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REM sleep behavior disorder in Parkinson's disease

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Abstract Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder characterized by loss of normal muscle atonia during REM sleep with recurrent dream enactment and excessive motor activity. It is a frequent feature in patients with Parkinson's disease (PD) and other alpha-synucleinopathies, and can occur at any stage of the disease. RBD could be considered a premotor clinical manifestation, and can antedate by many years the motor symptomatology. The prognostic value of RBD for the risk of developing PD still needs to be established. This review article focuses on the clinical aspects, screening and diagnostic criteria as well as therapeutic aspects of RBD in PD patients. Pathophysiological pathways are also briefly reviewed.

Keywords REM sleep behavior disorder (RBD) · Parkinson's disease · Polysomnography

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder characterized by loss of normal muscle atonia during REM sleep with recurrent dream enactment and excessive motor activity (Boeve et al. 2007). It can occur in the absence of any other obvious associated neurologic disorder or in association with a neurodegenerative disease, in which case it is regarded as symptomatic RBD. When no neurologic disorder is obvious, RBD could be considered as idiopathic (iRBD). Many authors regard this term with caution, since there are prospective studies that show a predisposition for developing neurodegenerative disease and especially alpha-synucleinopathies in patients with iRBD (Iranzo et al. 2006; Claassen et al. 2010; Schenck et al. 2003). RBD is frequently associated with Parkinson's disease (PD), Lewy body dementia or multiple system atrophy (MSA), and in many cases can even antedate the occurrence of motor symptoms by decades (Boeve et al. 2007; Comella et al. 1998; Gagnon et al. 2002). This review article seeks to summarize the available data concerning RBD and PD.

Definition

The current criteria for defining RBD are those published in 2005 by the AASM (American Academy of Sleep Medicine 2005). Refinements are needed that take into account the new scoring methods of polysomnography (PSG), and especially the definition of REM sleep without atonia (RSWA) and its frequent co-incidence with neurodegenerative disease (Frauscher et al. 2012). New ICSD-criteria will be published in early 2014.

According to the AASM the diagnosis of RBD requires the following:

1. Presence of RSWA on PSG.
2. At least one of the following:

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(a) sleep-related, injurious, potentially injurious, or disruptive behaviors by history (i.e., dream enactment behavior), and/or
(b) abnormal REM sleep behavior documented during polysomnographic monitoring.

3. Absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder.
4. The sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder (American Academy of Sleep Medicine 2005).

Clinical symptoms

The symptomatology described by either the patient or the bed partner is useful in making the probable diagnosis of RBD and of differentiating the nocturnal manifestations from other symptoms associated with PD, such as hallucinations, dyskinesias, dystonic postures or restless legs syndrome. Patients can exhibit abnormal jerky or abrupt movements, but the movements can, in rare cases, look like a physiological movement during wakefulness. It has been described by Isabelle Arnulf's group that some PD patients show almost normal movements during RBD when they have abnormal movements during the daytime (Cochen De Cock 2013). Vocalizations are common and can be represented by screaming, murmuring, laughing, or just small parts of speeches made during REM sleep. These are, most of the time, the expression of dreams. Upon awaking the patients recall the content of the dream as threatening; they are often in the role of the victim or trying to defend themselves. Others, especially those with concomitant dementia might have no memory of their dreams. During these dream enactments the movements can be so violent that the patient can hurt him or herself, and in some cases also the bed partner. Therefore, many PD patients and bed partners sleep in separate beds or adjust their sleeping environment in such a way as to minimize the risk for lesions. The vocalizations can be manifested by laughing, crying, screaming or shouting, suggesting unpleasant dream mentation and being different from the person's typical spoken language during wakefulness (Boeve 2010). RBD frequency varies considerably from one night per month to several episodes each night (Boeve 2010).

Other nocturnal manifestations can mimic RBD in PD patients. For example, patients with obstructive sleep apnea can have unpleasant dreams and sometimes dream enactment, but when polysomnographically analyzed, EMG atonia is preserved during REM sleep (Iranzo and Santamaria 2005).

Hallucinations and psychotic episodes during the night may be mistaken for RBD especially in PD patients with dementia (where co-operating with the patient is difficult).

Periodic limb movements in sleep (PLMS) are also present in PD patients, but they have no relation to REM sleep and occur mostly in non-REM sleep stages. Studies have shown, however, that PLMS are more frequent in PD patients with RBD than in those without RBD (Sixel-Doring et al. 2011b).

PSG features

The scoring method proposed by Frauscher and colleagues recommends quantifying "any" (either tonic or phasic) EMG activity in the mentalis muscle and phasic EMG activity in right and left flexor digitorum brevis muscles in the upper limbs with a cutoff of 32 %, using 3 s mini-epochs. This method was tested in patients with idiopathic RBD (iRBD) and RBD associated with PD (Frauscher et al. 2012).

Screening for RBD

The definite diagnosis of RBD requires video-polysomnographic (vPSG) confirmation. Therefore, vPSG remains the gold standard for diagnosis, but this implies specific clinical settings and resources. Taking into account the importance of RBD as a predictor for neurodegenerative disease the diagnosis should be made as soon as possible. In centers where vPSG is not available or due to time constraints, questionnaires can be used for screening for RBD. The questionnaires that are validated to date are: the RBD screening questionnaire (RBDSQ), the Mayo sleep questionnaire (MSQ), the REM behavior disorder questionnaire-Hong Kong (RBDQ-HK) and the RBD single-question screen (RBD1Q) (Lam et al. 2013).

RBDSQ is a 13-item questionnaire that focuses on the main symptoms of RBD according to the ICSD-2 (Stiasny-Kolster et al. 2007). It was demonstrated that it is useful in patients with sleep disorders, where it has been validated with a good validity at a cutoff value of 5 out of 13 points. If applied in a PD population a cutoff score of 6 out of 13 is recommended for a probable RBD diagnosis (Stiasny-Kolster et al. 2007). It is easily administered and gives satisfactory results. However, it cannot properly differentiate RBD from other parasomnias (Lam et al. 2013).

The MSQ is used to screen for RBD and other sleep disorders (Boeve et al. 2011). It was validated in a population with neurodegenerative disorders and could

therefore be useful as a screening tool for RBD in PD patients. Its value resides in the information acquired from the bed partner and its ease of administration, but it cannot be used if no bed partner or spouse information is available (Lam et al. 2013).

The RBDQ-HK is a self-administered questionnaire consisting of 13 questions. Each item is assessed on two levels: lifetime occurrence and 1-year frequency (Li et al. 2010). The 1-year frequency is useful for disease monitoring in clinical studies. It might be necessary to adapt the time frame of this scale to a shorter interval to be better used in clinical studies.

The RBD1Q consists of a single yes/no question: "Have you ever been told or suspected yourself that you act out your dreams while asleep (for example punching, flailing your arms in the air, making running movements etc.?" The scale has good sensitivity (93.8 %) and specificity (87.2 %), but was validated only in patients from specialized sleep disorders clinic, where the patients are supposed to have more severe RBD and who were seeking medical treatment for their well-known problem (Lam et al. 2013).

The four scales mentioned above can be used for screening for RBD and can be administered to patients or bed partners; however, the gold standard remains the vPSG. It is still not known which of these questionnaires will be the method of choice used for screening for RBD in the general population. All questionnaires have been validated in clinical populations who were already educated to some extent about their sleep problems.

After diagnosing RBD, one should clarify the severity of the symptoms. Assessing the severity may be useful in monitoring the disease and the effect of medication. The RBD severity scale (RBDSS) developed by Sixel-Döring and colleagues (Sixel-Doring et al. 2011a) evaluates the motor behavior and vocalizations during vPSG monitoring in PD patients (Sixel-Doring et al. 2011a). Motor events are quantified from 0 until 3 as follows: "0"—no visible motor activity presence of RWA, "1"—small movements or jerks, "2"—proximal movements including violent behavior and "3"—axial movements including bed falls. Vocalizations are rated as: "0" (absent) or "1" (any sleep associated sound, other than respiratory noises) (Stiasny-Kolster et al. 2007).

Epidemiology and demographic data

Epidemiological studies have reported a male predominance in iRBD patients (Boeve 2010; Schenck et al. 1987). This is also true for RBD in a PD patient population, but the male/female ratio seems to be lower than that for iRBD patients (Tang et al. 2009; Sixel-Doring et al. 2011b). RBD is reported to occur between 15 and 47 % of patients with clinically defined PD (Gagnon et al. 2002). This wide rage is explained by the fact that only a few studies have used PSGs when estimating RBD. One study showed that one-third of PD patients met the diagnostic criteria for RBD on PSG, but a higher percentage (58 %) presented RWA, which could be considered a preclinical form of RBD in PD (Gagnon et al. 2002). Sixel-Döring and colleagues have performed a large PSG supported study and detected RBD in 46 % of PD patients (different disease stages) with any sleep complaint (Sixel-Doring et al. 2011b). One problem in assessing the incidence of RBD in PD using PSG is the interindividual night-to-night variability for RBD. The RBD severity score differed in 60 % of a cohort of PD patients between the first and second night in the sleep laboratory (Sixel-Doring et al. 2011a). This can induce false negative results after one-night PSG. Those with clinical complaints and one-night PSG that is negative for RBD should perhaps be investigated for at least one additional night (Sixel-Doring et al. 2011a).

The DeNoPa study included de novo PD patients and healthy controls and sought to investigate non-motors signs in early PD compared to controls. A two-night vPSG was carried out. 40 (25 %) out of the 159 PD patients showed RBD according to ICSD-2 criteria on PSGs, compared to only 2 (2 %) out of the 110 controls. 81 (51 %) subjects with PD were identified as having REM behavioral events (RBE), a new term that was introduced as the authors detected significantly more small motor events during REM in PD subjects compared to the control cohort, thus suggesting RBE is a new pre-RBD. The RBDSQ identified only 30 % of RBE subjects in the PD group, and cannot be considered an appropriate tool for screening early RBD compared to formal PSG (Mollenhauer et al. 2013). A different study reported similar rates (30 %) of RBD in 57 treatment naive PD patients (Plomhause et al. 2013).

RBD as a predictor for development of PD

RBD is considered to be an early manifestation or even the beginning of neurodegenerative disorders. Alpha-synucleinopathies are more commonly associated with RBD compared to tauopathies, this being defined as selected vulnerability (Boeve et al. 2013). This observation implies that selective brainstem neuronal networks are affected in alpha-synucleinopathies, and either to a lesser extent or not at all in other disorders such as tauopathies (Boeve et al. 2007). From the clinical phenotype both syndromes are similar and nigral dysfunction is present in alpha-synucleinopathies as well as in tauopathies. It is, therefore, still unclear which abnormality in the brainstem is responsible for this selective expression of RBD in patients with alpha-synucleinopathies (Boeve et al. 2007). In many cases RBD

precedes the motor manifestations by years or even decades. This is also the case for PD as an alpha-synucleinopathy. The first published report in this direction showed a mean duration of 12.7 years between RBD diagnosis and development of a parkinsonian syndrome (Schenck et al. 1996). Other studies reported time spans of about 10 years (Boeve et al. 2003; Iranzo et al. 2006). In 2010 Claasen et al. published a retrospective case series of patients with much longer latencies, up to 50 years, suggesting that these cases are becoming more frequent (Claassen et al. 2010). Other non-motor symptoms, like anxiety, have been also demonstrated to precede PD at longer time intervals (Shiba et al. 2000). A recent report claims that as much as 80 % of elderly males with newly developed iRBD will eventually develop a parkinsonian syndrome (Schenck et al. 2013a). Since the diagnosis of PD can only be made according to UK Brain Bank Criteria (Hughes et al. 1992) when motor symptoms are present, a suitable biomarker is needed for potential future neuroprotective trials.

A number of studies from centers in Japan have used cardiac (123)I-metaiodobenzylguanidine (MIBG) spectroscopy to show that iRBD could represent a light form of Lewy body pathology (Miyamoto et al. 2006) A reduced cardiac MIBG uptake is consistent with a loss of adrenergic terminals in the heart. This has been observed in PD patients, but not in patients with MSA, which affects mostly the central nervous system (Braune et al. 1999). Miyamoto et al. (2006) have demonstrated a reduction in cardiac MIBG uptake in iRBD patients with the same magnitude as in PD patients, thus implying that iRBD could be an early premotor manifestation of Lewy body pathology. Other authors have shown an even greater decrease in cardiac sympathetic innervation in iRBD compared to PD patients (Kashihara et al. 2010).

Clinical features of PD patients with RBD

Studies have shown that PD patients with RBD differ from those without RBD. PD-RBD patients have more severe cognitive, autonomic and motor symptoms than those without RBD, thus leading the authors to the assumption that PD with RBD could represent a different PD phenotype (Vendette et al. 2007; Gagnon et al. 2009). PD-RBD patients present more often a severe akinetic rigid form of PD, have a poorer response to dopaminergic treatment and usually have higher levodopa-equivalent doses. The risk of developing dementia in a 4-year follow-up was considered to be about 45 % (13 out of 27 patients) in PD patients with RBD and 0 % (0 out of 15 patients) in PD patients without RBD (Postuma et al. 2012). In a cohort of more than 400 PD patients, an association was found between older age and higher dose of levodopa with PD–RBD patients compared to PD without RBD (Sixel-Doring et al. 2012). These studies were performed on treated PD patients.

The recent study by Plomhause et al. (2013) could not detect any significant difference in cognitive or sleep variables between treatment-naïve PD patients with and without RBD, thus questioning the previous hypothesis of different PD phenotypes (Plomhause et al. 2013). These results may be also due to the early disease staging, the short disease duration and the lack of treatment. A longer follow-up time would better clarify the relationship between cognitive impairment and RBD in PD patients (Plomhause et al. 2013).

Pathophysiology of RBD

The possible pathophysiological pathways of RBD in humans result from animal studies, lesional and neuropathological studies. The number of autopsy studies of iRBD brains as well as the number of patients with RBD potentially caused by lesions in the brainstem is small. Therefore, most of the data are extrapolated from animal studies. It remains to be determined if there are species-specific differences in REM sleep control and how similar the control structures are between the cat and rat models and humans (Boeve et al. 2007).

Animal studies have suggested that atonia during REM sleep is produced via two motor systems: one that induces atonia and the other one that suppresses motor activity (Boeve 2010). The absence of motor activity in normal REM is supposed to occur due to active inhibition of spinal motoneurons and reduced drive within locomotor generators (Boeve et al. 2007). Inhibition of the spinal motoneurons occurs through the magnocellular reticular formation (MCRF), which takes place via the ventrolateral reticulospinal tract. Pontine nuclei and forebrain structures also seem to be involved in this complex circuit (Boeve et al. 2007). One important study has described a possible brainstem flip–flop switch, consisting of mutually inhibitory REM-off and REM-on areas in the mesopontine tegmentum, that switch in a rapid way (Lu et al. 2006). Other studies have demonstrated the presence of "REM-on" cell populations in the subcoeruleus region which are essential for REM sleep and muscle atonia (Siegel 2006).

In humans, the structures responsible for REM sleep are thought to be the sublaterodorsal nucleus (SLD), which is the equivalent to the subcoeruleus and peri-locus coeruleus (peri-LC) in the cat, and the penduculopontine nucleus and the MCRF. The SLD is presumed to project to spinal motoneurons by either direct or indirect pathways. Lesions in the SLD cause reduced excitation of the MCRF, and via this indirect route cause a reduction of the inhibition of the spinal motoneurons (Boeve 2010). There are most probably supratentorial influences involved in these circuits and a

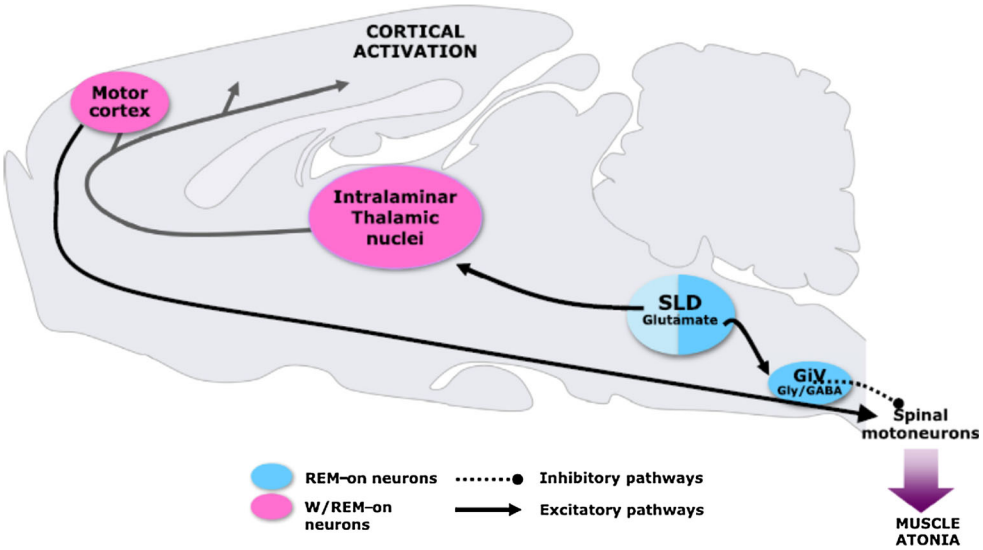

Fig. 1 State of the network responsible for REM sleep and its potential dysfunction(s) during iRBD. During REM sleep, the REM-on glutamatergic neurons of the SLD excite the REM-on gamma-aminobutyric acid (GABA)/glycinergic neurons localized in the ventral medullary reticular formation [raphe magnus (RMg) and the ventral (GiV) and a (Gia) gigantocellular reticular nuclei], which hyperpolarize cranial and spinal motoneurons. REM-on glutamatergic neurons of the SLD also excite intralaminar thalamocortical neurons, which in turn activate the cortex. In iRBD patients, the descending but not the ascending SLD glutamatergic neurons might have degenerated. Another possibility is that the GiV GABA/glycinergic neurons degenerated. Phasic muscle twitches occurring during REM sleep and violent movement of RBD patients could be induced by direct or indirect glutamatergic projections from motor cortex neurons to spinal and cranial motoneurons. *GiV* ventral gigantocellular reticular nucleus, *Glu* glutamate, *Gly* glycine, *SLD* sublaterodorsal nucleus. Reprinted from Luppi et al. (2013) with permission from Elsevier

variety of stimuli could alter the locomotive drive for example, other primary sleep disorders, structural lesions in the brainstem and also neurodegeneration (Boeve 2010) (further description see Fig. 1).

Further morphological studies are needed to determine exactly which neuronal populations determine RBD pathology in humans. This calls for future postmortem studies of patients with iRBD or RBD associated with neurodegenerative disease (Boeve 2010).

RBD in the context of Braak hypothesis

According to Braak's theory, (Braak and Del Tredici 2009) the second stage of PD would imply dysfunction of the SLD, MCRF and peri-LC structures that could lead to RWA or RBD. It seems that prominent degeneration in the SLD could be the critical nucleus involved (Boeve 2010). This temporal sequence of Lewy body pathology could explain why RBD precedes parkinsonism and cognitive decline (stages 3 and 4) (Boeve 2010).

Management of RBD in PD patients

The three main aims of RBD therapy are the same in PD patients as well as in iRBD. These are as follows: to decrease the frequency and severity of abnormal vocalizations, decrease the frequency and severity of abnormal motor behaviors and decrease the unpleasant dreams or nightmares (Boeve 2010). A sufficient treatment for RBD should provide an improvement of sleep for the patient, as well as a better family and social life, taking into account the disturbing noises and the risk of injuries to both the patient and the bed partner. To minimize injuries, patients are advised to use mechanical protection, such as mattresses near the bed, or a bedside barrier.

Medical treatment is represented most commonly by clonazepam or melatonin. To date, there is only one double-blind, placebo-controlled study of RBD that utilized melatonin in a fixed dose of 3 mg at bedtime in iRBD (Kunz and Mahlberg 2010). For PD-RBD, no studies are available.

Clonazepam has been widely used, especially in patients without significant cognitive impairment or obstructive sleep apnea, with a good outcome at doses between 0.25 and 1 mg per night (Schenck and Mahowald 1990).

It is not completely clear why clonazepam improves RBD. Clonazepam binds to the benzodiazepine alpha-receptors, promoting GABAergic inhibition, thus reducing phasic activity in REM sleep, but RWSA can still be observed on vPSGs of patients taking this drug (Boeve 2010; Brooks and Peever 2011). It does, however, reduce motor behavior during RBD.

Melatonin decreases motor behaviors in REM sleep in transgenic mice, and partially restores REM muscle atonia (Brooks and Peever 2011). It seems to stabilize circadian clock variability by re-entraining the suprachiasmatic nucleus (Kunz et al. 2004). It therefore improves sleep efficiency and reduces sleep latency (Attenburrow et al. 1996).

Both medications seem to be efficacious and may act through complementary mechanisms. RBD patients taking clonazepam reported a higher subjective improvement of sleep quality when compared to melatonin, but melatonin was associated objectively with better outcomes regarding occurrence and severity of injuries (McCarter et al. 2013). Melatonin tends to have fewer side effects compared to clonazepam: nocturnal drowsiness and somnolence are not reported with melatonin.

Other agents that have been reported to improve RBD such as pramipexole, donepezil, clozapine, and quetiapine have been studied only in case reports or in a small number of patients (Gagnon et al. 2006). No confirmative data of either of these drugs are available. Clinical practice currently does not support these observations. Further prospective randomized clinical trials are needed to prove the definite efficacy of the available treatments for RBD.

One important issue is the role of selective serotonin reuptake inhibitors in the treatment regimens of many depressive patients and of PD patients as well. These agents could alter REM sleep physiology in such an extent that RBD may be induced, thus it may be useful to use other agents for treating depression in these patients (Onofrj et al. 2003; Schenck and Mahowald 2002).

To summarize, RBD is a common feature in PD patients and it has a great impact on the quality of life of these patients. The treatment options are only partly satisfactory; none of the available therapies succeeds in completely abolishing the risk of sleep-related injuries.

Of great importance is the prognostic value of RBD for the development of neurodegenerative diseases, including PD. This implies possible neuroprotective and disease modifying strategies. The International RBD Study Group has recently published an article, proposing designs and criteria for future treatment trials in RBD, especially in PD patients with RBD. Until then, more data is needed to decide whether RBD defines different PD subtypes or if RBD is a biomarker for neurodegeneration or for a specific PD subtype (Schenck et al. 2013b).

Conflict of interest The authors declare that they have no conflict of interest.

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