Rapid-eye-movement sleep behaviour disorder and neurodegenerative diseases

Jean-François Gagnon, Ronald B Postuma, Stéphanie Mazza, Julien Doyon, Jacques Montplaisir

Rapid-eye-movement (REM) sleep behaviour disorder (RBD) is characterised by loss of muscular atonia and prominent motor behaviours during REM sleep. RBD can cause sleep disruption and severe injuries for the patient or bed partner. The disorder is strongly associated with neurodegenerative diseases, such as multiple-system atrophy, Parkinson’s disease, dementia with Lewy bodies, and progressive supranuclear palsy. In many cases, the symptoms of RBD precede other symptoms of these neurodegenerative disorders by several years. Furthermore, several recent studies have shown that RBD is associated with abnormalities of electroencephalographic activity, cerebral blood flow, and cognitive, perceptual, and autonomic functions. RBD might be a stage in the development of neurodegenerative disorders and increased awareness of this could lead to substantial advances in knowledge of mechanisms, diagnosis, and treatment of neurodegenerative disorders.

Clinical description

Rapid-eye-movement (REM) sleep behaviour disorder (RBD) is classified as a parasomnia—i.e., a disorder in which undesirable physical events are predominant during sleep. RBD is characterised by abnormal and often violent behaviour when dreaming. Abnormal behaviour can be classified as simple (laughing, talking, shouting, and excessive jerking of body and limbs) or complex (swearing, gesturing, reaching, grabbing, arm flailing, slapping, punching, kicking, sitting up, leaping from bed, crawling, and running). Patients with RBD have a high proportion of aggressive content in their dreams, despite normal levels of daytime aggressiveness. Violent behaviour can result in sleep disruption and severe injuries, including ecchymoses, lacerations, and fractures for the patient or bed partner. Sleep-related injury was the reason for medical consultation in more than 75% of patients. RBD generally affects adults aged 50 years or above. RBD is predominantly reported in men; in two large cohorts of patients with RBD, more than 85% were men. The difference in sex might have a biological basis: it could be related to the role of sex hormones in the mediation of aggressive behaviour, or RBD might be less aggressive in women than in men and therefore less likely to lead to medical consultation.

Idiopathic versus secondary RBD

RBD can present alone—without concomitant medical disorders—and this is known as “idiopathic”. RBD is commonly reported in patients with neurodegenerative disorders, especially Parkinson’s disease, multiple-system atrophy, and dementia with Lewy bodies, and there is growing evidence linking idiopathic RBD and early signs of these disorders. Therefore, RBD associated with these neurodegenerative disorders should be considered as part of the disease. However, manifestations of RBD have been sporadically reported in a few cases of other neurological disorders such as Machado-Joseph disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, and Guillain-Barré syndrome, as well as in neurodevelopmental disorders such as autism. RBD is also commonly reported in narcolepsy, although this association has never been systematically studied. Patients with narcolepsy and RBD have several similarities such as increased periodic leg movements in sleep and both disorders are associated with REM sleep dysregulation—loss of REM sleep muscle atonia in RBD and inappropriate occurrence of atonia during wakefulness (cataplexy) in narcolepsy. Brain mechanisms responsible for RBD in narcolepsy are still unknown. Narcolepsy in human beings is characterised by hypocretin cell loss in the hypothalamus, a region that has strong connections with brainstem structures implicated in REM sleep and muscle atonia, especially the locus coeruleus. Decreased hypocretinergic input to these brainstem structures can contribute to RBD. In a recent study, five cases of RBD were reported in people with voltage-gated potassium channel antibody-associated limbic encephalitis. Resolution of RBD, concomitant to that of the limbic syndrome, has been reported after immunosuppressive treatment in three patients. The results of this study suggest a substantial contribution of the limbic system to the pathophysiology of RBD.

RBD can also occur during treatment with various psychotropic drugs (pharmacologically-induced RBD). For example, increased muscular activity during REM sleep has been reported in healthy people given tricyclic antidepressants or serotonin-specific or norepinephrine reuptake inhibitors such as fluoxetine, paroxetine, citalopram, sertraline, and venlafaxine. Antidepressants can also induce RBD manifestations in patients with parkinsonism, depression, or narcolepsy. These drugs increase serotonergic or noradrenergic neurotransmission in the CNS and these neurotransmitters have an inhibitory effect on the REM sleep mechanism; however, the exact mechanism by which they suppress REM sleep atonia and ease dream enactment behaviour is unknown. Further studies are needed to clarify this issue, as well as the possibility that antidepressants might...
ease symptoms in patients with RBD or those at risk of RBD, such as patients with Parkinson’s disease or narcolepsy.

RBD has been reported with noradrenergic antagonists (bisoprolol) and during withdrawal from alcohol. In this review, we focus on RBD associated with neurodegenerative disorders (synucleinopathies and tauopathies).

Polysomnographic features
One of the defining features of REM sleep is the suppression of muscular activity (or atonia), a characteristic that is not reported during wakefulness or other sleep stages. RBD is characterised by the presence of chin or limb electromyographic activity during REM sleep (figure) with concomitant vigorous behavioural manifestations as seen on videotape recording. Subclinical RBD refers to muscle activity and mild limb failing or yelping during REM sleep (seen on polysomnography) without complaints of abnormal motor behaviours during sleep. Another feature of RBD is REM sleep without atonia, this is characterised by polysomnographic evidence of muscular activity during REM sleep without a clinical history of abnormal sleep behaviour or presence of abnormal behavioural manifestations during sleep laboratory verification. The association between REM sleep without atonia and the development of RBD is unknown, and a longitudinal follow-up study of patients with REM sleep without atonia is needed.

Diagnostic criteria
REM sleep without atonia was first reported in patients with neurodegenerative disorders. Early reports also described REM sleep without atonia and behavioural manifestations during REM sleep with the use of tricyclic antidepressants or during alcohol withdrawal. RBD was recognised as a distinct clinical disorder by Schenck and colleagues in 1986. In 1990, RBD was incorporated into the International Classification of Sleep Disorders, and in 1997 minimal diagnostic criteria for RBD included the presence of limb or body movements associated with dream mentation, and at least one of the following criteria: harmful or potentially harmful sleep behaviour; dreams that seem to be “acted out”; sleep behaviour that disrupts sleep continuity. Polysomnographic features of RBD were not necessary for diagnosis; however, polysomnographic recording has important advantages. Polysomnographic criteria of RBD are more sensitive than clinical criteria. In addition, other sleep disorders can mimic RBD, such as obstructive sleep apnoea, sleepwalking, or night terrors. Therefore, it is important to note, with audiovisual recording, that behavioural symptoms occur specifically during REM sleep, and that other polysomnographic abnormalities, such as sleep-disordered breathing or epileptic activity, are absent. Finally, polysomnography is the only way to detect subclinical RBD and REM sleep without atonia. Therefore, in the latest version of the International Classification of Sleep Disorders, polysomnographic recording is mandatory for diagnosis of RBD (panel 1).

Prevalence of RBD
Few studies have looked at the prevalence of RBD in the general population. In one study, computerised, deductive telephone interviews of a representative sample of the general population (including patients with neurological disorders) of more than 4900 individuals age 15–100 years were done and the estimated prevalence of RBD was 0.5%. In another study in Hong Kong on a representative community sample of 1034 elderly people of age 70 years or above, everyone was interviewed with a screening question on the presence of sleep-related injuries and 0.8% reported a history of sleep-related injury. Those with suspected sleep disorders had physical and psychiatric assessment and a sleep recording; four people were confirmed to have RBD, giving an estimated prevalence of RBD of 0.38%. One of the four patients with RBD had Parkinson’s disease; two patients had been hospitalised previously for sleep-related injury but their sleep disorder had not been recognised. One conclusion of this study is that RBD in elderly people is under recognised.

Pathophysiology
Animal studies with electrophysiological, lesional, and neuropharmacological models have shown that the occurrence and maintenance of muscle atonia during REM sleep needs the interaction of several neuronal systems in the brainstem. These structures include the magnocellular, gigantocellular and paramedian nuclei, the locus coeruleus-subcoeruleus complex, the raphe nucleus, the pedunculopontine nucleus, and the nigrostriatal system. These brainstem structures show...
region can induce RBD. However, using proton magnetic-resonance spectroscopy, no abnormalities have been reported with regard to several metabolic measures (N-acetylaspartate, creatine, choline, and myo-inositol) in the brainstem of patients with RBD or Parkinson’s disease (with or without RBD).

Single-photon emission CT of patients with RBD have shown a reduction in striatal dopamine transporters and PET showed a reduced density of striatal dopaminergic terminals. Eisenbein and colleagues reported a continuum of reduction in striatal dopamine transporters on single-photon emission CT in patients with subclinical RBD, clinical RBD, and Parkinson’s disease. Gilman and colleagues also studied the correlation between REM sleep muscle atonia and density of striatal dopaminergic and thalamic cholinergic terminals in patients with RBD associated with multiple-system atrophy. A significant correlation was reported between REM sleep muscle atonia and striatal dopaminergic transmission, however thalamic cholinergic transmission was uncorrelated. However, whether dysfunction of the nigrostriatal dopaminergic system is the primary cause of RBD is unclear.

In summary, although many specifics are unknown, a dysfunction of one or several neuronal pathways in the brainstem (nigrostriatal dopaminergic neurons, noradrenergic or cholinergic neurons of the locus coeruleus or subcoeruleus complex, serotoninergic neurons of the raphe nucleus, cholinergic neurons of the pedunculopontine nucleus) probably causes the pathogenesis of RBD (panel 2).

**Treatment**

There are no randomised, double-blind, placebo-controlled studies that have assessed the efficacy of any treatment for RBD. Clonazepam (0.5–2 mg before bedtime), has been reported as highly effective in two large cohorts of patients with RBD and it is well tolerated in most cases. This drug suppresses behavioural symptoms and reduces phasic REM muscle activity in patients with RBD but does not restore REM-sleep muscle atonia. Side-effects include daytime somnolence, cognitive impairment, and aggravation of obstructive sleep apnoeas. However, about 10% of patients have no therapeutic response to clonazepam. Melatonin has also produced beneficial effects in patients with RBD. The use of cholinesterase inhibitors (donepezil and rivastigmine) and dopaminergic

---

**Panel 1: Diagnostic criteria for RBD according to the International Classification of Sleep Disorders**

- Presence of REM sleep without atonia: excessive amounts of sustained or intermittent elevation of submental electromyographic tone or excessive phasic submental or limb electromyographic twitching
- At least one of the following is present:
  1. History of sleep-related injurious, potentially injurious, or disruptive behaviours
  2. Abnormal REM-sleep behaviours documented during polysomnographic monitoring
- Absence of electroencephalographic epileptiform activity during REM sleep, unless RBD can be clearly distinguished from any concurrent REM-related seizure disorder
- The sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

**Panel 2: Brainstem structures with abnormalities in patients with RBD**

- Substantia nigra (nigrostriatal pathway)
- Locus coeruleus–subcoeruleus complex
- Pedunculopontine nucleus
- Dorsal vagus nucleus
- Dorsal raphe nucleus
- Gigantocellular reticular nucleus

---

**Review**

Review multiple system atrophy in six, and dementia with Lewy-body variant of Alzheimer’s disease in two, of brainstem nuclei were done, revealed pathological vagus nucleus, the gigantocellular reticular nucleus, and the substantia nigra. Abnormalities were less

abnormalities in all patients (such as neuronal loss, increased number of neurons, depigmentation, gliosis, or Lewy bodies) in the locus coeruleus–subcoeruleus complex and the substantia nigra. Abnormalities were less consistent or severe in the dorsal raphe nucleus, the dorsal vagus nucleus, the gigantocellular reticular nucleus, and the pedunculopontine nucleus.

In most patients with RBD, MRI studies have not revealed any abnormalities; however, ischaemic lesions in pontomesencephalic regions were reported in three patients. Three other reports have also suggested that tumour, ischaemic infarct, or surgery in the pontine
drugs for the treatment of RBD is still controversial. Although a few studies report beneficial effects of cholinergic drugs,78–81 other studies find no positive effects.78–81 One study of the dopaminergic agonist pramipexole found reduction in the frequency or intensity of sleep motor behaviour in patients with RBD and a reduction of simple behaviour during REM sleep in the laboratory,8 another study found no effect.89

In summary, except for clonazepam, most treatments have only been studied in small groups of patients and most studies have serious methodological restrictions, such as the absence of polysomnography to confirm treatment efficacy77–80 or RBD diagnosis.78–81 For these reasons, clonazepam is the treatment of choice for RBD but melatonin is an alternative for patients with cognitive impairment, daytime somnolence, or obstructive sleep apnoeas.

RBD and neurodegenerative disorders

RBD in synucleinopathies

RBD is associated with neurological disorders in 38–75% of cases.4,5,11 It is particularly common in neurodegenerative disorders characterised by intraneuronal deposition of α-synuclein (synucleinopathies),4 such as Parkinson’s disease, multiple-system atrophy, and dementia with Lewy bodies.

RBD in Parkinson’s disease

In the late 1960s, abnormal muscular activity during REM sleep was reported in patients with Parkinson’s disease.10,13,14 15–34% of patients with Parkinson’s disease have clinical symptoms of RBD.46 RBD diagnosed by polysomnography has been reported in 33% of patients (11/33) with Parkinson’s disease.4 In four cases, the patient or bed partner did not report abnormal motor behaviour during sleep; these cases are, therefore, subclinical RBD. REM sleep without atonia and no behavioural manifestations was reported in another eight patients (24%). Therefore, REM sleep without atonia occurred in 58% of patients with Parkinson’s disease. RBD has also been reported in patients with juvenile parkinsonism.8,30 The association between the first occurrence of RBD symptoms and those of Parkinson’s disease is variable; RBD symptoms can appear first, simultaneously, or after motor manifestations of Parkinson’s disease.7 The presence of RBD in patients with Parkinson’s disease is not related to the severity of the disease, the use of dopaminergic drugs, or the occurrence of dementia.7,8,30 However, RBD might be associated with an increased risk of hallucinations.86

RBD in multiple-system atrophy

In the 1970s, REM sleep without atonia was reported in patients with multiple-system atrophy7 and, since then, several studies have confirmed a strong association between these two disorders.18,51–53 RBD was detected with polysomnography in all patients with multiple-system atrophy.7 Why RBD is more common in multiple-system atrophy than in Parkinson’s disease is unclear. The distribution of neurodegeneration in multiple-system atrophy is usually more widespread than in Parkinson’s disease, and commonly includes severe atrophy of pontine structures that might be involved in REM-sleep muscle atonia. One study77 with six patients with pure autonomic failure—a form of synucleinopathy with clinical presentation similar to that of multiple-system atrophy—did not find RBD. However, a more recent study with three cases of pure autonomic failure revealed RBD in all patients,6 further supporting the view that RBD is associated with every type of synucleinopathy.

RBD in dementia with Lewy bodies

Although no study has systematically assessed the frequency of RBD in patients with dementia with Lewy bodies, a strong association between these two disorders has been reported.5,13,44,89 On the basis of these observations, RBD is now a suggestive criterion for dementia with Lewy bodies.6 For cases in which there is a diagnostic dilemma, sleep-laboratory investigation is highly recommended to confirm the presence of RBD in patients with dementia with Lewy bodies.

RBD in parkinsonism with parkin mutations

There have been cases of RBD in patients with parkinsonism associated with parkin gene mutations,87 a disorder originally thought to be devoid of α-synuclein degeneration. However, a recent study88 reported the presence of Lewy bodies in a large kindred with parkin mutations, reinforcing the association between RBD and synucleinopathies.

RBD in tauopathies

Neurodegenerative disorders called tauopathies, such as progressive supranuclear palsy, Alzheimer’s disease (also classified as an amyloidopathy), corticobasal degeneration, Pick’s disease, and pallidopontonigral degeneration, are characterised by intracellular inclusions of the protein tau in the affected neurons. Until recently, RBD had been considered to be rare in tauopathies.96 However, recent studies find RBD or REM sleep without atonia in a substantial number of patients with tauopathies and therefore the question of specificity of the RBD-synucleinopathy association arises.

RBD in progressive supranuclear palsy

Abnormal muscle activity during REM sleep in patients with progressive supranuclear palsy was first reported in the 1970s89 and, since then, several other cases have been described.1,3,11,40,89 A recent study showed the presence of REM sleep without atonia in four (27%) of 15 patients with probable progressive supranuclear palsy.92 Two of these patients had complex motor behaviours suggestive of RBD, but post-mortem histopathology was not available in either of the cases.
**RBD in Alzheimer’s disease**

One patient with autopsy-confirmed Alzheimer’s disease met the polysomnographic criteria and RBD was reported, but subsequent post-mortem analyses showed it to be the Lewy-body variant of Alzheimer’s disease. In a recent study of 14 patients with Alzheimer’s disease, there was one polysomnography-confirmed case of RBD and four cases of REM sleep without atonia. However, autopsy was not done on any of these patients and so the Lewy-body variant cannot be ruled out.

**RBD in corticobasal degeneration and Pick’s disease**

REM sleep without atonia was reported in four patients with probable corticobasal degeneration. After a follow-up of 1 year, complex motor behaviour during REM sleep consistent with RBD developed in one of these patients. However, no large-scale study has estimated the prevalence of RBD in corticobasal degeneration. To our knowledge, no cases of RBD have been reported in patients with Pick’s disease.

**RBD in pallidopontonigral degeneration**

Recently, 11 members of the pallidopontonigral degeneration kindred, irrespective of sleep-related complaint, were studied in the sleep laboratory and four had subsequent neuropathological examination. None of these individuals had polysomnographic or behavioural symptoms of RBD even though autopsies in three affected individuals revealed marked nigral degeneration and mild degenerative changes in the locus coeruleus and pontine nuclei.

There are large amounts of evidence that RBD is a common feature of synucleinopathies (table), especially in Parkinson’s disease, multiple system atrophy, and dementia with Lewy bodies. Clinical or polysomnographic manifestations of RBD are rare in other neurodegenerative disorders, such as tauopathies, and there are no published cases of RBD associated with a tauopathy without Lewy bodies found at autopsy. Overall, these observations suggest that RBD is most probably associated with synucleinopathy degeneration. However, tauopathies commonly affect lower brainstem structures and therefore are more likely to produce RBD.

**RBD as an early stage in the development of neurodegenerative disorders**

RBD commonly precedes, by several years, the first symptoms of neurodegenerative disorders. Olson and colleagues reported that RBD symptoms preceded those of Parkinson’s disease in 13 (52%) of 25 patients by a median of 3 years (range 1–30 years). Schenck and colleagues found that a parkinsonian syndrome developed in 11 (38%) of 29 patients initially diagnosed with RBD after 5 years of follow-up. 7 years later, results showed that 19 (65%) patients of the same cohort had developed a parkinsonian syndrome.

A potential explanation for these results comes from studies of pathological progression of Parkinson’s disease. Braak and colleagues have described six stages of the pathological process in Parkinson’s disease. During stages one and two, at a time in which motor symptoms are absent, Lewy bodies and Lewy neurites are found in the dorsal motor nucleus of the vagal nerve, the olfactory bulb or anterior olfactory nucleus, the lower raphe nuclei, the gigantocellular reticular nucleus, and the coeruleus–subcoeruleus complex. Several of these regions can probably be implicated in the pathophysiology of RBD.

The hypothesis that RBD is an early manifestation of a neurodegenerative disorder has been supported by studies showing neurobiological deficits in patients with RBD without concomitant medical disorders similar to those found in multiple-system atrophy, dementia with Lewy bodies and, particularly, Parkinson’s disease.

**Electroencephalographic abnormalities**

Slow waking electroencephalographic activity can indicate risk of cognitive impairment. Slow waking electroencephalographic activity in patients with RBD is characterised by high theta power in frontal, temporal, and occipital brain areas. Similar electroencephalographic changes have been reported in patients with Parkinson’s disease and dementia with Lewy bodies. One study reported that in patients with Parkinson’s disease without evidence of dementia, only those with a concomitant RBD have slowing of waking electroencephalographic activity (high theta power in frontal, temporal, parietal, and occipital brain regions). Another study also reported slow electroencephalographic activity during slow-wave sleep (higher delta power) in RBD. The functional implication of these findings will need to be further elucidated.

**Cerebral-blood-flow impairments**

As mentioned previously, neuroimaging studies with single-photon emission CT and PET have showed nigrostriatal dopaminergic dysfunction in RBD. Single-
photon emission PET has shown reductions of cerebral blood flow in the frontal cortex andpons of patients with RBD.121,122 These patterns of cerebral blood flow abnormalities are relatively similar to those in patients with Parkinson’s disease.121,122

Cognitive deficits
Dysfunction of verbal and non-verbal learning and visuospatial constructional abilities has been reported in patients with RBD.111,123,124 Neuropsychological studies of patients with Parkinson’s disease, multiple system atrophy, and dementia with Lewy bodies also reveal a cognitive profile characterised by visuospatial constructional abnormalities, verbal and non-verbal learning impairments that predominantly affect the recognition process and executive dysfunctions.124–126 Deficits in executive function have been noted only in patients with Parkinson’s disease associated with RBD.127 However, this latter study had major methodological restrictions, such as the absence of a healthy control group for comparison and no polysomnography to confirm diagnosis of RBD.

Perceptual abnormalities
Recent studies have revealed abnormalities in olfactory identification and discrimination and decreased colour-vision discrimination in patients with RBD.125,126,127 Olfactory and colour discrimination impairment are highly correlated with subclinical motor abnormalities detected in RBD; this suggests that both disorders have the same underlying disease process.127 Similar olfactory dysfunction and abnormalities in colour vision have been previously described in patients with Parkinson disease, multiple system atrophy, and dementia with Lewy bodies.110,116–119 Olfactory dysfunction is an important risk factor for late development of Parkinson disease.117 The presence of these perceptual abnormalities in patients with RBD in the absence of clinical manifestations of parkinsonism further supports the hypothesis that RBD represents an early stage of a neurodegenerative process.

Autonomic dysfunction
Autonomic dysfunction is common in dementia with Lewy bodies, Parkinson’s disease, and widely present in multiple-system atrophy.107,118 In many cases, autonomic symptoms can precede the development of parkinsonism in these disorders. Autonomic dysfunction has also been reported during wakefulness in up to 64% of patients with RBD.128 Moreover, this study reported a reduction of tonic and phasic heart-rate variability during sleep. Reduced cardiac and electroencephalographic activation associated with periodic leg movements during sleep has also been reported in RBD.129 These results suggest a dysfunction of the autonomic system and of cortical reactivity to internal stimuli in RBD similar to those found in synucleinopathies.

Conclusions
Until recently, RBD had been thought to be a mere sleep disorder. However, findings reviewed here strongly support the hypothesis that RBD, except for pharmacologically induced forms, might be a pathological stage in the development of neurodegenerative disorders. Another important observation is that not all patients with RBD have early markers of neurodegenerative disorders. A longitudinal study of a large cohort of patients with RBD should identify which marker or combination of markers predict progression toward a neurodegenerative disorder. These findings might have significant clinical implications. For example, the development of neuroprotective therapy for neurodegenerative disorders is hampered by the fact that the neurodegenerative process is already well-established by the time a patient develops motor symptoms. Identification of patients before motor symptoms develop will increase the potential benefits of neuroprotective therapy. In addition, a systematic and regular neurological follow-up of patients with RBD is important to promptly identify and treat the symptoms of neurodegenerative disorders as they appear.

Contributors
J-FG designed and developed the framework of the review, did the literature search, and wrote the first draft. RBP, SM, JD, and JM made additions to the review and all authors approved the final version.

Conflicts of interest
We have no conflicts of interest.

Acknowledgments
The authors thank Dominique Petit and Tore Nielsen for critically reviewing the paper and the Canadian Institutes of Health Research (operating grant to JM and postdoctoral studentship to JFG) for financial support. JM holds a Canadian Government Chair on Sleep Disorders.

References
Review


7 Friedman HJ. Presumed rapid eye movement behavior disorder in Machado-Joseph disease [spinocerebellar ataxia type 3]. Mov Disord 2002; 17: 150–53.


21 Montplaisir J, Michaud M, Demeele R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. Sleep Med 2000; 1: 163–67.


110 Schenck CH, Bundlie SR, Mahowald MW. REM behavior disorder (RBD): delayed emergence of parkinsonism and/or dementia in 65% of older men initially diagnosed with idiopathic RBD, and an analysis of the minimum & maximum tonic and/or phasic electromyographic abnormalities found during REM sleep. Sleep 2003; 26: A116.


