Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by excessive muscle activity and undesirable motor events during REM sleep. RBD occurs in approximately 0.5% of the general population, with a higher prevalence in older men. RBD is a frequent feature of dementia with Lewy bodies (DLB), but is only rarely reported in Alzheimer’s disease. RBD is also a risk factor for α-synuclein-related diseases, such as DLB, Parkinson’s disease (PD), and multiple system atrophy. Therefore, RBD has major implications for the diagnosis and treatment of neurodegenerative disorders and for understanding specific neurodegeneration patterns. Several markers of neurodegeneration have been identified in RBD, including cognitive impairments such as deficits in attention, executive functions, learning capacities, and visuospatial abilities. Approximately 50% of RBD patients present mild cognitive impairment. Moreover, RBD is also associated with cognitive decline in PD.

Keywords: sleep, cognition, elderly, REM sleep behavior disorder, mild cognitive impairment, Parkinson’s disease, dementia with Lewy bodies

RBD SUBTYPES
There are different forms of RBD. The acute form is triggered by certain psychotropic drugs (pharmacology-induced RBD), such as antidepressants (Gagnon et al., 2006a). RBD is also strongly associated with certain neurological disorders (symptomatic RBD), including narcolepsy, Machado–Joseph disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, and Guillain–Barre syndrome (Gagnon et al., 2006b; Iranzo et al., 2009). Symptomatic RBD can also be induced by focal lesions (vascular or inflammatory), tumors, or neurodegenerative processes in brainstem regions responsible for normal REM sleep muscle atonia (Fontaine et al., 2006b; Iranzo et al., 2009; Limousin et al., 2009). In fact, RBD is very frequent in synucleinopathies, a class of neurodegenerative diseases characterized by abnormal deposition of α-synuclein proteins. For instance, RBD affects about 33–46% of patients with Parkinson’s disease (PD; Gagnon et al., 2002; Sixel-Döring et al., 2011), 75% of patients with dementia with Lewy bodies (DLB; Ferman et al., 2011), and almost 100% of patients with multiple system atrophy (MSA; Vetrugno et al., 2004). Synucleinopathies share a common brainstem neurodegeneration with RBD, which may explain their strong association. On the other hand, RBD is rare in tau-related diseases such as Alzheimer’s disease (AD), progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia (Gagnon et al., 2006b; Iranzo et al., 2009). RBD is therefore a useful feature to consider for differential diagnosis between DLB and AD. In fact, inclusion of RBD as a core clinical feature improves the DLB diagnosis accuracy (Ferman et al., 2011).
et al., 2011). Finally, RBD can appear alone (“idiopathic” RBD or iRBD) without any associated condition (Gagnon et al., 2006b; Iranzo et al., 2009). However, the term “idiopathic” is subject to challenge because iRBD may be a risk factor for synucleinopathies (Fantini et al., 2005; Ferini-Strambi, 2011).

**“IDIOPATHIC” RBD AS A RISK FACTOR FOR SYNUCLEINOPATHIES**

Three longitudinal studies performed in a sleep disorders center found that RBD is a significant risk factor for developing synucleinopathies. Schenck et al. (1996) reported in 29 iRBD patients that 38% had parkinsonism 3.7 years after RBD diagnosis. Another study in 44 iRBD patients found that 36% developed a synucleinopathy 5.1 years following RBD diagnosis (Iranzo et al., 2006). Of the converted patients, 56% developed PD, 38% DLB, and one patient developed MSA. Four additional patients with iRBD met the criteria for mild cognitive impairment (MCI) at follow-up. In 2009, our group published the follow-up results on a large cohort of 93 patients with iRBD: 28% developed a neurodegenerative disease 4.8 years following RBD diagnosis (Postuma et al., 2009a). Of the diseased patients, 54% developed PD, 42% DLB, and one patient developed MSA. Using a life table (survival) analysis, the risk for developing a synucleinopathy in iRBD patients was estimated at 18% after 5 years, 41% after 10 years, and 52% after 12 years (Postuma et al., 2009a).

In the only population-based study to date, Boot et al. (2012) followed 651 cognitively intact participants, including 44 individuals with baseline clinical iRBD. After a median of 3.8 years, only 2% of iRBD patients developed PD, whereas 32% met MCI criteria. Although the conversion rate was far lower than in previous clinical studies, the iRBD patients had a 2.2-fold increased risk of developing MCI or PD over non-RBD patients. A potential explanation for the link between RBD symptoms and the development of synucleinopathies comes from studies on the pathological progression of synucleinopathies (Braak et al., 2003; Halliday et al., 2011). In the first stages, before clinical motor symptoms appear, Lewy bodies and Lewy neuritis can be found in brainstem areas involved in RBD pathophysiology. The gradual progression of the neurodegeneration to more rostral brain structures would subsequently cause symptoms characteristic of synucleinopathies. This may explain why RBD is an early symptom in certain patients with synucleinopathies. These results show the importance of performing neuroological and neuropsychological assessments to detect early signs of a synucleinopathy or MCI in iRBD patients, particularly for those referred to a sleep disorders center.

**MARKERS OF NEURODEGENERATION IN “IDIOPATHIC” RBD**

Several markers of synucleinopathies have been identified in iRBD. Recent studies have reported that the severity of the loss of REM sleep muscle atonia (Postuma et al., 2010), olfaction and color vision impairments (Postuma et al., 2011a), substantia nigra hyperechogenicity, and decreased striatal dopamine transporters uptake (Iranzo et al., 2010a) can predict the development of synucleinopathies in iRBD (Postuma et al., 2011b). Other studies have found cognitive (Ferini-Strambi et al., 2004; Gagnon et al., 2009), sublethor (Postuma et al., 2009b), waking EEG (Fantini et al., 2003), autonomic (Miyamoto et al., 2006; Postuma et al., 2009b), and functional and structural neuroimaging (Unger et al., 2010; Hanyu et al., 2011; Scherlier et al., 2011; Vendette et al., 2011) anomalies in iRBD, similar to those reported in synucleinopathies (Gagnon et al., 2006b; Postuma et al., 2011b).

**COGNITIVE DECLINE IN RBD**

**POOR COGNITIVE PERFORMANCE IN “IDIOPATHIC” RBD**

Increasing evidence shows that iRBD patients perform poorly on neuropsychological tests (Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009; Marques et al., 2010; Fantini et al., 2011). However, results vary across studies depending on which cognitive domain is impaired (Table 1). Population heterogeneity, small sample size, and the use of different cognitive tasks with variable sensitivity to detect deficits and variable specificity to a cognitive domain may explain these discrepancies. In general, attention, executive functions, episodic verbal memory (mainly free recall capacities), and non-verbal learning are the most affected domains in iRBD (Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009; Marques et al., 2010; Fantini et al., 2011). Additionally, some studies reported in iRBD anomalies in visuospatial/visuo-perceptive abilities (Ferini-Strambi et al., 2004; Iranzo et al., 2010b; Marques et al., 2010; Fantini et al., 2011), but this remains controversial (Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009). In fact, the presence of visuospatial (or non-verbal) learning impairment appears to be related to the extent of cognitive decline in iRBD patients (Iranzo et al., 2006; Molano et al., 2010; Fantini et al., 2011), as reported in RBD-associated neurodegenerative diseases such as PD or DLB (Ferman et al., 2002; Gagnon et al., 2009). On the other hand, language and praxis appear to be well preserved in iRBD, although these functions have received little research attention.

**Table 1 | Controlled studies on cognitive performance in “idiopathic” rapid eye movement sleep behavior disorder.**

| Cognitive domains | Terzagli et al. (2008) | Massicotte-Marquez et al. (2008)a | Gagnon et al. (2009)a | Marques et al. (2010) | Ferini-Strambi et al. (2004)b | Fantini et al. (2011)b |
|-------------------|----------------------|---------------------------------|----------------------|----------------------|--------------------------|----------------------|
| Attention/executive functions | Yes | Yes | Yes | Yes | Yes | No |
| Verbal episodic memory | Yes | Yes | Yes | Yes | Yes | Yes |
| Non-verbal memory | Yes | – | – | – | Yes | Yes |
| Visuospatial abilities | No | No | No | Yes | Yes | Yes |

*a,b Share common participants; Yes = patients show poorer performance than controls (p < 0.05); No = similar performance between patients and controls.*
Box 1 | Case report.

Mister X is a 62-year-old man referred to a memory clinic for cognitive assessment. He complains about his reduced abilities to concentrate and recall information. The scan is normal. No vascular risk factors or major psychiatric symptoms are found. The neuropsychological exam shows mild deficits in cognitive tests assessing attention and episodic verbal memory (affected free recall capacities with preserved recognition). Daily life activities are reported as satisfactorily accomplished. Based on this clinical profile, Mister X meets the criteria for mild cognitive impairment. When questioned about his sleep, he reports the presence of violent behaviors associated with vivid dreams. His wife confirms this and reports that she sleeps in a separate bed to avoid potential injury. Mister X is referred to a sleep disorders center to confirm a diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD). The polysomnographic recording shows excessive chin muscle tone during REM sleep with no other anomalies. When these results are combined with the reports of dream-enactment behaviors, Mister X meets the RBD diagnosis criteria. Unfortunately, subsequent assessments at the memory clinic reveal cognitive decline, particularly in executive functions and visuospatial abilities. In addition, at the last visit, the patient reports a significant impact of the cognitive impairment on his daily life activities and shows signs of parkinsonism. The diagnosis of probable dementia with Lewy bodies is confirmed.

MCI IN “IDIOPATHIC” RBD

Mild cognitive impairment is known to be an intermediate state between normal cognitive functioning and dementia (Gauthier et al., 2006). MCI can be diagnosed according to the following criteria: (1) subjective cognitive complaint by the patient or a relative, (2) cognitive decline on neuropsychological testing compared to age- and education-equivalent individuals, and (3) preserved daily life activities (Gagnon et al., 2009; Albert et al., 2011). MCI can be subdivided into different subtypes according to the number (single-domain vs. multiple-domain) and nature (amnestic vs. non-amnestic) of the cognitive domains impaired (Petersen and Morris, 2005). MCI is a risk factor for dementia such as AD, DLB, or vascular dementia (Gauthier et al., 2006). However, the progression of MCI is also highly variable. Some MCI patients remain with mild cognitive deficits for many years whereas a substantial proportion return to normal cognitive functioning (Ganguli et al., 2004; Gauthier et al., 2006; Fischer et al., 2007). Moreover, several factors may disrupt cognition in elderly individuals, including psychiatric symptoms, medication side effects, respiratory conditions (sleep apneas, chronic obstructive pulmonary disease), and vascular diseases. Consequently, clinicians and researchers should be careful not to directly link MCI to the future development of a neurodegenerative disease or to consider MCI as part of a neurodegenerative disease.

Mild cognitive impairment is a frequent feature of iRBD (Iranzo et al., 2006; Gagnon et al., 2009; Molano et al., 2010). In iRBD patients referred to a sleep disorders center, MCI frequency was estimated at up to 50% compared to 8% in healthy subjects (Gagnon et al., 2009). The main MCI subtype reported was non-amnestic MCI single-domain with predominant attention and executive dysfunctions. No study to date has systematically followed seven iRBD patients for many years. All patients met MCI criteria and subsequently developed Lewy body disease, which was confirmed by autopsy. This suggests that iRBD patients with MCI are at higher risk for developing DLB.

CONCLUSION

Box 1 summarizes a case report of an individual referred to a memory clinic for cognitive decline and subsequently diagnosed with PD. This case shows the importance of identifying RBD in patients with cognitive impairment. A better understanding of this sleep disorder would enable a deeper grasp of the underlying pathophysiology and diagnosis of synucleinopathies, and would contribute to the development of neuroprotective treatments.

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