The clinical and pathophysiological relevance of REM sleep behavior disorder in neurodegenerative diseases

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SUMARY

REM sleep behavior disorder (RBD) is characterized by vigorous movements associated with unpleasant dreams and increased electromyographic activity during REM sleep.1,2 RBD may be idiopathic (IRBD) or secondary to neurological diseases, particularly those involving the brainstem such as multiple system atrophy.

Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by violent dream-enacting behaviors associated with nightmares and abnormal increased phasic and/or tonic electromyographic activity during REM sleep.1,2 RBD may be idiopathic (IRBD) or secondary to neurological diseases, particularly those involving the brainstem such as multiple system atrophy.

Abstract

RBD may be idiopathic or related to neurodegenerative diseases, particularly multiple system atrophy, Parkinson’s disease and dementia with Lewy bodies. RBD may be the first manifestation of these disorders, antedating the onset of parkinsonism, cerebellar syndrome, dysautonomia, and dementia by several years. RBD should thus be considered an integral part of the disease process. When effective, neuroprotective strategies should be considered in subjects with idiopathic RBD. Patients with other neurodegenerative diseases, though, such as spinocerebellar ataxias, may also present with RBD. When clinically required, clonazepam at bedtime is effective in decreasing the intensity of dream-enacting behaviors and unpleasant dreams in both the idiopathic and secondary forms. When part of a neurodegenerative disorder the development of RBD is thought to reflect the location and extent of the underlying lesions involving the REM sleep centers of the brain (e.g., locus subceruleus, amygdala, etc.), leading to a complex multiple neurotransmitter dysfunction that involves GABAergic, glutamatergic and monoaminergic systems.

RBD is mediated neither by direct abnormal alpha-synuclein inclusions nor by striatonigral dopaminergic deficiency alone.

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RBD was first described as a medical entity in humans by Schenck and colleagues in 1986. The same authors were the first group to report that RBD may occur in subjects with chronic neurological diseases, including MSA and narcolepsy. They also first found that subjects diagnosed with IRBD eventually develop parkinsonism. These observations have been confirmed in other prospective studies. Emerging neurological disorders in IRBD subjects at our sleep center were MSA, PD, DLB and mild cognitive impairment. This has been recently confirmed by another group of investigators.

Hence, RBD should no longer be considered as a sleep disorder in isolation, but rather integrated as one component of a neurological disease. Moreover, it should be regarded as a potential early marker for MSA, PD and DLB. During the last four years, several aspects of RBD have been extensively reviewed in more than 15 publications. In this article we review our current understanding of the clinical characteristics and significance of RBD pathophysiology in neurodegenerative diseases and address some controversial issues. Also, we provide demographical, clinical and polysomnographic detailed data on 231 patients from our sleep center diagnosed by clinical history and videopolysomnography (VPSC) with IRBD and RBD secondary to MSA, PD and DLB (Tables 1–3).

### Clinical aspects of RBD

**The clinical spectrum of RBD**

RBD usually emerges after the age of 50. Its prevalence is estimated to be less than 1% of the population. RBD patients display abnormal motor and vocal behaviors during REM sleep that have different degrees of severity across different nights. Severity may also vary through a single night, usually being more intense at the end of the night. In our experience reviewing VPSC of patients with RBD, motor behaviors are more frequent than vocal behaviors and range from mild limb jerking to jumping out of bed. Typical motor and vocal behaviors include punching, kicking, beating, biting, knocking off the nightstand, sitting on the bed, jumping out of bed, whis-pering, talking, shouting, swearing, crying, laughing and singing. Consequently, patients and bed partners may suffer lacerations, contusions and fractures. In some patients, non-violent behaviors (e.g., gesturing, elaborated pseudo-purposeful behaviors, whistling) may occasionally coexist with the typical violent behaviors. Recalled dreams commonly have a negative emotional content and include being attacked, robbed, or chased by unfamiliar people for known or unknown reasons. In these dreams patients are threatened and react verbally or physically against the offender being rarely the primary aggressor. Other common nightmares include being frightened or attacked by animals (snakes, bulls, lions, donkeys, etc.) and falling off a cliff. A few patients recall funny dreams, which may be associated with smiling and laughing during sleep.

<table>
<thead>
<tr>
<th></th>
<th>MSA (n = 67)</th>
<th>DLB (n = 17)</th>
<th>PD (n = 65)</th>
<th>IRBD (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>56.7%</td>
<td>94.1%</td>
<td>70.8%</td>
<td>86.3%</td>
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<tr>
<td>Age at diagnosis of RBD (years)</td>
<td>61.5 ± 7.9</td>
<td>74.2 ± 6.5</td>
<td>65.8 ± 7.5</td>
<td>68.4 ± 6.7</td>
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<tr>
<td>Age at RBD onset (years)</td>
<td>54.7 ± 10.2</td>
<td>65.3 ± 11.8</td>
<td>61.0 ± 7.7</td>
<td>61.0 ± 8.8</td>
</tr>
<tr>
<td>RBD duration (years)</td>
<td>7.3 ± 6.9</td>
<td>8.9 ± 10.4</td>
<td>4.6 ± 4.0</td>
<td>7.2 ± 7.2</td>
</tr>
<tr>
<td>Age at disease onset (years)</td>
<td>57.1 ± 8.2</td>
<td>71.7 ± 8.4</td>
<td>56.2 ± 9.7</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>4.4 ± 2.7</td>
<td>3.2 ± 4.4</td>
<td>9.6 ± 6.0</td>
<td>N/A</td>
</tr>
<tr>
<td>RBD preceding disease onset (%)</td>
<td>52.2%</td>
<td>100%</td>
<td>18.5%</td>
<td>N/A</td>
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Table 1: Demographic and clinical findings of 231 RBD patients with MSA, DLB, PD and the idiopathic form seen at our sleep center. RBD was confirmed by VPSC in all subjects.

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<tr>
<td>Self-awareness of behaviors (%)</td>
<td>23.9%</td>
<td>29.4%</td>
<td>35.4%</td>
<td>53.9%</td>
</tr>
<tr>
<td>Unpleased dream recall (%)</td>
<td>65.7%</td>
<td>82.4%</td>
<td>86.2%</td>
<td>92.1%</td>
</tr>
<tr>
<td>Most frequent unpleasant dreams</td>
<td>39.8%</td>
<td>41.2%</td>
<td>53.1%</td>
<td>58.8%</td>
</tr>
<tr>
<td>Chased by someone (%)</td>
<td>35.8%</td>
<td>47.1%</td>
<td>53.8%</td>
<td>52.9%</td>
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<td>Falling from a cliff (%)</td>
<td>29.9%</td>
<td>11.8%</td>
<td>44.6%</td>
<td>48.0%</td>
</tr>
<tr>
<td>Attacked by animals (%)</td>
<td>26.9%</td>
<td>29.4%</td>
<td>32.3%</td>
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Table 2: Findings of reported dream content and witnessed abnormal behaviors in 231 RBD patients with MSA, DLB, PD and the idiopathic form seen at our sleep center. RBD was confirmed by VPSC in all subjects.

n: number of subjects, RBD: Rapid eye movement sleep behavior disorder, MSA: Multiple system atrophy, DLB: Dementia with Lewy bodies, PD: Parkinson's disease, IRBD: idiopathic RBD, VPSC: video-polysomnography.

### Table 2

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<td>32.3%</td>
<td>42.2%</td>
</tr>
<tr>
<td>Treatment with clonazepam (%)</td>
<td>29.9%</td>
<td>35.3%</td>
<td>46.2%</td>
<td>65.7%</td>
</tr>
<tr>
<td>Dose of clonazepam (mg/day)</td>
<td>0.58 ± 0.20</td>
<td>0.90 ± 0.65</td>
<td>0.66 ± 0.35</td>
<td>0.94 ± 0.93</td>
</tr>
</tbody>
</table>

n: number of subjects, RBD: Rapid eye movement sleep behavior disorder, MSA: Multiple system atrophy, DLB: Dementia with Lewy bodies, PD: Parkinson's disease, IRBD: idiopathic RBD, VPSC: video-polysomnography.
the patients are effectively treated with clonazepam. Some patients report long periods of remission while others report a gradual worsening of symptoms. Effective clonazepam treatment, however, does not prevent development of a neurodegenerative disease in subjects initially diagnosed as having IRBD.8

RBD manifestations depend on the amount of time spent in REM sleep. The use of antidepressants may be related to a subjective improvement in RBD symptomatology because these medications decrease REM sleep time. Paradoxically, the use of antidepressants has been associated with development of RBD, likely due to their ability to increase muscular activity during REM sleep.31–33

The male predominance in RBD

More than 80% of the patients presenting to sleep centers with IRBD are men.3,27,34,35 In our experience, a strong male predominance is also observed in DLB patients with RBD (unpublished data). In PD, the male predominance has been observed in most but not all series.36 Interestingly, the male predominance is not evident in MSA, probably because RBD occurs in most, if not all, patients with MSA, and this disease has no gender predominance.27,37

The origin of the male preponderance in RBD is unknown. It has been hypothesized that sex hormone abnormalities might account for this male predominance and for the violent nature of the RBD-associated behaviors.2 However, two studies in male patients with IRBD and RBD linked to PD showed no differences in morning circulating sex hormone levels between patients and controls.

Aside from hormonal issues, there are other possible explanations for the male predominance of patients with RBD presenting at sleep centers. First, RBD may be milder in female and produce less vigorous and disruptive behaviors, thereby making female patients less prone to seek medical help. This hypothesis is supported by 1) the finding that in PD the mildest form of RBD (subclinical increased submental tonic electromyographic activity in REM sleep) is equally frequent in men and women, whereas clinically evident RBD is more common in men,40 2) the result of an epidemiological study showing that subjects with a milder clinical form of RBD do not seek medical attention41 and by 3) the fact that unpleasant dream content in RBD is somewhat different between males and females.42 RBD-related dream content in men usually compromise physical and vocal self-defense against unknown attackers. In contrast, dream content in women includes sensation of threat and fear and being chased, while physical aggression against someone is rarely reported.42 A different explanation for the male predominance is a referral bias. RBD may manifest similarly in women and men, but women may be more embarrassed by their condition and ashamed to seek medical consultation. It is also possible that women are more capable than men in detecting sleep disorders of their bed partners (such as snoring, apneas, and abnormal sleep behaviors) and are more prompt to seek medical attention for them.

Polysomnography in the diagnosis of RBD

In 2005, the International Classification of Sleep Disorders (ICSD-2) established that the diagnosis of RBD should be based on both clinical and PSG criteria.1 Demonstration of increased electromyographic activity during REM sleep by PSG is required mainly because RBD-like behaviors may occur in people with and without neurodegenerative disorders who are affected by obstructive sleep apnea,43 somnambulism,44,45 nocturnal epilepsy, hallucinations, confusional states and patients with unusually prominent periodic leg movements of sleep also involving the head, trunk and upper limbs (personal observations). In these situations, termed as pseudo-RBD, only VPSG can diagnose these disorders and exclude RBD (Figs. 1–4). Alternatively, RBD may incidentally coexist with obstructive sleep apnea, somnambulism, epileptiform activity,4,29,46 and confusional awakenings. Only VPSG can detect these conditions occurring in the same patient. Furthermore, VPSG increases the sensitivity of diagnosing RBD because a proportion of patients are unaware of their abnormal behaviors during the night.27 Therefore, the presence of RBD may be either underestimated or overestimated when based only on clinical history.

Correct diagnosis of RBD is particularly important in subjects without evidence of an underlying neurological disease because this parasomnia may be its initial manifestation.8,25 Misdiagnosis of RBD may carry unnecessary emotional consequences and medical practice liability. Moreover, correct diagnosis of RBD is important because patients with RBD may injure themselves and their bed partners, and because this parasomnia can be treated effectively with clonazepam.15 It is not recommended, however, to prescribe clonazepam before ruling out other conditions that may mimic RBD symptomatology47 such as obstructive sleep apnea.43,48

We think that when either IRBD is suspected or the intensity of the sleep behaviors requires initiation of clonazepam, VPSG is required to diagnose this parasomnia. In contrast, if sleep behaviors are clinically mild, appear in the setting of a known neurodegenerative disease such as PD, and sleep apnea is unlikely by clinical history, the need for a sleep study is debatable. In some instances like in PD, clinical interview with both the patient and bed partner may show a high specificity and sensitivity.36 However, it should be noted that obstructive sleep apnea is common in patients with PD and normal body mass index.48 Unpleasant dreams and vigorous sleep behaviors may be present in patients with severe obstructive sleep apnea.43 In RBD subjects with comorbid severe obstructive sleep apnea, treatment with continuous positive airway pressure

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Table 3

Polysomnographic findings in 211 RBD patients with MSA, DLB, PD and the idiopathic form seen at our sleep centre. RBD was confirmed by VPSG in all subjects.

<table>
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<th>PD (n = 45)</th>
<th>IRBD (n = 102)</th>
</tr>
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<tbody>
<tr>
<td>Sleep efficiency (%)</td>
<td>64.2 ± 16.0</td>
<td>74.9 ± 10.8</td>
<td>65.9 ± 17.0</td>
<td>73.9 ± 12.8</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>285.4 ± 74.0</td>
<td>346.5 ± 52.5</td>
<td>309 ± 91.8</td>
<td>340.5 ± 68.4</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>34.3 ± 31.4</td>
<td>36.6 ± 40.0</td>
<td>21.7 ± 21.4</td>
<td>25.5 ± 21.5</td>
</tr>
<tr>
<td>Arousal index</td>
<td>22.1 ± 13.3</td>
<td>27.7 ± 20.5</td>
<td>25.4 ± 17.6</td>
<td>23.3 ± 13.9</td>
</tr>
<tr>
<td>Stage I (%)</td>
<td>17.2 ± 11.4</td>
<td>24.2 ± 18.2</td>
<td>19.0 ± 14.1</td>
<td>22.2 ± 12.6</td>
</tr>
<tr>
<td>Stage II (%)</td>
<td>44.8 ± 12.6</td>
<td>46.6 ± 14.9</td>
<td>47.2 ± 14.6</td>
<td>46.3 ± 11.4</td>
</tr>
<tr>
<td>Stage III–IV (%)</td>
<td>21.8 ± 14.7</td>
<td>17.3 ± 13.4</td>
<td>163 ± 9.8</td>
<td>14.2 ± 9.1</td>
</tr>
<tr>
<td>REM (%)</td>
<td>16.0 ± 9.3</td>
<td>11.8 ± 7.5</td>
<td>17.5 ± 8.0</td>
<td>17.6 ± 7.3</td>
</tr>
<tr>
<td>REM sleep latency (min)</td>
<td>140.0 ± 85.9</td>
<td>195.5 ± 109.3</td>
<td>134.0 ± 88.2</td>
<td>131.2 ± 6.3</td>
</tr>
<tr>
<td>REM sleep stages (n)</td>
<td>2.4 ± 1.3</td>
<td>1.9 ± 0.8</td>
<td>2.6 ± 1.4</td>
<td>2.8 ± 1.1</td>
</tr>
<tr>
<td>PLMS index</td>
<td>27.9 ± 36.8</td>
<td>21.5 ± 34.6</td>
<td>10.4 ± 17.9</td>
<td>12.8 ± 22.3</td>
</tr>
<tr>
<td>Apnoea-hypopnea index</td>
<td>10.5 ± 11.4</td>
<td>14.1 ± 17.3</td>
<td>13.9 ± 19.3</td>
<td>13.4 ± 16.4</td>
</tr>
</tbody>
</table>

n, number of subjects; RBD, Rapid eye movement sleep behaviour disorder; MSA, multiple system atrophy; DLB, dementia with Lewy bodies; PD, Parkinson’s disease; IRBD, idiopathic RBD; PLMS, periodic leg movements in sleep.
alone decreases the frequency and intensity of unpleasant dream recall and abnormal sleep behaviors but RBD persists. This occurs in patients with IRBD and PD patients with RBD (unpublished observation).

Clinical, electromyographic and video-classification of RBD

Measuring the characteristics and severity of RBD is important when monitoring the efficacy of medications. It is also of interest because it is thought that RBD frequency and intensity may vary over time, although this has never been assessed. It should be noted, though, that RBD occurs every night but with a high inter-night variability in its intensity. A recent study showed that a single night of PSG with synchronized audiovisual monitoring was adequate in the diagnosis of RBD in most patients. The following attempts have been made to classify RBD by clinical history, REM sleep electromyographic features and the abnormal behaviors seen in audiovisual recordings.

![Fig. 1.](image1.png)


![Fig. 2.](image2.png)

A) Excessive phasic electromyographic activity and intermittent increased tonic electromyographic activity in the chin with normal atonia in the limbs during REM sleep in a patient with RBD. B) Abnormal phasic electromyographic burst of all the muscles recorded associated with a sudden body jerk during REM sleep in a patient with RBD. (Abbreviations as in Fig. 1).
Clinical history

In the first edition of the International Classification of Sleep Disorders (ICSD-1) severity of RBD was classified in mild, moderate and severe. These categories were defined according to the intensity and frequency of the witnessed behaviors as follows:

Mild: RBD that occurs less than once per month; only mild discomfort for the patient or bed partner.

Moderate: RBD that occurs more than once per month but less than once per week; usually associated with physical discomfort to the patient or bed partner.

Fig. 3. A) Increased phasic electromyographic activity during REM sleep only in the lower limbs with muscle atonia in the chin and upper limbs in a patient with RBD. B) Increased phasic electromyographic activity during REM sleep only in the upper limbs with muscle atonia in the chin and lower limbs in a patient with RBD. (Abbreviations as in Fig. 1).

Severe: RBD that occurs more than once per week; associated with physical injury to patient or bed partner.

This classification was not validated by any study. Despite its potential interest and use in some studies, the classification was removed from the second edition of the International Classification of Sleep Disorders in 2005. We think that this system, in the absence of any other clinical classification could be a reasonable way of classifying RBD intensity and frequency by clinical history. However, its main limitation is that it is totally dependent on the patient and bed partner ability to detect the behaviors occurring at night. Its use is very limited in RBD patients that sleep alone because many are unaware of their nocturnal behaviors.

Electromyographic analysis

No accepted methodology exists to measure the excessive electromyographic activity occurring in REM sleep, and cut-off values that can distinguish normality from RBD are lacking. Several systems have been proposed to quantify the electromyographic activity, either visually or based on computerized systems. There is a lot of variability among the different proposed systems, with different duration of epochs (7.5, 10, 20 or 30 s) and mini-epochs (2, 3 or 7.5 s). Some authors have evaluated only the tonic activity, only the phasic activity, or both the tonic and phasic activities. Others have used a different approach defining short and long lasting electromyographic activity. There is also variability in the muscles used for analysis with several combinations including: (1) exclusively the mentalis or the submentalis, (2) the mentalis or submentalis plus left and right anterior tibialis and (3) the mentalis or submentalis plus right and left anterior tibialis, and either the brachioradialis, biceps brachii, extensor digitorum or carpi radialis. The SINBAR (Sleep-Innsmouth-Barcelona) group found that simultaneous recording of the mentalis, flexor digitorum superficialis and extensor digitorum brevis muscles detects the highest rate of phasic EMG activity during REM sleep in subjects with RBD.

Video analysis

It should be noted that minor distal limb movements in REM sleep occur in normal people. Motor and vocal behaviors displayed by RBD patients are variable. Four different classification systems have been proposed. The first three classify the behaviors according to their nature into simple and complex, or into elementary and complex. A fourth classification system classifies the behaviors severity into mild, moderate and severe. Overall, there is a clear need for a consensus classification of the clinical, electromyographic and video aspects of RBD. This could produce progress in our understanding of this sleep disorder.

Treatment of RBD

Treatment of RBD may be required in the following situations:

1) To prevent injuries in patients with violent dream-enacting behaviors.
2) To decrease the intensity of unpleasant dreams in those subjects disturbed by this uncomfortable experience.
3) To avoid disturbing the bed partner’s quality of sleep.

No prospective placebo-controlled trials have been performed for any therapy of RBD. In idiopathic and secondary RBD, symptoms usually respond dramatically to small doses of clonazepam (0.25–4 mg) at bedtime. Clonazepam decreases the frequency and severity of both dream-enacting behaviors and unpleasant dream recall in the first week of treatment. In our experience, the mean effective dose of clonazepam is 1 mg and tolerance is rarely seen. However, some patients may require up to 4 mg to achieve some clinical benefit. For unknown reasons a few patients do not respond to clonazepam, particularly those with IRBD (personal observations). Side effects of clonazepam include dizziness, somnolence, impotence and urinary incontinence at night. One study involving 5 IRBD patients showed that clonazepam decreases the phasic, but no the tonic, electromyographic activity in the submentalis muscle during REM sleep. The beneficial effect of clonazepam might be related to its GABAergic activity depressing motor reflexes at the spinal cord level, promoting glycnergic activity and thereby reducing muscular activity. However, this does not explain why other benzodiazepines have been found not to ameliorate RBD symptoms.

Melatonin (3–12 mg at bedtime or 30 min before bedtime) is also effective in patients with idiopathic and secondary RBD. Its beneficial effect occurs within the first week of treatment. Unlike clonazepam, melatonin decreases the tonic, but not the phasic, electromyographic activity in the submentalis muscle in subjects with RBD. It has been speculated that melatonin improves RBD due to restoration of the REM sleep circadian rhythm. Melatonin can be useful in refractory cases to clonazepam, when clonazepam is associated with side effects, and when clonazepam is not indicated due to the presence of other addicted sleep apneas and severe somnolence. The co-administration of small doses of clonazepam and melatonin may also be effective in some patients (personal observations).

Methods of self-protection from injury, such as placing a mattress on the floor or removal of furniture from the room, may be necessary. It is recommended to minimize the use of antidepressants and lipo-philic beta-blockers such as bisoprolol because these medications may induce or aggravate RBD.

RBD in the setting of neurodegenerative diseases

RBD often antedates the full-blown clinical presentation of several neurodegenerative diseases, suggesting that this sleep disorder should be considered part of the neurodegenerative process rather than a predisposing factor. Therefore, it can be argued whether the idiopathic form of RBD really exists. On the other hand, neurologists should be aware that their patients with established MSA, PD and DLB may present with RBD. These three diseases have several molecular, clinical and morphologic abnormalities in common, such as substantia nigra cell loss resulting in parkinsonism that responds to dopaminergic agents to a variable extent. However, like other non-motor symptoms, the presence of RBD in these diseases is mainly explained by the intrinsic neurodegenerative process beyond the substantia nigra. In this section we review the relevance and characteristics of RBD in the setting of some neurodegenerative diseases. In Tables 1–3 we present clinical, demographical and PSG characteristics of 231 RBD patients confirmed by PSG with IRBD, MSA, PD and DLB seen at our sleep center.

The natural history of idiopathic RBD

Idiopathic RBD is diagnosed when a patient with VPSG confirmation of RBD has no evidence of a neurological disease or other possible causes. In many IRBD patients, though, subclinical abnormalities can be detected, such as olfactory deficits, color vision impairment, cognitive deficits on neuropsychological tests, subtle cortical electroencephalographic slowing, dystautonomic abnormalities, reduced cardiac 123-I Metaiodobenzylguanidine (MBG) scintigraphy, decreased dopamine transporter imaging, and increased substantia nigra echogenicity. All these features have also been described in patients with the established classic motor and cognitive features of MSA, PD and DLB. Furthermore, neuropathological examination in two IRBD patients showed the...
has been shown that neurodegenerative diseases frequently develop in RBD patients followed at sleep centers. Schenck et al. first reported development of parkinsonism in 11 of 29 (38%) men at a mean interval of 12.7 years after RBD onset and 3.7 years after the diagnosis of RBD. After an additional seven years of follow-up, the proportion of subjects that developed parkinsonism and/or dementia increased to 65%. In a second series, we showed that 20 of 44 (45%) IRBD patients developed a neurological disorder after a mean interval of 11.5 years from RBD onset and after a mean follow-up of 5.1 years from the diagnosis of IRBD. Emerging disorders were PD in nine patients (two with associated dementia), DLB in six, MSA with predominant cerebellar syndrome in one, and mild cognitive impairment in four in whom visuospatial dysfunction was prominent. The finding that patients who developed a disorder were those with longer follow-up suggested that conversion rate (45%) could increase with the passage of time. This was confirmed after two years of follow-up when one patient with IRBD developed PD, two patients with mild cognitive impairment converted into DLB, and seven subjects with IRBD developed mild cognitive impairment. Also, two PD patients developed mild cognitive impairment. Overall, in our center 64% of IRBD patients have developed a neurological disorder after a mean clinical follow-up of 7 years. An additional patient with IRBD and mild cognitive impairment who was lost to follow-up for four years recently presented with marked dementia, rigid-akinetic parkinsonism and recurrent paranoid delusions. In another study, 26 of 93 (27%) IRBD patients seen at a sleep center developed PD in 14 cases, DLB in 7 cases, MSA in 1 case and dementia of unknown origin in 4 cases. Diagnosis of these diseases was based on clinical examination or telephone interviews. The estimated 5-year risk of neurodegenerative disease was 17.7%, the 10-year risk was 40.6% and the 12-year risk was 52.4%.

**RBD in multiple system atrophy (MSA)**

MSA is a progressive, sporadic, adult-onset neurodegenerative disorder characterized by a combination of parkinsonism, cerebellar syndrome and autonomic failure. Neuropathology shows neuronal loss, astrogliosis and alpha-synuclein positive glial cytoplasmic inclusions in many brain structures, including the striatum, amygdala, cerebellum and brainstem nuclei (e.g., substantia nigra, locus ceruleus and pedunculopontine nucleus). Multiple central neurotransmitter systems are impaired including dopaminergic, cholinergic, serotonergic, adrenergic, noradrenergic and glutamatergic.

**Prevalence of RBD in MSA**

A majority of patients with MSA have RBD with a prevalence of 90.5–100%. In one study, 21 consecutive MSA patients without sleep behavioral complaints underwent VPSG that demonstrated typical RBD features in 19 (90.5%). In another study, VPSG showed RBD in 35 out of 37 (95%) consecutive patients. In our experience, all 73 MSA patients who were referred to our sleep center from April 1997 to December 2008 for different reasons (suspected RBD, stridor or sleep fragmentation) had RBD on VPSG. Taken together, we think that in a patient with suspected MSA, the absence of RBD (particularly if it is formally excluded by VPSG) should seriously question the diagnosis of this disease. RBD is currently considered a red flag for the diagnosis of MSA.

**Clinical characteristics of RBD in MSA**

Self-awareness of abnormal sleep behaviors and unpleasant dream recall is variable among MSA subjects with RBD. In one study, 27 of 39 (69%) consecutive MSA patients with RBD or their relatives reported dream-enacting behaviors. Interestingly, most of the 12 that did not report dream-enacting behaviors were sleeping alone at their home. In another study, only seven of 21 (33%) MSA patients with RBD recalled vivid dreams. In our first published case series comprising 26 consecutive MSA cases with RBD free of psychoactive drugs, 77% of the patients were unaware of their abnormal behaviors, which were only noticed by bed partners. Recall of unpleasant dreams was absent in 35% of the patients. In our experience involving 67 MSA patients with RBD, 51 (46%) were not aware of their abnormal behaviors and 24 (33%) did not recall unpleasant dreams (Table 1).

The strong male predominance seen in the idiopathic form of RBD, and in those RBD forms associated with PD and DLB is much less evident in MSA, where 33–61% of the patients are men. This may be explained by the simple fact that most, if not all, patients with MSA have RBD. The male/female ratio of RBD in MSA reflects the roughly 1:1 male/female ratio of the disease.

RBD in MSA is unrelated to age, disease severity, disease duration, clinical subtype (parkinsonian or cerebellar), or to any other demographic or clinical feature.

**Onset of RBD in MSA**

RBD may be the first symptom of MSA. In one study of 27 RBD patients aware of their dream-enacting behaviors, RBD preceded the waking motor symptoms in 12 (44%). In another study with 19 patients, RBD features were reported by the patients or their relatives as the first manifestation of the disease in 3, concomitant with other symptoms in 9, and developed after the onset of waking symptoms in the remaining 7. In our series, RBD onset antedated parkinsonism, cerebellar and dysautonomic onset in 35 of 67 (52%) patients by a mean of 7.0 ± 7.2 years (range, 1–38 years). In our sleep center two patients with IRBD developed the dysautonomic and motor features of cerebellar subtype of MSA, two and four years after the diagnosis of IRBD. We have recently reported a patient presenting with dysautonomia, stridor during sleep and RBD without parkinsonism or cerebellar syndrome in whom brain pathology disclosed MSA after sudden death during wakefulness.

**Polysomnography of RBD in MSA**

Typically, VPSG shows marked increase of submental tonic electromyographic activity during REM sleep which is greater than in IRBD and PD. Also, phasic electromyographic activity is usually excessive in REM sleep.

In a few MSA subjects with RBD, we have observed brief episodes of sudden slump and limb jerks during non-REM sleep similar to, but less complex than, those occurring in the same patient during REM sleep (Fig. 5). Also, aperiodic limb movements are frequent in non-REM sleep. These non-REM sleep motor abnormalities in MSA patients with RBD are indicators of disso- ciate states of sleep. Intrusion of components of one state into another has been reported in patients with RBD associated to neurodegenerative dementia (complex motor behaviors in non-REM sleep stages 1–2), narcolepsy (muscle atonia during wakefulness), antidepressant treatment (e.g., rapid eye movements in non-REM sleep) and in a patient with a mesopontine cavernoma that evolved towards a status dissociatus (an indeterminate state where wakefulness and sleep stages cannot be distinguished by PSG means) after surgery.

**Pathophysiology of RBD in MSA**

The finding that in MSA brainstem cell loss is consistently widespread and severe may explain the high prevalence of RBD in this disease. It was first reported that cell loss in the cholinergic pedunculopontine and laterodorsal nuclei was the cause of RBD in MSA. The same authors, however, reported later that the severity
of cholinergic neuronal loss in these nuclei was not different between 8 MSA patients with clinical history suggestive of RBD and 3 without suspected RBD by history and concluded that damage of these cholinergic nuclei was probably not the primary mechanism of RBD. However, this conclusion may be invalid since those 3 patients with history not suggestive of RBD did not undergo VPSG. Correct diagnosis or exclusion of RBD in MSA can only be disclosed when VPSG is performed.

Treatment of RBD in MSA

Severity of RBD in MSA ranges from mild in asymptomatic patients to severe with some patients suffering rib fractures after falling out of the bed. Clonazepam is effective to treat RBD in MSA. Before prescribing clonazepam, it is desirable to rule out stridor and obstructive sleep apnea by VSPG, since this medication may worsen existing apneas by aggravating upper airway obstruction at the level of the larynx and the pharynx, a common feature in MSA. Melatonin could be used to treat RBD in MSA patients with upper airway obstruction.

RBD in Parkinson’s disease (PD)

PD is clinically characterized by levodopa responsive parkinsonism. PD is associated with other features such as depression, dementia, hyposmia and several sleep disorders including RBD. PD is morphologically characterized by progressive neuronal loss and Lewy bodies in the substantia nigra pars compacta and other brainstem structures, including dorsal vagal nucleus, gigantocellular reticular nucleus, locus ceruleus, locus subceruleus, pedunculopontine nucleus, dorsal raphe and nucleus of the solitary tract. Neurodegeneration may involve the amygdala, nucleus basalis of Meynert, limbic cortex, hippocampus, the posterior hypothalamus and neocortex.

Prevalence of RBD in PD

PD may occur in patients with idiopathic PD and PD secondary to genetic mutations. RBD occurs in PD patients untreated or treated with dopaminergic agents. When diagnosis is based solely on clinical history, the prevalence of RBD in idiopathic PD varies from 15% to 46%. These figures are somewhat lower than the ones reported when diagnosis of RBD is performed using clinical and VPSG criteria, which range between 46 and 58%. This is because some PD patients are not aware of the abnormal sleep behaviors that can only be disclosed by VPSG.

Most of the studies have evaluated RBD in nondemented and non-hallucinator idiopathic PD subjects. One study in 45 nondemented patients found that 18 (40%) showed either clinical RBD (16%) or subclinical REM sleep without atonia (24%). In another study, nineteen out of 33 patients with mild to moderate idiopathic PD had REM sleep without submental atonia. Of these, 11 reported clinical RBD, whereas the remaining 8 either were unaware of sleep behaviors or REM sleep without atonia was not associated with abnormal motor manifestations on their VPSG. One study evaluating 10 Park2 patients by clinical history and VPSG found RBD in 6 (60%).

Clinical characteristics of RBD in PD

Sixty-five percent of the PD patients with RBD are unaware of their RBD-related symptoms and 24% do not recall frightening dreams. Sixty-five to seventy-five percent of the PD patients with RBD are men, a figure similar to the frequency of men in PD.

The presence of RBD in PD has been associated with longer parkinsonism duration, orthostatic hypotension, and treatment of parkinsonism with a higher dose of dopaminergic agents. RBD is more common in the rigid-akinetic clinical subtype of the disease than in the tremoric subtype.

It has not been studied if RBD is more common in demented than in nondemented PD patients. It has been suggested, though, that RBD may be a marker for the development of dementia in PD because nondemented PD patients with RBD are more likely to show electroencephalographic slowing during wakefulness and poorer performance in executive function, verbal memory and visuospatial abilities in neuropsychological test. However, it has
been argued that these findings may simply reflect a more widespread neurodegenerative disease affecting the brainstem causing RBD and the cortex causing cognitive abnormalities. Moreover, longer duration of PD is linked to the development of both dementia and RBD.

The relationship between visual hallucinations and RBD remains controversial. RBD in PD is not associated with age, disease severity, motor fluctuations, dyskinesias, depression, hyposmia, hypersomnia, sleep benefit, sleep architecture or longer daily doses of levodopa equivalent.

Onset of RBD in PD

When idiopathic PD patients exhibit RBD, this parasomnia precedes the onset of parkinsonism in 18–22% of the cases. Unlike MSA, RBD rarely precedes parkinsonism when parkinsonian signs develop before the age of 50. In patients initially diagnosed with RBD who later develop PD 1 year after RBD onset (mean of 72 years) is older than reported for PD patients in the community (mean of 62 years), and 2) the most frequent parkinsonism subtype is the rigid-akinetic type which responds to levodopa. In subjects with Park2 mutations RBD develops after parkinsonism onset.

Polysomnography of RBD in PD

Most of the studies evaluating RBD in PD have been based on clinical history only. We here emphasize again the need to perform VPSG in PD subjects in order to assess the occurrence of RBD and to exclude other sleep disorders that present with similar symptoms. On one hand, many of the PD patients with RBD are unaware of their RBD-related symptoms and do not recall frightening dreams. On the other hand, somnambulism, confusional awakenings and sleep apnea may mimic RBD symptoms in PD. The sensitivity of specialized interviews for identifying RBD in patients with PD varies from 33% to 95%.

Interestingly, VPSG analysis in PD with RBD shows that movements seen in REM sleep are faster and smoother than those occurring during wakefulness.

Pathophysiology of RBD in PD

In PD, the brain structures that modulate REM sleep such as the gigantocellularis reticular nucleus, subceruleus region and amygdala are damaged reflecting the high prevalence of RBD in this disease. The finding that RBD frequently occurs in the rigid-akinetic subtype of the disease may suggest that in these patients the ventrolateral region of the substantia nigra pars compacta is more severely damaged.

Treatment of RBD in PD

In idiopathic PD, severity of the RBD symptoms ranges from mild to severe. In patients with Park2 mutations RBD severity is usually mild. Most of the cases respond to clonazepam. There is no clear evidence that dopaminergic agents influence the development, evolution and severity of RBD. Pramipexole and sulpiride may suggest that in these patients the ventrolateral region of the substantia nigra pars compacta is more severely damaged.

RBD in dementia with Levy bodies (DLB)

DLB is the second most common cause of neurodegenerative dementia after Alzheimer’s disease (AD). DLB is clinically characterized by dementia, parkinsonism, recurrent visual hallucinations and fluctuations in cognition and alertness. DLB is diagnosed if dementia precedes or appears within one year before onset of parkinsonism, whereas PD later complicated with dementia (PDD) is diagnosed if dementia occurs more than one year after onset of parkinsonism. The pattern of RBD in DLB is characterized by deficits of visuospatial ability, attention and executive frontal function. Memory is also impaired. The cognitive profile in DLB is similar to that reported in PDD and different from that reported in AD.

Neuronal loss, gliosis and Lewy neurites and Lewy bodies are found in the brainstem (substantia nigra, locus ceruleus, etc.), limbic system (amygdala, transentorhinal cortex and cingulate) and neocortex (frontal, temporal and parietal). The combination of brainstem and cortical Lewy bodies is necessary for the pathologic diagnosis of DLB. There are no striking neuropathological differences in the brain between DLB and PDD. The neurodegenerative process in DLB involves widespread central cholinergic, histaminergic, noradrenergic and dopaminergic deficiency.

Characteristics of RBD in DLB

The literature on RBD in DLB is limited, and, to the best of our knowledge, no published studies exist that address the prevalence and demographic, clinical, therapeutic and VPSG characteristics of RBD in consecutive patients with DLB. Available data, though, seems to reflect that RBD is very frequent among patients with DLB, predominates in men and usually precedes the onset of dementia. The presence of RBD in DLB has recently been addressed by a single group of investigators from the Mayo Clinic in Rochester, Minnesota. In one study, it was noted that at least 50% of patients with DLB have RBD but no further details were given. The same group presented in abstract form that REM sleep without atonia was found in 65 of 78 (83%) DLB patients who underwent sleep medicine consultations. Another study evaluated whether some clinical aspects of fluctuations could distinguish DLB from AD and found that 50 of 70 (72%) DLB patients reported symptoms suggestive of RBD.

We have identified 17 consecutive DLB patients with RBD confirmed by VPSG who were referred to our sleep center (unpublished data). Sixteen patients were male and the mean age of RBD onset was 65 years. In all instances RBD preceded the onset of cognitive complaints. Unpleasant dream recall was absent in 3 (17.6%) patients and 10 (58.8%) were unaware of their nocturnal behaviors. Postmortem neuropathological examination in three patients confirmed the diagnosis of DLB. On the other hand, 12 other patients diagnosed with IRBD in our center have subsequently developed DLB after several years of close clinical follow-up. Postmortem examination in one of them confirmed the diagnosis of DLB. Furthermore, 15 additional patients diagnosed with IRBD in our center have developed mild cognitive impairment that was mainly characterized by the same neuropsychological pattern seen in DLB. It is our experience in some IRBD patients that cognitive and motor symptoms may appear in tandem or separated just by a few months.

RBD as a diagnostic feature of DLB

Established in 2005, current consensus criteria for DLB state that diagnosis of probable DLB can be made in subjects with dementia plus RBD and at least one of the three core features (parkinsonism, visual hallucinations and fluctuations). The diagnosis of possible DLB can be established in a patient with dementia plus RBD in the absence of any of the three core features. The current criteria consider RBD as a suggestive feature of the disease because “it has been demonstrated to be more frequent in DLB than in other dementing disorders.” This statement is based on a single retrospective study published in 1998 involving 37 consecutive patients with dementia plus RBD. Thirty-four of these patients (92%) were male. In 35 (96%) RBD symptoms preceded or occurred simultaneously with the cognitive complaints. Of the 37 patients, 23 fulfilled the 1996-consensus criteria for probable DLB (dementia...
plus at least two of the following: parkinsonism, visual hallucinations and fluctuations), and all fulfilled criteria for possible DLB (dementia plus one of the following: parkinsonism, visual hallucinations and fluctuations). The diagnosis of DLB was confirmed in the three patients that underwent autopsy and supported the contention that the combination of dementia and RBD most often reflects DLB. The same group of authors observed that when patients with dementia plus RBD are compared with a group of patients with neuropathological confirmed AD, neurocognitive testing shows poorer performance in visuospatial abilities, attention and letter fluency. This neurocognitive profile is found in autopsy proven DLB patients and subjects with PDD. Taken together, the clinical combination of dementia and RBD indicates underlying Lewy body disease, namely DLB and PDD. This is in agreement with neuropathological studies in patients with autopsies demonstrating the occurrence of DLB plus RBD showing cell loss and Lewy bodies in the brainstem (locus ceruleus and substantia nigra), limbic system (amygdala and enthorinal) and neocortex.

RBD in Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia and is characterized by tau deposits, amyloid plaques and neurofibrillary tangles in the hippocampus, limbic system and cortex. Only one study has evaluated the occurrence of RBD in AD using PSG. In this study, 15 patients with mild to moderate dementia underwent VPSG. None of the patients had a clinical history of RBD. One patient had increased submental tonic electromyographic in REM sleep and abnormal behaviors, supporting the diagnosis of subclinical RBD. Three patients had REM sleep with increased muscle tone but without abnormal behaviors on PSG. The finding that neuronal damage in the brainstem is less prominent may explain why RBD is not frequent in patients with AD.

RBD in progressive supranuclear palsy and related disorders

Progressive supranuclear palsy is a tauopathy involving the brainstem, basal ganglia, and many other brain areas. It is characterized by dementia, poor levodopa responsive parkinsonism, vertical gaze palsy and falls. The first reported case of RBD linked to progressive supranuclear palsy was a 70-year-old woman presenting with inhibition of speech during wakefulness and intelligible somniloquy at night due to RBD. Parkinsonism developed one year before the onset of RBD. In a series of 15 progressive supranuclear palsy patients who underwent PSG, 2 had clinical RBD and 4 exhibited REM sleep with increased tonic electromyographic activity. Clinical manifestations of RBD were severe in one patient, but none of the patients were aware of their abnormal sleep behaviors (Isabelle Arnulf, personal communication). In a recent study, 7 of 20 (35%) patients had clinical RBD. In our sleep center, we have identified five progressive supranuclear palsy patients with RBD confirmed by PSG (unpublished data).

Guadeloupean parkinsonism is a progressive supranuclear palsy-like syndrome related to the ingestion of a toxic ingredient found in a tropical plant called sor sor. Pathology reveals tau protein deposits in the brainstem and basal ganglia. One study involving 9 patients undergoing VPSG showed that seven (78%) had RBD. These patients were five men and two women, and in three (43%) RBD antedated parkinsonism onset. Intensity of RBD was severe. All seven patients recalled nightmares and were aware of their abnormal behaviors (Isabelle Arnulf, personal communication).

The finding that RBD may be found in two taupathies such as progressive supranuclear palsy and Guadeloupean parkinsonism argues against RBD as an exclusive feature of the synucleinopathies (MSA, PD and DLB).

RBD in Huntington disease

Huntington disease is a genetic neurological disorder characterized by progressive dementia, chorea and psychiatric disturbances linked to expanded CAG repeats in the Huntington gene. Pathological studies demonstrate severe atrophy of the putamen and caudate, and, to a lesser extent, of the cortex. In one study, three of 25 (12%) patients had VPSG confirmed RBD. Two were aware of their abnormal behaviors at night, but these behaviors were considered clinically mild (Isabelle Arnulf, personal communication).

RBD in spinocerebellar ataxias

Spinocerebellar ataxias are inherited neurodegenerative disorders that result from mutations in different genes. These diseases affect the spinocerebellar tracts, cerebellum, brainstem and many other structures in the brain. They are clinically characterized by progressive ataxia and a wide variety of other neurological symptoms and signs such as polyneuropathy and parkinsonism. Spinocebellar ataxia type 3 (Machado Joseph disease) is an autosomal dominant disorder linked to CAG-trinucleotide repeat expansions in the axtin–3 gene. It is characterized by progressive cerebellar syndrome associated with ophthalmoplegia and extrapyramidal signs. Neurodegeneration involves the cerebellum, spinocebellar tracts and brainstem. One study described the presence of symptoms suggestive of RBD in 12 of 22 (56%) patients but VPSG was not performed. Another study reported RBD confirmed by PSG in a 61-year-old man. Duration of the cerebellar syndrome was 40 years and RBD duration was one year, consisting of at least five dream–enactment episodes that resulted in falling out of bed. We described the presence of VPSG confirmed RBD in 5 of 9 (55%) patients, 4 men and 1 woman, with a mean age of 48 years and a mean ataxia duration of 14 years. In two patients RBD preceded the ataxia onset by 10 and 8 years. After this publication from our group we have identified another three spinocerebellar ataxia type 3 patients with RBD. RBD has also been described in spinocerebellar ataxia type 1, type 2142,143 and type 8 (personal observation). We saw a 22-year-old man with Friedreich ataxia and severe RBD where VPSG showed abnormal behaviors that mainly affected the head and trunk in REM sleep (personal observation).

The pathophysiology of RBD

The finding that RBD is frequent in subjects with MSA, PD and DLB led to the speculation that the pathogenesis of this parasomnia could be linked to synuclein pathology or dopamine deficiency alone. There are several questions that need to be answered regarding the pathophysiology of RBD.

Does alpha-synuclein pathology cause RBD?

Alpha-synuclein is a normal brain protein that is thought to be involved in synaptic vesicle transport. Diseases characterized by abnormal alpha-synuclein aggregates in the nervous system include MSA, PD, DLB and pure autonomic failure, which are sometimes termed synucleinopathies. Gliarial cytoplasmic inclusions of abnormal alpha-synuclein are the characteristic pathological finding in MSA. Lewy bodies are not found in MSA. The
main component of Lewy bodies, the histological hallmark of DLB and PD, is alpha-synuclein. The histological hallmark of DLB and PD, is alpha-synuclein. It has been speculated that RBD is linked to accumulation of alpha-synuclein aggregates. This conclusion is based on the following observations. First, Lewy bodies were found in the autopsied brains of the two published IRBD patients with no clinical evidence of a neurodegenerative disease. Second, pathology in RBD subjects with comorbid parkinsonism and/or dementia demonstrates widespread Lewy bodies in the brain. Third, RBD is very frequent in those neurodegenerative disorders characterized by deposition of alpha-synuclein, such as MSA, PD and DLB. Conversely, RBD is not described, absent or uncommon in several neurodegenerative disorders lacking alpha-synuclein inclusions including pallido-ponto-nigral degeneration, AD, frontotemporal dementia, corticobasal degeneration, Wilson disease and amyotrophic lateral sclerosis.

Available data, though, indicate that RBD in the setting of a neurodegenerative disease is not an exclusive finding of a synucleinopathy. RBD occurs in several disorders involving intracellular accumulation of other abnormal proteins such as ataxins, parkin and tau. RBD has been found in disorders in which synuclein pathology is generally lacking such as spinocerebellar ataxias, parkinsonism with Parkin mutations, progressive supranuclear palsy, Guadeloupean parkinsonism and Huntington disease. Conversely, RBD is uncommon in patients with pure autonomic failure, a disorder where Lewy bodies are found in the central and autonomic nervous systems. Taken together, we believe that there is no strong evidence indicating that RBD is caused by the abnormal deposition of a single protein like alpha-synuclein. Moreover, it is unclear whether Lewy bodies are a toxic aggregation contributing to neuronal death or have a neuroprotective role.

Does nigrostriatal dopaminergic deficiency play a central role in RBD?

It has been hypothesized that dysfunction of the dopaminergic nigrostriatal system plays an important role in the pathogenesis of RBD. It occurs frequently in MSA, PD, and DLB, three neurodegenerative diseases where substantia nigra neuronal loss is prominent. There are published reports of a few patients who experienced subjective improvement of RBD symptoms after the administration of dopaminergic agents. A unique episode of RBD was triggered during PD surgery after unilateral microlesion in or near the substantia nigra pars compacta. A PET study showed that in MSA patients with RBD the tonic electromyographic activity during REM sleep is correlated to decreased nigrostriatal dopamine projections. In some patients with IRBD, FP-CIT-SPECT (1-N-fluoropropyl-2β-carbomethoxy-3β-iodo-phenyl-nortophrane single photon emission computed tomography) shows reduced striatal dopamine transporters. However, this observation may alternatively represent a comorbid finding and not the primary pathogenic determinant of RBD, as subjects with IRBD frequently develop a neurodegenerative disorder associated with substantia nigra cell loss (e.g., MSA, PD and DLB). In PD, parkinsonism only manifests when the substantia nigra pars compacta reaches a 60–70% of cell loss. Thus, it is possible that FP-CIT-SPECT in IRBD is detecting subjects close to 60–70% substantia nigra neuronal loss at a high risk for developing parkinsonism, rather than explaining the pathophysiology of RBD. Moreover, dopamine transporter FP-CIT-SPECT is abnormal in idiopathic PD regardless of the presence or absence of RBD.

Besides, there are many lines of evidence suggesting that dopaminergic deficiency is not directly responsible for RBD pathogenesis:

1) RBD or REM sleep without atonia does not occur in about half of the PD patients.
2) In some PD patients with RBD, the paranoidia onset clearly antedates the onset of parkinsonism.
3) Total levodopa equivalent dose and the use of dopamine agonists are not different between PD patients with and without RBD.
4) In PD patients with RBD, total levodopa equivalent dose is not associated with measures of RBD severity, such as submental tonic electromyographic percentage, submental and limb phasic electromyographic percentage, self-reported severity of the RBD symptoms, and severity of the behaviors detected on VPSG.
5) The use of dopaminergic agents usually does not improve RBD.

In PD, pramipexole, a dopamine agonist, does not improve RBD symptoms and VPSG RBD-related measures. Dopaminergic agents in subjects with IRBD and RBD secondary to PD increase the tonic electromyographic activity during REM sleep. Moreover, in some PD patients, RBD onset was temporarily associated with the initiation of levodopa dopamine agonists, and selegiline.

6) In PD, surgical techniques (e.g., deep brain subthalamic stimulation) do not ameliorate RBD while provide effective control of the parkinsonian dopaminergic motor symptoms. The use of dopaminergic agents usually does not improve RBD. In PD, pramipexole, a dopamine agonist, does not improve RBD symptoms and VPSG RBD-related measures. Dopaminergic agents in subjects with IRBD and RBD secondary to PD increase the tonic electromyographic activity during REM sleep. Moreover, in some PD patients, RBD onset was temporarily associated with the initiation of levodopa dopamine agonists, and selegiline.

7) Two conditions that respond to dopaminergic agents, restless legs syndrome and periodic leg movements in sleep, are not more common in PD patients with RBD than without RBD.
8) REM sleep without atonia and abnormal behaviors during REM sleep do not occur in the chronic MPTP-treated primate, an animal model of parkinsonism due to selective nigrostriatal deficiency (David Rye, personal communication).

9) Although not systematically studied, there are neither published reports of RBD precipitated by antipsychotic drugs blocking dopaminergic receptors nor descriptions of RBD occurring in subjects with drug-induced parkinsonism.

Based on the available data, we think that dopamine does not play a central role in the pathogenesis of RBD even though dopaminergic mechanisms may have some role in the modulation of REM sleep. The neural mechanisms generating and regulating REM sleep are complex and only partially known. Recent studies suggest that GABAergic and glutamatergic systems may be directly involved in the physiology of REM sleep onset, maintenance and atonia. It is not ameliorate RBD while provide effective control of the parkinsonian dopaminergic motor symptoms. The use of dopaminergic agents usually does not improve RBD. In PD, pramipexole, a dopamine agonist, does not improve RBD symptoms and VPSG RBD-related measures.

The mechanisms causing muscle atonia during REM sleep are complex. It has long been believed that muscle suppression in REM sleep is ultimately modulated by glycinergic inhibition of the motoneurons in the ventral horn of the spinal cord and in the cranial nerve nuclei. A recent provocative study in rats showed that blockade of glycinergic and GABAergic transmission at the trigeminal nucleus did not prevent or reverse REM sleep atonia in the masseter muscle. The authors of this study suggested that the mechanism mediating REM sleep atonia required reevaluation in order to find an unknown non-glycinergic biochemical link to the pathway.
substrate. This controversial study led to strong criticisms due to limitations of the techniques that were employed (lack of intracellular data, continuous drug delivery for 2–4 h, low concentrations of the substances that were delivered, possible diffusion of drugs in other surrounding nuclei in the brainstem, and the neural diversity and complexity of the trigeminal nucleus). These criticisms were elegantly defended by the authors. Other experts in the field have been less poignant stating that “is needed an open view of a number of simultaneous possibilities that can cause atonia and not a single holy grail” (e.g., glycine). The debate is still open.

**What does anatomy tell us?**

REM sleep is a complex state characterized by rapid eye movements, striated muscle atonia and desynchronized electroencephalographic activity. Dreams with emotional content occur predominantly in REM sleep. The precise anatomic network and biochemical mechanisms of REM sleep are still unclear. A large number of anatomic structures, however, are known to be directly or indirectly implicated in the generation of REM sleep. These structures include the magnocellularis reticular nucleus, locus subcereuleus, locus ceruleus, dorsal raphe, pedunculopontine nucleus, lateral dorsal tegmentum, periaqueductal grey matter, lateral pontine tegmentum, substantia nigra, hypothalamus, thalamus, amygdala, striatum, subthalamus, basal forebrain and neocortex.

Although initially it was thought that the central mechanisms regulating REM sleep were cholinergic and monoaminergic in nature, recent evidence indicates that the system responsible for REM sleep is more complex, involving critical GABAergic and glutamatergic neurotransmission. Recent studies in rodents suggest that REM sleep is mainly generated by GABAergic and non-GABAergic projections to the locus subcereuleus in the brainstem, which then project through direct and indirect glutamatergic pathways to the cortex, thalamus, basal forebrain, amygdala, ventromedial medulla and spinal cord. The pontine tegmentum and medial medulla are critical areas for muscle atonia generation in REM sleep. In animals, experimental lesions in the dorsolateral pontine tegmentum eliminate muscle atonia and induce abnormal behaviors during REM sleep. The site and extent of the lesions in the pons determine the severity of the behaviors that the animal releases, ranging from prominent limb twitches to locomotion and attack behaviors. Selective experimental lesions in the ventromedial medulla also produce REM sleep without atonia associated with abnormal behaviors. On the other hand, the amygdala is connected with the brainstem nuclei that regulate muscle tone and probably modulates the emotional component of dreams occurring in REM sleep. Cats with unilateral damage to the central nucleus of the amygdala preceded by bilateral pontine lesions exhibit attack behaviors associated with increased electroencephalography activity during REM sleep. Also, cats with brainstem lesions and normal limbic system exhibit REM sleep without atonia and abnormal behaviors. It should be noted that results in animals may depend on the species studied (rodents, felines, dogs, non human primates and humans).

In humans, RBD can be caused by a structural unilateral or bilateral focal lesion (e.g., stroke, tumor, demyelinating plaque) confined to the brainstem. Also, RBD can be produced by direct damage of those supratentorial structures anatomically connected with the brainstem nuclei modulating REM sleep. For example, RBD has been described in neurological disorders sparing the brainstem but damaging either the limbic system (limbic encephalitis associated with antibodies to voltage-gated potassium channels) or posterior hypothalamus (narcolepsy). In these disorders, RBD is probably caused by functional dysregulation of the brainstem REM sleep related structures rather than by their primary damage. Narcolepsy is believed to be an autoimmune disorder which is characterized by loss of hypocretin-producing neurons in the posterior hypothalamus. The occurrence of RBD in narcolepsy may be explained by hypocretin deficiency since hypocretin neurons have wide projections to several brainstem nuclei which regulate REM sleep atonia.

In neurodegenerative diseases where RBD is frequent, such as MSA, PD and DLB, pathological changes are common in the

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**Fig. 6.** Patient with idiopathic RBD who 5 years later developed PD that was confirmed at autopsy. While the patient is talking and waving his arms against an imaginary offender, there is excessive tonic and phasic electromyographic activity first in the chin and upper limbs spreading to the lower limbs. Movement artifacts are seen in the EEG leads, EKG and respiratory bands. Without looking at the video it is very difficult to distinguish here if the patient is awake or asleep. EOG: electrooculogram. C3, C4, O1, O2: electrode positions according to the 10/20 International system, referenced to combined ears (Ac). Chin: electromyography of the mentalis muscle. L and R Bic: electromyography of the left and right biceps brachii. L and R TA: electromyography of the left and right tibialis anterior. Nasal: nasal air flow. Oral: oral air flow. Thor: thoracic respiratory movements. Abd: abdominal respiratory movements. EKG: electrocardiogram.
brainstem structures modulating REM sleep (e.g., locus sub-
cereus, pedunculopontine nucleus, gigantocellularis reticular
nucleus) and amygdala.191,188–189 In contrast, full-blown expression
of RBD is uncommon in diseases associated with widespread
brainstem cell loss and little limbic system damage, such as
progressive supranuclear palsy.132 as well as in diseases with no
marked brainstem cell loss (e.g., AD).128 It is tempting to speculate
that in RBD motor behaviors reflect brainstem impairment while
RBD frightening dreams reflect amygdalar dysfunction. Cortical
areas may also be involved in the pathogenesis of RBD, since
patients sometimes display purposeful long motor elaborated and
complex behaviors, sing, and give long speeches 36 (Fig. 6).
However, these elaborated behaviors may alternatively represent
a dissociated sleep/wake phenomena rather than REM sleep with
increased motor and vocal activity.130 Taken together, we think that
RBD is the result of a dysfunction in the brainstem nuclei that
modulate REM sleep and their anatomical inputs from other
regions.

**Does the Braak et al. ascending hypothesis for Parkinson’s disease fit with the time of appearance of RBD?**

Braak et al.191,192 postulated that in sporadic PD, Lewy pathology
(Lewy bodies and Lewy neurites) begins in the dorsal motor nucleus
of the vagus nerve in the medulla (stage 1) and advances
upwards through the magnocellularis reticular nucleus and the
subcereus-cereus complex (stage 2), the substantia nigra, the
pedunculopontine nucleus and the amygdala (stage 3), the
temporal mesocortex (stage 4), and finally reaches the neocortex
(stages 5 and 6). Braak et al. suggested that stages 1 and 2 correspond
to a pre-parkinsonian motor state of PD, stages 3 and 4 to the
development of parkinsonism, and stages 5 and 6 to parkinsonism
associated with cognitive impairment.191,192 This temporal sequence
of Lewy pathology in PD may account for the finding that in some
patients RBD (stage 2) antedates the onset of parkinsonism (stage
3). Seven to nine years after RBD onset in PD, corticotectal
projections, dopaminergic projections from the substantia nigra
to the pedunculopontine nucleus and the amygdala (stage 3), the
ceruleus, reticular formation and dorsal vagal nucleus)199 This stage
system does not fit with the common observation that RBD precedes dementia in DBL.

A grading system similar to that for PD has not been proposed in
MSA yet. Grading neuropathology on MSA is currently based in the
presence of neuropathological changes in the nigrostriatal and
olivopontocerebellar systems. The state of the brainstem and limbic
structures that modulate REM sleep is not evaluated in the current
proposed morphological MSA grading system.200

In summary, based on the available evidence we think that RBD
when occurring in neurodegenerative diseases is probably
explained by regional distribution and severity of neuronal
dysfunction in the brainstem structures that regulate REM sleep
and their anatomic connections. Subjects without RBD are probably
those in whom neuronal dysfunction does not occur in these
regions or in whom the threshold for clinical symptomatology is
not exceeded. RBD is not mediated by either abnormal alpha-syn-
uclein inclusions or striatonigral dopaminergic deficiency alone.
The Braak et al. staging system in sporadic PD only fits with the
observation of RBD preceding parkinsonism.

**Practice points**

1. A significant proportion of patients (8–35%) with RBD is
not aware of having dream-enacting behaviors.
2. A significant proportion of patients (50–75%) with RBD
do not recall unpleasant dreams.
3. Clinical history with the bed partner is essential to
suspect RBD.
4. Videopolysomnography is needed to confirm the diag-
osis of RBD and exclude other conditions presenting with
similar symptoms.
5. Clinical follow-up of patients with the idiopathic form of
RBD is necessary for early detection of the development of
multiple system atrophy, Parkinson’s disease and
dementia with Lewy bodies.
6. RBD is frequent in the setting of multiple system atrophy
(90–100%), Parkinson’s disease (46–58%) and dementia
with Lewy bodies (approximately 70%).
7. In a patient with parkinsonism or cerebellar syndrome
the absence of RBD confirmed by VPSG argues against
multiple system atrophy
8. RBD is rare in patients with Alzheimer’s disease.
9. In a patient with dementia the presence of RBD supports
the diagnosis of dementia with Lewy bodies against
Alzheimer disease and other forms of cognitive
impairment.
10. Clinical symptoms of RBD may be mild, moderate or
severe. When needed, clonazepam is effective to treat
RBD symptoms. Melatonin may also be effective.

**Research agenda**

1. To find biomarkers for identifying those patients with
idiopathic RBD who are at a high risk for developing the
characteristic motor, autonomic and cognitive symp-
томs of multiple system atrophy, Parkinson’s disease
and dementia with Lewy bodies.
2. To evaluate the effect of neuroprotective strategies in
patients with idiopathic RBD.
3. To find effective drugs for treating RBD symptoms when
clonazepam fails or causes side effects.
4. To elucidate the precise physiopathology of RBD.
References


The most important references are denoted by an asterisk.
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