PD patients (41.2 vs. 52.9%) (12).

In vivo studies (13,14) revealed that reduced glycine and GABA inhibition (involved in the suppression of muscle activity during sleep) resembles RBD phenomena and may share a common pathway with the pathophysiology of PD. Despite the fact that the main dysfunction in PD is related to dopaminergic loss, there is some evidence that also shows an impairment of GABA and glycine function (13,15). Moreover, in the evolution of PD, there is first a reduction of nondopaminergic cells, and then the characteristic dopaminergic loss. Therefore, some authors suggest that loss of glycine and GABA inhibition may explain initial RBD pathophysiology, while progressive dopaminergic impairment may explain worsening of both RBD and PD symptomatology (13).

Circadian rhythm also modulates the pathophysiology of RBD. In healthy subjects, the amount of REM sleep increases over night (especially in the second part of the night), but this pattern is not characteristic for RBD patients (16). There is data suggesting that patients with RBD have lost the clock-dependent increase of rapid eye movements index (calculated as number of rapid eye movements per minute), probably as a consequence of melatonin dysfunction (16).

One large multicenter study analyzed 172 brain autopsies of patients with previously diagnosed RBD. The neuropathologic examination confirmed the association between RBD and synucleinopathies (in 94% of cases of neurodegenerative disorders); the occurrence of RBD usually preceded the development of parkinsonism, cognitive impairment or autonomic dysfunction (17).

3. Biomarkers and clinical correlations

Cesari *et al* recently proposed an automated system that may be able to estimate the probability of RBD development using electroencephalographic (EEG) and electrooculographic (EOG) signaling. The most important finding of the study was that micro-sleep instability is a relevant characteristic occurring even in prodromal stages of RBD and therefore it may be considered a possible biomarker to identify RBD in PD patients (18).

Another association may exist between the levels of uric acid, parkinsonism and RBD. Several mechanisms were proposed to explain the specific neurodegeneration of the substantia nigra found in PD, one of them being the oxidant stress hypothesis. Uric acid may induce neuroprotective effects (19); in PD patients, the levels of uric acid are low within the substantia nigra. A recent study suggested that the functional connectivity in substantia nigra may be correlated with serum uric acid levels and that this relationship varies between PD patients with or without RBD, idiopathic RBD and controls (20).

There are several studies suggesting that RBD is associated with impaired olfactory function. Hyposmia is a well-documented marker of prodromal PD (7). Stiasny-Kolster *et al* revealed that RBD is associated with disturbances of the olfactory function. The authors found that 97% of the RBD patients presented an increased olfactory threshold, while 63% of these patients had lost the ability to differentiate odors. Among the 30 RBD patients included in the study, 5 patients had parkinsonian features on clinical examination and 3 patients had signs of nigrostriatal degeneration, as evaluated using SPECT (21). Postuma *et al* found that patients with idiopathic RBD (without PD) had not only olfactory dysfunction, but also impaired color discrimination (22).

RBD is also associated with cognitive decline. According to Schenck *et al*, 82% of older patients presenting RBD developed parkinsonism or dementia (23).

Rolinski *et al* demonstrated that RBD patients (at risk to develop PD) manifested identical deficits in visual short-term memory task (VSTM) similar to PD patients, independently on sensorimotor deficits (especially impaired dexterity). The 4-VSTM task assesses mainly the recall precision, which was impaired in RBD and in PD patients, suggesting a common pattern of 'random corruption of memory' in both groups. The authors suggest that the pattern of VSTM may be a cognitive marker for prodromal PD (24).

There are several associations between RBD and other comorbidites. Antiparkinsonian treatment may influence the severity of RBD symptoms. According to a study conducted on 250 PD patients, doses of levodopa were significantly associated with worse RBD symptoms, unlike therapy with dopamine agonists (25).

RBD is also associated with autonomic dysfunction. Orthostatic hypotension may predict RBD in PD patients with 81% sensitivity and 86% specificity (26). Heart rate variability (for instance R-R interval and the index of beat-to-beat variability) was reduced in idiopathic RBD in comparison with controls. This finding did not correlate with the possibility to further develop neurodegenerative disorders (27). Myocardial scintigraphy in RBD patients shows reduced ^{123}I-MIBG uptake, corresponding to the degeneration of postganglionic sympathetic neurons at this level (28). Evidence has revealed that the cardiac scintigraphy results may vary depending on the underlying neurodegenerative disease (29), while according to other data, the reduction of ^{123}I-MIBG uptake is more prominent in RBD compared to early PD, and therefore it may not be a predictor of neurodegenerative disorders (30).

Several studies have found that RBD is correlated with cognitive dysfunction (31,32). Cognitive dysfunctions (especially delayed memory function) were more prominent in PD patients with RBD than in PD patients without RBD (33). One proposed explanation is the degeneration of pedunculopontine nucleus and nucleus basalis of Meynert, which have important cholinergic connections with various structures including the cerebral cortex and thalamic nuclei (33). Other domains of cognition affected in patients with both PD and RBD were episodic verbal memory, executive and visuoperceptual functions (34).

An 8-year follow-up study revealed that RBD was correlated with the occurrence of hallucinations, independently of disease duration or motor stage, age or sex, but depending on therapy with dopaminergic drugs (35). The association between visual hallucinations and RBD was demonstrated in a study conducted by Gjerstad *et al* (36). The common pathway

for both RBD and visual hallucination may be a cholinergic dysfunction (37). Other non-motor symptoms encountered in RBD patients are depression and fatigue (38).

PD patients with RBD have an increased disease severity and a more accelerated motor progression (39). There may be a probable association between RBD and freezing and falls (26). Parkinsonian rigidity is also influenced by the presence of RBD symptoms. Patients with mild or moderate PD and REM sleep without atonia presented more pronounced and symmetric forearm rigidity, in comparison to controls. The early neurodegeneration of the brainstem circuitry which regulates the muscle tone may explain this finding (40).

Even if RBD produces sleep fragmentation and frequent awakenings, excessive daytime sleepiness or fatigue were uncommonly associated with RBD (41). Nevertheless, patients with PD and RBD have higher scores when evaluated with Epworth Sleepiness Scale, suggesting more daytime sleepiness (33,42).

4. Assessment

History taking from the patient and especially from the bed partner/caregiver may be essential to raise the suspicion of RBD. The confirmation of the diagnosis and in-depth assessment is performed using polysomnography (PSG), which identifies the lack of normal sleep atonia during the REM stages. Video-PSG monitoring may be useful to confirm the associated abnormal motor behavior (41). PSG can distinguish RBD from other alternative causes, such as sleep apnea or non-REM (NREM) parasomnias. RBD was found to prevail in the last part of the night (in more than half of patients) (1).

In clinical practice, when video-PSG is not widely available, the use of scales and questionnaires may help the clinician to screen for RBD (43). In this regard, several tools have been validated: The REM Sleep Behavior Disorder Screening Questionnaire (RBD-SQ) (44), the Hong-Kong REM Sleep Disorder Questionnaire (RBDQ-HK) (45), the Mayo Sleep Questionnaire (46), the Innsbruck REM Sleep Behavior Disorder Inventory (47), the REM Sleep Behavior Disorder Severity Scale (RBDSS) (48) or the single-question tool to screen for dream-enactment (49).

5. Treatment

A first measure for the safety of a patient during nighttime is to adjust the sleep-environment rendering it less harmful for the patient and bed partner (50).

Clonazepam (0.25-2 mg, 30 min prior to sleep) is recommended as the first-line therapeutic option for RBD (51).

It has been demonstrated that exogenous melatonin (2-6 mg) has some beneficial effects on RBD by reducing symptom severity and risk of injuries (52). Novel melatonin receptor agonists, such as agomelatine [25-50 mg before bedtime (53)] or ramelton [8 mg prior to bedtime (54)] may offer clinical improvement of the RBD symptoms (52).

Pramipexole may be used as a third-line therapeutic option, despite the fact that the beneficial effects have been controversial (55). Acetylcholinesterase inhibitors were found to decrease frequency and intensity of RBD (51). Rotigotine was found to partially improve RBD in PD patients (56).

6. Conclusions

RBD is a common sleep disorder encountered in both pre-motor and motor stages of PD. Screening for RBD is mandatory in PD, by obtaining a detailed medical history, using screening questionnaires and then confirming the diagnosis using video-PSG. Management of RBD in PD is challenging, however clonazepam, melatonin and certain antiparkinsonian drugs were found to be efficient.

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Authors' contributions

SD and CFP substantially contributed to the conception of the review, drafted the manuscript and revised it critically for important intellectual content. OFP and DT substantially contributed to the conception of the review and revised it critically for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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