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Rapid Eye Movement Sleep Behavior Disorder and the Link to Alpha-Synucleinopathies

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Abstract

Rapid eye movement (REM) sleep behavior disorder (RBD) involves REM sleep without atonia in conjunction with a recurrent nocturnal dream enactment behavior, with vocalizations such as shouting and screaming, and motor behaviors such as punching and kicking. Secondary RBD is well described in association with neurological disorders including Parkinson's disease (PD), multiple system atrophy (MSA), and other conditions involving brainstem structures such as tumors. However, RBD alone is now considered to be a potential harbinger of later development of neurodegenerative disorders, in particular PD, MSA, dementia with Lewy bodies (DLB), and pure autonomic failure. These conditions are linked by their underpinning pathology of alpha-synuclein protein aggregation. In RBD, it is therefore important to recognize the potential risk for later development of an alpha-synucleinopathy, and to investigate for other potential causes such as medications. Other signs and symptoms have been described in RBD, such as orthostatic hypotension, or depression. While it is important to recognize these features to improve patient management, they may ultimately provide clinical clues that will lead to risk stratification for phenoconversion. A critical need is to improve our ability to counsel patients, particularly with regard to prognosis. The ability to identify who, of those with RBD, is at high risk for later neurodegenerative disorders will be paramount, and would in addition advance our understanding of the prodromal stages of the alpha-synucleinopathies. Moreover, recognition of at-risk individuals for neurodegenerative disorders may ultimately provide a platform for the testing of possible neuroprotective agents for these neurodegenerative disorders.

Keywords

REM sleep; REM behavior disorder; alpha-synucleinopathy

Introduction

Rapid eye movement (REM) sleep, which occupies approximately 20–25% of total sleep time, is a cyclical sleep state, occurring in intervals of 90–120 minutes during the night. Normally, during REM sleep, there is active inhibition of motor activity, which results in

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complete or near- complete muscle atonia. Atonia results from an interplay of multiple neurotransmitter systems, with a decrease in excitatory activity and increase in the inhibitory glycinergic and GABAergic premotor neuronal input to motor neurons.

However, the processes resulting in REM atonia can become disrupted, leading to REM sleep without atonia (RSWA)(Barone et al. 2015), which is a finding noted during an overnight polysomnogram (PSG) via abnormally increased electromyogram tone during REM sleep. REM sleep behavior disorder (RBD) is an abnormal condition consisting of RSWA in conjunction with a history of recurrent nocturnal dream enactment behavior.

The diagnosis of idiopathic RBD occurs when none of the conditions known to cause secondary RBD are present (see below), and when other conditions with possible abnormal nocturnal behaviors have been ruled out (obstructive sleep apnea or epilepsy, for example) (Iranzo and Santamaria 2005, Peever et al. 2014). Potential risk factors for RBD include smoking, head injury, pesticide exposure, and having worked as a farmer(Postuma et al. 2012).

The diagnosis of secondary RBD occurs when there is an associated condition preceding it and likely contributing to its etiology(Peever et al. 2014), the most important being the alpha-synucleinopathies (Table 1). These conditions, including Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB)(Gagnon et al. 2006, Manni et al. 2011), and pure autonomic failure (PAF)(Kaufmann et al. 2017) are so named because of the characteristic intracellular protein accumulation of alpha-synuclein, that may be visualized in a subset of synucleinopathies (for example PD and DLB) as Lewy bodies (Figure 1)(Postuma et al. 2009, Classen and Schnitzler 2010). It is unclear whether RBD is linked to the alpha-synucleinopathies via aggregated intracellular material, or through a common anatomic pathology(Ebben et al. 2012).

Of import is the fact that, in addition to secondary RBD occurring in the alpha-synucleinopathies, RBD can also precede the onset of alpha-synucleinopathy by decades(Iranzo et al. 2014). RBD is now therefore described as part of the "pre-motor" PD stage, and many individuals with RBD will develop PD(Iranzo et al. 2014, Visanji and Marras 2015). As a result, an underlying pathology that impacts both REM atonia and midbrain dopaminergic centers has been postulated(Chen et al. 2013). This idea aligns with earlier publications postulating a spread of alpha-synuclein pathology through brainstem and other regions that could explain sleep abnormalities preceding motor abnormalities on an anatomical basis, the "Braak hypothesis"(Braak et al. 2003). Research into RBD therefore would ideally improve our ability to counsel patients, particularly with regard to prognosis, and would advance our understanding of the prodromal stages of the alpha-synucleinopathies. Moreover, recognition of at-risk individuals for neurodegenerative disorders may ultimately provide a platform for the testing of possible neuroprotective agents for these neurodegenerative disorders.

In this review, we address the underlying physiology of REM sleep, the putative pathophysiology of RSWA and RBD, the conditions known to be associated with RBD,

including the alpha-synucleopathies, and the clinical factors that seem to herald the emergence of neurodegeneration in the context of RBD(Iranzo et al. 2016).

Rapid Eye Movement Sleep and Muscle Control

REM sleep, first described in 1953(Aserinsky and Kleitman 1953), consists of low voltage fast electroencephalographic (EEG) activity, rapid eye movements, and muscle atonia. REM sleep is informally known as “dream sleep” due to the finding that waking subjects from REM sleep results in reports of dreaming(Dement and Kleitman 1957). Initial experiments(Aserinsky and Kleitman 1953, Dement and Kleitman 1957, Jouvet 1962) demonstrated the characteristic features of EEG and electromyogram (EMG) parameters that have come to define REM sleep. Normal REM sleep has been demonstrated to include corticohippocampal activation similar to wakefulness in addition to atonia of the postural muscles to prevent movement(Chen et al. 2013).

Evidence supports a number of key structures within the brainstem, whose activity is precisely integrated to produce REM sleep (Figure 2). Proposed models of REM sleep physiology(Ng and Pavlova 2013) involve the laterodorsal tegmentum (LDT) and the pedunculopontine tegmentum (PPT), which reside in the pontomesencephalic junction of the brainstem and consist of two populations of cholinergic neurons(Mitani et al. 1988). There exist a group of neurons most active in REM sleep, and another group active in both REM sleep and wakefulness(Luebke et al. 1992, Leonard and Llinas 1994, McCarley et al. 1995). Via muscarinic and nicotinic acetylcholine receptors, connections from the LDT and PPT send excitatory signals to neurons in the pontine reticular formation (PRF) and mesencephalic reticular formation (MRF), which then result in producing the classic characteristics of REM sleep such as low voltage fast EEG activity, rapid eye movements, and muscle atonia(Ng and Pavlova 2013).

Muscle control in REM sleep is mostly based in the pons(Baghdoyan et al. 1984, Boissard et al. 2002, Lu et al. 2006), and has been reported under different names, including the pontine inhibitory area, subcoeruleus nucleus, nucleus reticularis pontis oralis (dorsal division), perilocus coeruleus alpha, and the sublaterodorsal tegmental nucleus (SLD)(Peever et al. 2014), the latter being the term used in this review.

The neurons of the SLD, most active during REM sleep(Siegel et al. 1991, Maloney et al. 1999, Boissard et al. 2002, Boissard et al. 2003, Lu et al. 2006), release glutamate(Clement et al. 2011) to trigger muscle atonia(Lai and Siegel 1988, Boissard et al. 2002). Experimentally produced small lesions of the SLD result in RSWA without affecting REM sleep amount, whereas larger lesions not only produce RSWA, but also affect the amount and duration of REM sleep(Boissard et al. 2002, Lu et al. 2006). Thus, as REM sleep architecture is generally unaffected in RBD, it is likely that there exists a smaller lesion of SLD neurons in this condition(Peever et al. 2014). SLD neurons send glutamatergic signals to the inhibitory glycinergic/GABAergic interneurons in layer VII of the spinal cord(Vetrivelan et al. 2009), and it has been proposed that these interneurons in turn antagonize excitatory inputs from the motor cortex and brainstem to motor neurons(Lu et al. 2006, Chen et al. 2013). REM atonia may also be achieved by SLD neurons activating

inhibitory circuits located in the ventromedial medulla (VMM)(Lai and Siegel 1988, Schenkel and Siegel 1989, Holmes et al. 1994). Neurons of the VMM are hypothesized to send glycinergic projections directly to spinal motor neurons(Hossaini et al. 2012) and activate GABA-and glycine-containing neurons in the ventral and alpha gigantocellular reticular nucleus, which would then inhibit skeletal motor neurons(Lai and Siegel 1988, Vetrivelan et al. 2009, Peever et al. 2014).

Studies suggest that excessive phasic movements in RBD may result, at least in part, from lack of normal input from GABA and glycine sources(Peever et al. 2014). Intracellular recording studies demonstrate that bursts of motor neuron excitation, resulting from glutamatergic inputs, leads to muscle twitches during REM sleep(Soja et al. 1995); blocking glutamate receptors prevents these twitches(Burgess et al. 2008). Additionally, GABA and glycine inputs normally inhibit REM muscle twitches(Brooks and Peever 2008), and pharmacological blockade of these inputs increases glutamate-induced motor twitches during REM sleep(Brooks and Peever 2008, Brooks and Peever 2012).

Since motor neurons receive both inhibitory and excitatory inputs during the phasic periods of REM sleep, the stronger input determines how they respond. In fact, during phasic periods, the postsynaptic inhibitory drives that control motor neuron activity during the tonic periods are actually enhanced(Chase and Morales 1982, Morales and Chase 1982, Chase and Morales 1983), but when excitatory inputs are more potent, rapid eye movements, and twitches/jerks of postural, masseter, digastric, hypoglossal, ocular, diaphragmatic, lingual and other muscles occurs(Chase 2013).

REM Sleep Behavior Disorder

RBD is a parasomnia consisting of RSWA in combination with a history of recurrent nocturnal dream enactment behavior(Schenck et al. 1986, Olson et al. 2000, Schenck and Mahowald 2002, Arnulf 2012). According to the International Classification of Sleep Disorders, 3rd edition (ICSD-3), the clinical diagnosis of RBD requires: 1) the presence of RSWA on overnight PSG and 2) either sleep-related injurious, potentially injurious, or disruptive behaviors by history, and/or abnormal REM sleep behavior documented during PSG monitoring(American Academy of Sleep Medicine 2014). Additionally, there must be an absence of epileptiform activity on electroencephalography during REM sleep, and the sleep disorder cannot be better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder (Figure 3).

While the neural circuitry involved in RBD has not yet been identified, researchers have proposed various regions, including the primary and premotor cortices, with input from the basal ganglia, or from brainstem or spinal cord motor generators(Grillner and Zangger 1979, Noga et al. 1988, Blumberg and Lucas 1994). Resultant muscle activity ranges from twitches to dream mentation-linked actions(Manni et al. 2009), possibly associated with violent, defensive nightmares(Olson et al. 2000).

The overall prevalence of RBD is not known, but has been estimated to be 0.4–0.5% in the general population(Ohayon et al. 1997), whereas up to 2% may be affected after the age of

60(Kang et al. 2013) and up to 6%, after the age of 70(Boot et al. 2012). While RBD is found predominantly in men, there may an under-diagnosis in women due to less violent REM sleep behaviors(Peever et al. 2014).

It is unknown if there is a truly genetic basis for RBD. However, a questionnaire-based study revealed a positive family history of dream enactment behaviors for RBD (14%) compared with controls (5%)(Dauvilliers et al. 2013). Additionally, an association has been reported between RBD and human leukocyte antigen (HLA) class II genes, one study demonstrating the presence of the DQwl (DQB1*05, 06) allele in 84% of Caucasian men with RDB were positive compared with 56% in the control group(Schenck et al. 1996).

Conditions Associated with RBD

It has been reported that roughly half of PD patients have RSWA or RBD(Gagnon et al. 2002, Iranzo et al. 2006, Sixel-Doring et al. 2011), and PD patients with comorbid RBD may present with more rapid motor progression and cognitive dysfunction. A recent study found alterations in the left and right cingulum and left and left inferior occipital fasciculus in PD patients with RBD, suggesting that these areas may serve as potential landmarks in understanding the brain changes that occur with PD(Rahmani et al. 2016). No difference in RBD prevalence was found between men and women with PD in another recent study, and women were noted to report significantly fewer aggressive behaviors during REM sleep(Bjornara et al. 2013). The presence of RBD is also considered to be supportive of the diagnosis of DLB(Boeve et al. 2007). Ferman et al followed 234 consecutive patients with dementia until autopsy, and patients with a history of RBD were 6 times more likely to have autopsy-confirmed DLB than other neurodegenerative dementia conditions(Ferman et al. 2011). Similarly, most patients with MSA exhibit RBD(Iranzo et al. 2005). One study of 42 MSA patients demonstrated that RBD is present in up to 88%, and was even present in some patients that reported no symptoms; in this cross-sectional analysis, more than half of MSA patients report symptoms of RBD before the onset of motor deficits(Palma et al. 2015).

Despite the recent focus on alpha-synucleinopthies, multiple other conditions have been reported in association with RBD (Table 2). Other degenerative diseases associated with RBD, such as Huntington’s disease, Alzheimer’s disease, corticobasal degeneration(Lo Coco et al. 2009), and amyotrophic lateral sclerosis(Ebben et al. 2012) have been reported. RSWA and RBD have also been reported in acute inflammatory demyelinating polyneuropathy (Guillain–Barré syndrome), and in several of these cases spontaneous complete remission occurred concomitantly with neurological recovery(Schenck et al. 1986, Cochen et al. 2005).

RBD has been demonstrated following focal neurological insults at the brainstem level, including those from ischemic(Culebras and Moore 1989, Kimura et al. 2000, Xi and Luning 2009) or hemorrhagic(Provini et al. 2004) strokes, brainstem tumors(Schenck and Mahowald 2002, Zambelis et al. 2002), demyelinating plaques(Plazzi and Montagna 2002, Tippmann-Peikert et al. 2006, Gomez-Choco et al. 2007), and inflammatory lesions(Limousin et al. 2009). In all of the observations listed, an area of the pons was damaged; for example, focal lesions of the SLD due to stroke or inflammation may produce

RBD(Iranzo and Aparicio 2009); and animal studies have demonstrated that unilateral lesions are sufficient(Zagrodzka et al. 1998, Boeve et al. 2007).

One case of acute RBD occurred immediately following implantation of an electrode into the subthalamic nucleus as a treatment for PD. It was hypothesized that a microlesion in or near the pars compacta of the substantia nigra was the direct cause of RBD, via the interruption of descending inputs to the pontine REM sleep regulatory regions. The authors also surmised that a substantia nigra lesion might have been responsible for the emergence of RBD, suggesting that basal ganglia circuits could potentially be involved in motor control during REM sleep(Piette et al. 2007).

Limbic encephalitis has been demonstrated as having an association with RBD(Iranzo et al. 2006, Compta et al. 2007, Lin et al. 2009, Manni et al. 2011), but as there has been a lack of detected brainstem involvement in the cases reported, the hypothesis of an involvement of the limbic system in the pathogenesis of RBD(Manni et al. 2011) has been raised. The limbic system is activated during normal REM sleep, resulting in the emotional content of dreams(Hobson and Pace-Schott 2002), and data from animal studies imply that the limbic system may play a role in the pathogenesis of RBD, especially the amygdala(Zagrodzka et al. 1998, Boeve et al. 2007).

There is one case with PSG assessment in the context of alcohol withdrawal reported in the literature, which demonstrated disruption of the sleep-wake cycle, and a state similar to RSWA directly arising from wakefulness. Chronic alcohol abuse is known to down-regulate GABA-ergic post-synaptic receptors, and the authors hypothesized that acute alcohol withdrawal led to impairment of limbic system GABA-ergic transmission(Plazzi et al. 2002).

There exist reports of RBD occurring in the context of mental stressors. For example, in a study of 27 military veterans with RBD, 15 had post-traumatic stress disorder (PTSD), and 20 were identified who reported a previous major stressful event(Husain et al. 2001). One hypothesis for this association is that increased noradrenaline turnover can result from repeated traumas, which then may result in its depletion in the LC, which may, in turn, inhibit the cholinergic LDT nucleus. Hence, LC dysfunction may play a role in both RBD and PTSD(Husain et al. 2001) as the LC and LDT nuclei are involved in REM sleep regulation(Manni et al. 2011).

RSWA and/or RBD are common in narcolepsy with cataplexy, but rare in narcolepsy without cataplexy(Schenck and Mahowald 1992, Olson et al. 2000, Nightingale et al. 2005, Ferri et al. 2008, Mattarozzi et al. 2008); one study of 16 patients with narcolepsy and cataplexy found that 50% exhibit RSWA(Dauvilliers et al. 2007). RBD in the context of narcolepsy tends to occur at a much younger age than RBD (may even appear during childhood(Bonakis et al. 2009, Lloyd et al. 2012)), and it has been hypothesized that narcoleptic patients with RBD display a distinct form of the disease(Oudiette et al. 2012). While hypocretin deficiency is a suggested reason for RSWA in narcolepsy with cataplexy, the mechanism in those without cataplexy is not known(Knudsen et al. 2010, Khalil et al. 2013). Interestingly, a recent study measuring six cerebrospinal fluid biomarkers of

neurodegeneration, including alpha-synuclein and beta-amyloid, found no evidence to suggest tauopathy, synucleinopathy, and immunopathy in narcolepsy patients(Jennum et al. 2016). Given this data, how and why exactly RSWA and RBD are common in cases of narcolepsy with cataplexy is not known.

Finally, it is of import to note that children may develop RBD, which is typically associated with neurodevelopmental disabilities, narcolepsy, or the use of certain medications. It is believed that the etiology of childhood RBD is distinct from RBD in adults, as none have been reported to suffer with an extrapyramidal neurodegenerative disorder(Lloyd et al. 2012).

Medications Precipitating RSWA and RBD

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) have well-known associations with RSWA and RBD(Lee et al. 2016). One study found that 15% of patients taking the SSRI fluoxetine in a sleep clinic population were shown to have RSWA(Schenck et al. 1992), and other studies have demonstrated an increased prevalence of RSWA in patients taking antidepressants(Hoque and Chesson 2010, Boeve et al. 2013, Zhang et al. 2013). Recently, one study demonstrated a nearly 10-fold increase in risk for RSWA while taking these medications(Lee et al. 2016).

It is estimated that the odds ratio of developing RBD is 1.9 with antidepressant use(Hoque and Chesson 2010), but the factors that predict the risk of developing RSWA while on SSRI/SNRIs and its prevalence remains unknown. Other medications with known associations to RSWA and RBD include the tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, clomipramine, desipramine, protriptyline, trimipramine, and mirtazapine) (Hoque and Chesson 2010, Manni et al. 2011), and case reports have demonstrated acute RBD with the use of monoamine oxidase inhibitors (phenelzine and selegiline), a beta-adrenergic blocker (bisoprolol), and a cholinesterase inhibitor (rivastigmine)(Yeh et al. 2010).

It is thought that because these medications stimulate the serotonin system, and/or block acetylcholine transmission, they may induce RBD and RWSA(Winkelman and James 2004), possibly through prevention of normal sleep-related hypotonia (serotoninergic medications) or normal REM sleep-related atonia (anticholinergic medications). Additionally, the serotonergic medications may mediate REM sleep suppressive properties(Lu et al. 2006, Boeve et al. 2007), and produce a reversible alteration in the REM-on/REM-off circuitry, potentially leading to altered motor control during REM sleep(Manni et al. 2011).

At present, it is unclear whether antidepressant-associated RBD is a benign side effect of the medication, or, in fact, a marker of prodromal neurodegenerative disease. Postuma et al. (Postuma et al. 2013) reported that RBD patients taking antidepressants had less chance of developing neurodegenerative disease than those without antidepressant use. Similarly, a more recent study demonstrated that the prevalence of RBD among those on SSRI/SNRIs was lower than the larger group of sleep patients, which, as the authors point out, may be artifactual, or, it may represent the intriguing possibility that antidepressant exposure may be

protective against RBD(Lee et al. 2016). However, the presence of comorbid depression in RBD further complicates interpretation of antidepressant association with RBD.

Although a few case reports have shown improvement of RSWA and RBD upon discontinuation of fluoxetine(Parish 2007, Applebee et al. 2009), there is a suggestion from other studies that antidepressants may “unmask” RBD rather than cause it(Postuma et al. 2013), and it has been demonstrated that RBD can persist for at least 19 months after discontinuation of SSRI(Winkelman and James 2004). Finally, markers of prodromal neurodegeneration may still be present in those with antidepressant-associated RBD, which suggests that antidepressants trigger early clinical presentation of an RBD that is nonetheless still due to underlying neurodegeneration(Jiang et al. 2016).

Other Signs and Symptoms in RBD

Clinical and subclinical symptoms in patients with RBD can be quite disparate, suggesting that the extent of the neurological process, whether neurodegenerative or other, differs greatly among those affected(Postuma et al. 2006, Postuma et al. 2009). Areas affected in RBD are not restricted to the brainstem regions regulating REM sleep(Fantini et al. 2006, Postuma et al. 2006, Postuma et al. 2009, Iranzo et al. 2010, Iranzo et al. 2011, Postuma et al. 2012, Iranzo et al. 2013, Frauscher et al. 2014, Aguirre-Mardones et al. 2015, Vilas et al. 2015, Ferini-Strambi et al. 2004, Miyamoto et al. 2006, Postuma et al. 2011, Scherfler et al. 2011, Terzaghi et al. 2013, Iranzo et al. 2014, Sprenger et al. 2015) but may extend to regions such as the olfactory system, the nigrostriatal system, and the autonomic system(Iranzo et al. 2016). Clinical examples of more diffuse effects that have been detected in those with RBD include subtle parkinsonian signs(Postuma et al. 2006, Postuma et al. 2009, Postuma et al. 2012), olfactory loss(Fantini et al. 2006, Postuma et al. 2011), depression(Frauscher et al. 2014, Vilas et al. 2015), autonomic dysfunction such as constipation or orthostatic hypotension(Postuma et al. 2006, Postuma et al. 2009), color vision impairment(Postuma et al. 2011), and subtle cognitive dysfunction (demonstrated only through cognitive tests)(Ferini-Strambi et al. 2004, Terzaghi et al. 2013, Youn et al. 2016) (Table 3).

Imaging also supports more widespread involvement in some with RBD, with reduced striatal dopamine uptake in dopamine transporter imaging(Iranzo et al. 2010, Iranzo et al. 2011), substantia nigra hyperechogenicity in midbrain transcranial sonography(Iranzo et al. 2014), reduced metaiodobenzylguanadine uptake in cardiac scintigraphy(Miyamoto et al. 2006), and increased diffusivity and decreased fractional anisotropy in the brainstem nuclei in diffusion tensor imaging(Scherfler et al. 2011).

Pathology in RBD is not limited to the central nervous system. Although pain and sensory symptoms are uncommon in RBD, decreased small nerve fiber density has been reported in epidermal biopsies(Schrempf et al. 2016). Moreoever, aggregates of phosphorylated alpha-synuclein characteristic of the alpha-synucleinopathies have been detected in some instances of RBD in biopsies of autonomic nerve fibers innervating organs such as the colon(Sprenger et al. 2015) and the submandibular gland(Iranzo et al. 2016, Vilas et al. 2016). Autonomic

dysfunction is described in more detail in the following section since it has been particularly well studied.

Autonomic Dysfunction in RSWA and RBD

While the pathophysiological mechanisms of RBD are not fully understood(Gagnon et al. 2006), it is possible that brainstem structures contributing to the central autonomic network are affected(Lanfranchi et al. 2007). Those with RBD have been shown to have a reduction in heart rate variability (HRV), regardless of whether the development of alpha-synucleinopathy occurs in the future(Postuma et al. 2010). Interestingly, isolated RSWA was found to be associated with a similar dysfunction, although the clinical implications of this remain to be seen(Barone et al. 2015). While isolated RSWA is a clinical conundrum, in that its relevance is unclear presently(Boeve 2010), it has been postulated that autonomic dysfunction may be an integral component of the pathogenesis of RBD(Postuma et al. 2010), thus suggesting that isolated RSWA represents a preclinical form of RBD(Lam et al. 2013, Barone et al. 2015).

Additionally, through the use of cardiac metaiodobenzylguanidine scintigraphy, postganglionic degeneration of cardiac sympathetic neurons has been demonstrated in those with RBD(Miyamoto et al. 2006), as has the presence of abnormal beat-to-beat variability(Ferini-Strambi et al. 1996), an absence of REM-related cardiac and respiratory responses(Lanfranchi et al. 2007) and abnormalities in quantitative sudomotor axon reflex testing (QSART)(Benarroch et al. 2009). The majority of studies have demonstrated that in IRBD, autonomic dysfunction is present and predominantly involves the sympathetic and cardiovagal branches, but whether these dysfunctions in isolated RBD predict the development of a neurodegenerative disease is still controversial(Chiaro et al. 2017).

Despite only limited literature on the prevalence of RBD in PAF patients, intriguing possibilities have been suggested. For example, a recent prospective cohort of patients with PAF by Kaufmann showed that only those with RBD phenoconverted to PD, MSA, and DLB(Kaufmann et al. 2017). Similarly, in a case series by Plazzi et al. 4 out of 10 patients initially diagnosed with PAF were eventually diagnosed with MSA 5–7 years later(Plazzi et al. 1998). Those who were later diagnosed with MSA suffered with concomitant RBD, yet those who did not develop MSA were free from RBD. Additionally, 3 of the 4 MSA patients developed RBD symptoms shortly after or together with symptoms of autonomic failure, consistent with other reports describing a shorter interval of 1–5 years(Iranzo et al. 2013).

In a series of 8 PAF patients published by Miglis et al., 63 % met criteria for RBD, and all reported an autonomic symptom duration of at least 5 years without motor or cerebellar findings, making the progression to MSA unlikely(Miglis et al. 2017). Additionally, all 8 of these patients developed symptoms of dream enactment after developing autonomic failure, with an average time delay of 7.1 years. The authors noted that this may indicate a less aggressive brainstem involvement in PAF as compared to MSA(Miglis et al. 2017). Importantly, the timing of RBD symptoms relative to the emergence of autonomic symptoms may be useful to help distinguish these conditions, and, in fact, may provide a clue as to the likelihood of progression to an alpha-synucleinopathy(Miglis et al. 2017).

Factors in Prediction of Phenoconversion to Alpha-Synucleinopathy

Across multiple studies in independent cohorts there is consistent, although variable, association of RBD with risk of developing alpha-synucleinopathy(Hogl and Stefani 2017). Several longitudinal studies of patients with RBD have now demonstrated conversion to neurodegenerative syndromes. Schenck and colleagues(Schenck et al. 1996, Iranzo et al. 2013) reported that PD had developed in 11 (38%) of 29 patients with RBD within 4 years of the diagnosis(Iranzo et al. 2016). The majority (81%) of patients from the original cohort had been diagnosed with PD, DLB, or MSA 16 years later(Schenck et al. 2013). A different study demonstrated that the majority of 44 patients with RBD were diagnosed with PD, DLB, MSA, or mild cognitive impairment, with the risk of 35% at 5 years, of 73% at 10 years, and 92% at 14 years; and yet those who remained disease-free demonstrated findings such as decreased striatal dopamine transporter uptake or hyposmia, suggestive of -synucleinopathy(Iranzo et al. 2013, Iranzo et al. 2016). Similar results have been found in other cohorts(Wing et al. 2012, Postuma et al. 2015, Postuma et al. 2015, Youn et al. 2016), and the risk for phenoconversion from RBD to alpha-synucleinopathy increases with time following RBD diagnosis, with a median age of alpha-synucleinopathy diagnosis of approximately 75 years(Iranzo et al. 2016). Finally, a multi-center post-mortem study demonstrated that the overwhelming majority (98%) of 80 RBD patients suffering with parkinsonism or dementia had alpha-synuclein pathology in their brains(Boeve et al. 2013, Iranzo et al. 2016).

The diagnosis of alpha-synucleinopathies is based on the presence of specific motor and cognitive symptoms, but some patients develop a variety of other symptoms over a period of years during which the neurodegenerative process has been theorized to have already begun(Tolosa and Pont-Sunyer 2011, Donaghy et al. 2015, Iranzo et al. 2016). For example, RBD patients with a 2.5–5 year risk of phenoconversion to an alpha-synucleinopathy have been found to display substantia nigra hyperechogenicity, a reduction in dopamine transporter uptake in the striatum, hyposmia, and dysfunction of color vision perception(Iranzo et al. 2010, Postuma et al. 2011, Iranzo et al. 2016). In these cases, neurodegeneration can be monitored through dopamine transporter imaging (a progressive decline in striatal dopamine binding has been demonstrated), and through serial neuropsychological testing (which may demonstrate progressive deficits)(Iranzo et al. 2011, Terzaghi et al. 2013, Iranzo et al. 2016).

The manifestation of parkinsonism symptoms in patients with RBD who develop alpha-synucleinopathy is usually found to begin with hypomimia, hypophonia, and reduced arm swing, and of the akinetic-rigid subtype, as opposed to the tremor dominant subtype(Postuma et al. 2012). Most RBD patients who phenoconvert to PD do not present with resting tremor, but rather report complaints of motor slowness and shuffling gait with short steps(Iranzo et al. 2016). Facial akinesia, hypophonia, and reduced arm swing, followed by rigidity and akinesia are the first parkinsonian signs to appear, based on serial neurological examination(Postuma et al. 2012), whereas dementia, visual hallucinations, and delusions might appear several years following the diagnosis of PD(Iranzo et al. 2013).

It is difficult to predict which alpha-synucleiopathy disease that a patient with RBD will develop(Iranzo et al. 2016); however, clues exist, such as the fact that PD and DLB occur more frequently than MSA, and that the coexistence of nocturnal stridor is usually indicative of phenoconversion to MSA(Iranzo et al. 2016). Predictors of conversion to neurodegenerative diseases have been identified in longitudinal studies of those with RBD(Iranzo et al. 2010, Iranzo et al. 2011, Postuma et al. 2011, Postuma et al. 2012, Holtbernd et al. 2014, Postuma et al. 2015), and were similar between dementia-first and parkinsonism-first convertors(Postuma et al. 2011, Postuma et al. 2012). However, the onset of dementia in DLB is often preceded by mild cognitive impairment, a period lasting several years, during which time this is the major complaint(Iranzo et al. 2016). Although DLB and PD are overlapping processes(Berg et al. 2014), it has been suggested there are differences in mechanisms in those who develop dementia as their first neurodegenerative syndrome versus those who develop a primary parkinsonism, and an identification of specific markers for these different clinical syndromes in RBD would be quite important(Marchand et al. 2016).

Cross-sectional cognitive studies in RBD patients have demonstrated impaired attention and executive functions, episodic memory, and visuospatial abilities(Gagnon et al. 2012), and that approximately 50% of RBD patients have mild cognitive impairment (MCI), which is considered a risk factor for the development of dementia in PD and for DLB(Gagnon et al. 2012). In a prospective study of 76 RBD patients, followed over 3.6 years, Marchand et al found a distinct cognitive profile in patients who developed DLB: RBD patients who developed dementia first had poorer performance at baseline on all cognitive domains, and had a higher proportion of MCI at baseline, whereas RBD patients who developed parkinsonism first were similar to those who remained disease-free on cognitive tests performance and MCI diagnosis frequency(Marchand et al. 2016). They concluded that proper cognitive testing can be used to predict conversion subtypes, which could be used in future clinical trials in RBD in order to determine the impact of different interventions on cognitive decline(Marchand et al. 2016).

Three longitudinal studies on cognition have been performed in those with RBD(Fantini,et al. 2011, Terzaghi et al. 2013, Youn et al. 2016), which found deterioration in cognitive function, consistent with progression of neurodegeneration. It is not clear, however, if there is a baseline profile in RBD patients associated with primary conversion into dementia, as well as the optimal neurocognitive tests for early detection of prodromal DLB in RBD(Marchand et al. 2016). These three longitudinal studies indicate that there is a deterioration in cognition in RBD patients over time, especially in visual attention and visuospatial abilities. Relatively small sample sizes, however, did not allow statistical comparisons between patients who converted and those who remained disease-free(Fantini et al. 2011, Terzaghi et al. 2013), or between conversion subtypes (dementia-first vs. parkinsonism-first patients)(Youn et al. 2016).

The first of these studies followed 24 RBD patients and 12 healthy subjects for 2 years, and found worse delayed verbal memory and visuospatial abilities in patients at baseline and at follow-up, whereas worse visuospatial attention was also observed in patients at follow-up only(Fantini et al. 2011). The second study followed 20 RBD patients for 3.6 years, and

found worse cognitive performance in 45% of patients (mostly in visuospatial abilities) and worse scores on non-verbal logic and attentional measures(Terzaghi et al. 2013). The most recent study followed 84 RBD patients for an average of 50.8 months, and 18 had converted at follow-up, which included 1 patient with spinocerebellar ataxia, 10 with parkinsonism first (9 PD, 1 MSA), and 7 with dementia first (4 DLB, 3 Alzheimer's disease). Only visual attention at baseline differentiated between patients who developed a neurodegenerative disease from disease-free patients(Youn et al. 2016).

The exact pathophysiology of cognitive impairment in those RBD is unclear at this point, but it has been suggested to be due to a combination of subcortical and cortical dysfunctions(Marchand et al. 2016); structural neuroimaging studies have found cortical thinning, gray matter changes, and white matter anomalies in frontal areas, posterior regions, the substantia nigra, and brainstem structures(Unger et al. 2010, Scherfler et al. 2011, Rahayel et al. 2015, De Marzi et al. 2016, Ehrminger et al. 2016). MCI is a strong risk factor for dementia in RBD(Marchand et al. 2016), and heterogeneous MCI subtypes in RBD have been described, with attention/executive functions and visuospatial abilities as the main cognitive domains impaired(Gagnon et al. 2009, Molano et al. 2010, Terzaghi et al. 2013). Hypoperfusion on resting single-photon emission computerized tomography, mainly in posterior regions, along with more severe and widespread EEG slowing was demonstrated in RBD patients with concomitant MCI(Vendette et al. 2012, Rodrigues Brazete et al. 2013).

Marchand et al demonstrated that cognitive deficits reported in RBD are seen mostly in patients with dementia risk, and cognitive tests assessing attention and executive functions are useful in early detection of DLB in RBD patients(Marchand et al. 2016). The pattern of verbal-learning deficits in RBD patients reported by Marchand(Marchand et al. 2016) is similar to that reported in PD and mild DLB patients(Costa et al. 2014, Petrova et al. 2016). Adding a visuospatial task to the neuropsychological assessment increases the ability to predict the conversion to dementia in RBD patients, which is consistent with the prominent attention/executive functions and visuospatial declines noted early in DLB patients and in PD patients at risk of dementia(Goldman and Postuma 2014). Other studies demonstrate that patients who convert to DLB have poorer performance on cognitive tests measuring visuospatial functions at baseline, and hypometabolism in the parietal and occipital regions (visuospatial abilities)(Fujishiro et al. 2013, Cagnin et al. 2015). Finally, it has been shown that olfactory dysfunction could predict conversion into Lewy body disease(Mahlknecht et al. 2015)·(Mahlknecht et al. 2016).

Despite these clinical and research factors, there are post-mortem reports of RBD patients without phenoconversion, despite the presence of autonomic dysfunction and alpha-synuclein pathology. For example, there is a case report of an RBD patient who developed constipation, hyposmia, depression, and mild cognitive impairment, but not parkinsonism or dementia, and yet post-mortem examination demonstrated neuronal loss and alpha-synuclein deposits in the cardiac and myenteric plexus along with Lewy bodies in the olfactory bulb, medulla, pons, substantia nigra, nucleus basalis of Meynert, and amygdala (but not in the neocortex)(Iranzo et al. 2014, Iranzo et al. 2016).

Similarly, in another case report of a patient with RBD, the presence of nocturnal stridor, and dysautonomic features, but without motor abnormalities, the post-mortem examination revealed the presence of alpha-synuclein-positive glial cytoplasmic inclusions in the brain, which would be typical of MSA(Gaig et al. 2008, Iranzo et al. 2016, Vilas et al. 2016). Clinicians and researchers should not consider all RBD patients with MCI as having a neurodegenerative disease, as further studies are needed to better characterize the evolution of different MCI subtypes in the RBD population and to determine their phenotype and their predictive value for dementia(Marchand et al. 2016).

In a four-year follow-up investigation, the International RBD Study Group evaluated 279 RBD patients from 12 centers who had initially participated in a questionnaire study. Patients who converted were older. Neither caffeine, nor smoking, nor alcohol exposure was able to predict conversion. Unexpectedly, converted patients were less likely to have been exposed to pesticides and were more likely to have a family history of dementia. Motor and autonomic symptoms were also more frequently observed in converted patients, and among converted patients with dementia, clonazepam use was more frequent(Postuma et al. 2015). Also discovered by the study group was an unexpected association with lifetime use of antidepressants in patients with IRBD, an effect that was stronger than the association with depression alone. Furthermore, an association with ischemic heart disease was also observed(Frauscher et al. 2014).

Clinical Approach to RBD

The first questionnaire tool developed for RBD was the 13-item Stiasny-Kolster RBD-Screening Questionnaire (RBDSQ), which demonstrated 96% sensitivity, but only 56% specificity(Miyamoto et al. 2009). A Japanese version of this questionnaire demonstrated a sensitivity of 88.5% and specificity of 90.9% in apnea patients (and 96.9% in healthy subjects), and in PD patients a sensitivity of 84% and specificity of 96%(Nomura et al. 2011). The RBD-HK (Hong Kong) scale includes 13 questions, with two frequency assessments for each question (lifetime and 1-year frequency), with a sensitivity of 82% and 87% specificity(Li et al. 2010). Most recently, the RBD Single-Question Screen (RBD1Q) was developed, which consists of a simple yes/no response to the question “Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?” It was found to have a sensitivity of 93.8% and a specificity of 87.2%, and is thus considered to reliably detect disease(Postuma et al. 2012).

RBD in some cases places patients and their sleep partners at risk of physical injury during acting out of dreams(Ramos-Campoy et al. 2017). Self-inflicted injuries are reported to occur in 38–59% of patients (especially prior to treatment), and are usually resulting from hitting a wall or nightstand, or jumping out of bed(McCarter et al. 2014, Fernandez-Arcos et al. 2016). Whereas mild bruises, lacerations, and sprains are the most frequent injuries seen, extreme cases include dislocations, fractures, and rarely subdural hematomas(McCarter et al. 2014, Fernandez-Arcos et al. 2016).

The goal for symptomatic treatment of RBD is to reduce injury, but a sound basis of evidence for this remains lacking, and randomized controlled treatment trials are needed. Melatonin dosed 3–12 mg at bedtime is considered as the first-line therapy as there are few side effects(McCarter et al. 2013). Clonazepam 0.25–2.0 mg at bedtime can be used if initial melatonin is ineffective or intolerable, to decrease the occurrence of sleep-related injury caused by RBD. It should be used in caution in patients with dementia, gait disorders, or obstructive sleep apnea, and requires monitoring carefully over time(Aurora et al. 2010).

Pramipexole may be considered to treat RBD as a second-line therapy, but efficacy studies have shown contradictory results. Similarly, paroxetine or L-DOPA have not been conclusively demonstrated to improve RBD, and some studies suggesting that they may actually induce or exacerbate RBD. Limited data exists regarding the efficacy of acetylcholinesterase inhibitors, such as donepezil; however, they may be considered in those with a concomitant synucleinopathy(Aurora et al. 2010).

Other potential second- and third-line therapies include zolpidem, zopiclone, ramelteon, agomelatine, cannabinoids, benzodiazepines other than clonazepam, Yi-Gan San (traditional Chinese herbal medicine), desipramine, clozapine, carbamazepine, and sodium oxybate, all of which have anecdotal evidence only(Aurora et al. 2010, Jung and St Louis 2016). Other novel non-pharmacological approaches include a bed alarm system(Howell et al. 2011) and hypnosis(Larsen et al. 2016) (especially in those with psychiatric RBD), although these require further study(Jung and St Louis 2016).

Whereas the reduction of potentially injurious sleep behaviors in those with RBD is the priority in the majority of cases, others seek advice about the nature and long-term consequences of the disorder. Unfortunately, counseling and management guidelines do not yet exist for the care of those with RBD; in particular, parameters regarding what information the patient should receive regarding potential phenoconversion to an alpha-synucleinopathy have not been established(Iranzo et al. 2016). However, one approach put forth is to inform patients that, if certain symptoms arise, such as motor slowness or memory problems, they should consult their general practitioner, neurologist, or sleep specialist(Iranzo et al. 2016).

Ancillary testing, including neuroimaging, smell tests, or neuropsychological assessment, have, at this time, been deemed unnecessary because the results of such testing would not modify patient management(Iranzo et al. 2016). However, these instruments do have utility for research and will, ideally, be of clinical value in aiding risk stratification in the future(Fantini et al. 2006).

Discussion with Patients

The decision to discuss neurodegenerative risk and/or a prodromal disease diagnosis to a patient raises several ethical issues; unfortunately, systematic study of prognostic counseling in IRBD has been limited(Iranzo et al. 2016). Health care professionals must give patients sufficient information to enable them to make decisions that are adequately informed, and the disclosure of a diagnosis of a prodromal disease could have significant influence in

patient decision-making for the future, as well as potentially seek out treatment and interventions that could alter the course of the disease(Arnaldi et al. 2017).

Unfortunately, there is a lack of neuroprotective therapy for synucleinopathies, making the benefit of prompt diagnosis and counseling relatively modest in IRBD patients, especially when viewed in the context of that being aware of the risk of developing a neurodegenerative disease could be potentially harmful from a psychological perspective(Arnaldi et al. 2017).

Whether a practitioner should disclose prognostic information regarding phenoconversion risk to an idiopathic RBD patient, or perhaps even more problematically, to the patient with isolated RSWA, remains unclear, and there may be relative advantages or disadvantages to full disclosure vs. watchful waiting without disclosure with any individual patient(Arnaldi et al. 2017). In their comprehensive review of this complicated subject, Arnaldi et al posit that general disclosure of prognostic risk is usually appropriate, but must be balanced appropriately by existing uncertainties(Arnaldi et al. 2017).

Legal Implications in RBD

Physicians are increasingly being called upon to consider sleep as a possible contributory factor in legal proceedings, but there exists little evidence to support opinion in court, and guidelines for assessing someone suspected of committing a crime in the context of a parasomnia or during sleep are non-existent(Morrison et al. 2014).

When faced with a violent or illegal act said to arise from or occur during sleep, physicians should first establish whether the behavior was due to RBD or another parasomnia, nocturnal dissociative episode, malingering or a functional disorder (including Munchhausen's)(Morrison et al. 2014). The second step is to determine whether the behavior was the result of external or internal factors (pre-existing medical, psychological or psychiatric illness). It is then for the courts to answer the legal question of whether the disorder amounts to insanity or non-insane automatism(Wing et al. 2012). Violence during sleep in dementia, therefore, may result directly from the presence of RBD and this should be borne in mind when assessing the patient presenting with such a history(Morrison et al. 2014).

In RBD, the patient's eyes are usually closed, (in contrast to disorders of arousal where the eyes are usually reported as being open), and they appear to interact with their dream rather than their immediate environment, and the behaviors are usually restricted to the bedroom(Morrison et al. 2014). The behaviors are often brief and, if awoken, the individual is orientated with a recollection of a dream that corresponds to the behavior(Schenck et al. 2009). Although RBD can be aggressive or violent, this does not appear to correlate with the waking personality(Fantini et al. 2005).

Conclusion and Future Directions

RBD is a sleep disorder that deserves attention for many reasons. Symptomatic treatments may be beneficial, as well as adaptive strategies for patients and sleep partners. However, although many with RBD will not experience future development of other,

neurodegenerative conditions, the seriousness of this possibility and its implications has led to an increasing focus on this association.

A new diagnosis of RBD should therefore prompt a search for existing subtle signs of neurodegenerative disorders. Unfortunately, at this time, there is no established means of estimating the risk of future development of a neurodegenerative condition in a given individual, making it impossible to provide adequate guidance and counseling, and furthermore no effective therapies have yet been established that slow the neurodegenerative process in individuals with PD, DLB, or MSA. The reason for this lack has been postulated that the neurodegenerative process is too advanced for intervention by the time of diagnosis(Lang et al. 2013, Postuma et al. 2013). Therefore, RBD patients represent a potentially target-rich population for the testing of neuroprotective agents that would purportedly delay or stop the emergence of symptoms(Iranzo et al. 2016).

Further study of the RBD patient population would allow for an understanding of the range of severities of this condition between the sexes and across age groups, the rate of development of dementia in patients with mild cognitive impairment, and the identification of markers of neurodegeneration(Iranzo et al. 2016). For example, it has recently been reported that in patients with IRBD, glucocerebrosidase (GBA) gene variants are found more frequently than in controls, and are associated with impending PD and DLB; thus, IRBD patients carrying GBA variants could be studied with disease-modifying interventions aiming to restore the GBA metabolic pathway(Gamez-Valero et al. 2018). Additionally, patients with IRBD were recently found to have increased microglial activation in the substantia nigra along with reduced dopaminergic function in the putamen as detected through PET; but whether the presence of activated microglia in patients with IRBD represents a marker of short-term conversion to a clinically defined synucleinopathy in the near future remains to be determined(Stokholm et al. 2017). Other important clinical information that has yet to be discovered includes why RBD seems to predominate in men, the etiology of this disorder in those under 50 years of age(Lloyd et al. 2012), the role of antidepressant drugs as a precipitant of RBD.

Fortunately, there are now several observational cohort studies being undertaken, for example individuals with RBD are enrolling as part of the Parkinson’s Progression Markers Initiative (PPMI) study (http://www.ppmi-info.org); improved recognition of RBD may be useful in earlier diagnosis of the alpha-synuncleinopathies, in which early misdiagnosis is common(Adler et al. 2014). We suggest that those who are at higher risk of synucleinopathy also have associated risk factors, and/or signs and symptoms of a neurodegenerative disorder, that might be considered to be “RBD-plus”. Indeed, a recent study of 171 patients with RBD found widespread subtle impairment across multiple neuropsychiatric parameters, that are likely relevant to risk stratification(Barber et al. 2017). Based on a combination of testing and clinical findings, we suggest the term “RBD-plus” to such designate patients who may have a preclinical version of an alpha-synucleinopathy.

Finally, perhaps the most important need for research into this area of sleep and neurology is the discovery and testing of biomarkers to determine in whom and when a conversion to

alpha-synuncleinopathy would occur, and of a neuroprotective strategy to prevent ongoing neurodegeneration in identified at-risk individuals(Iranzo et al. 2016).

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Abbreviations

DLB	dementia with Lewy bodies
EEG	electroencephalogram
IRBD	idiopathic RBD
LC	locus coeruleus
LDT	laterodorsal tegmentum
MCI	mild cognitive impairment
MRF	mesencephalic reticular formation
MSA	multiple system atrophy
Msec	millisecond
PD	Parkinson’s disease
PGO	pontogeniculooccipital
PPT	pedunculopontine tegmentum
PRF	pontine reticular formation
PSG	polysomnogram
RBD	REM sleep behavior diorder
REM	Rapid eye movement
RSWA	REM sleep without atonia

UPDRS	Unified Parkinson Disease Rating Scale

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Highlights

1. Rapid eye movement behavior disorder (RBD) is a well-described parasomnia, summarized here.
2. RBD is associated with the development of the so-called alpha-synucleinopathies.
3. We review this association, as well as treatment options for the symptoms of RBD.

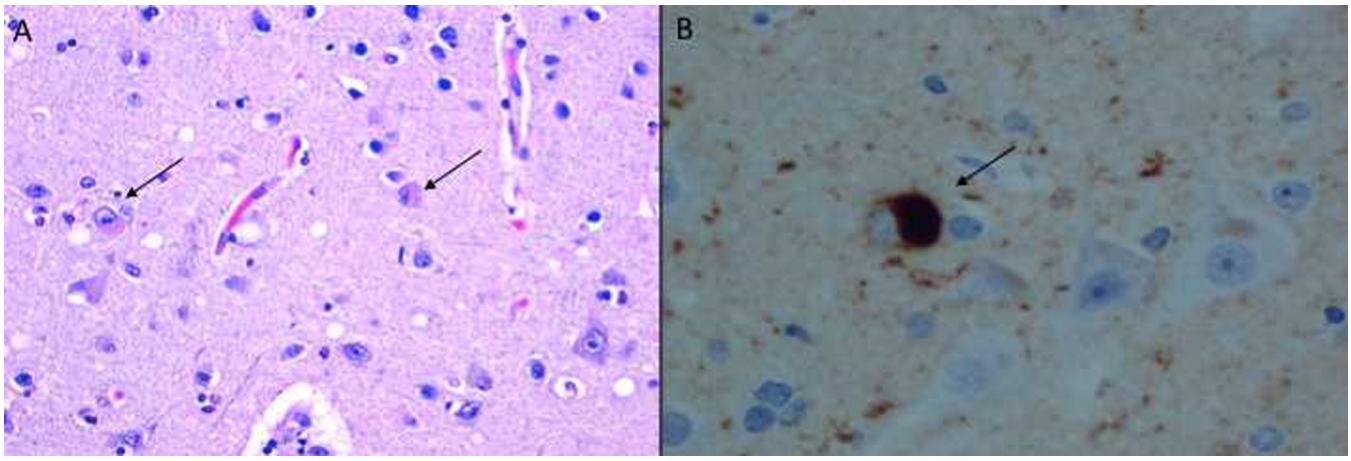

Figure 1:

Lewy bodies in the cortex of an individual with dementia with Lewy bodies (DLB) visualized by (A) hematoxylin and eosin staining, and (B) high magnification of immunostaining for alpha-synuclein, demonstrating intracytoplasmic localization of the Lewy body. Arrows mark examples of Lewy bodies. Photomicrographs courtesy of Dr Ehud Lavi, Weill Cornell Medical Center).

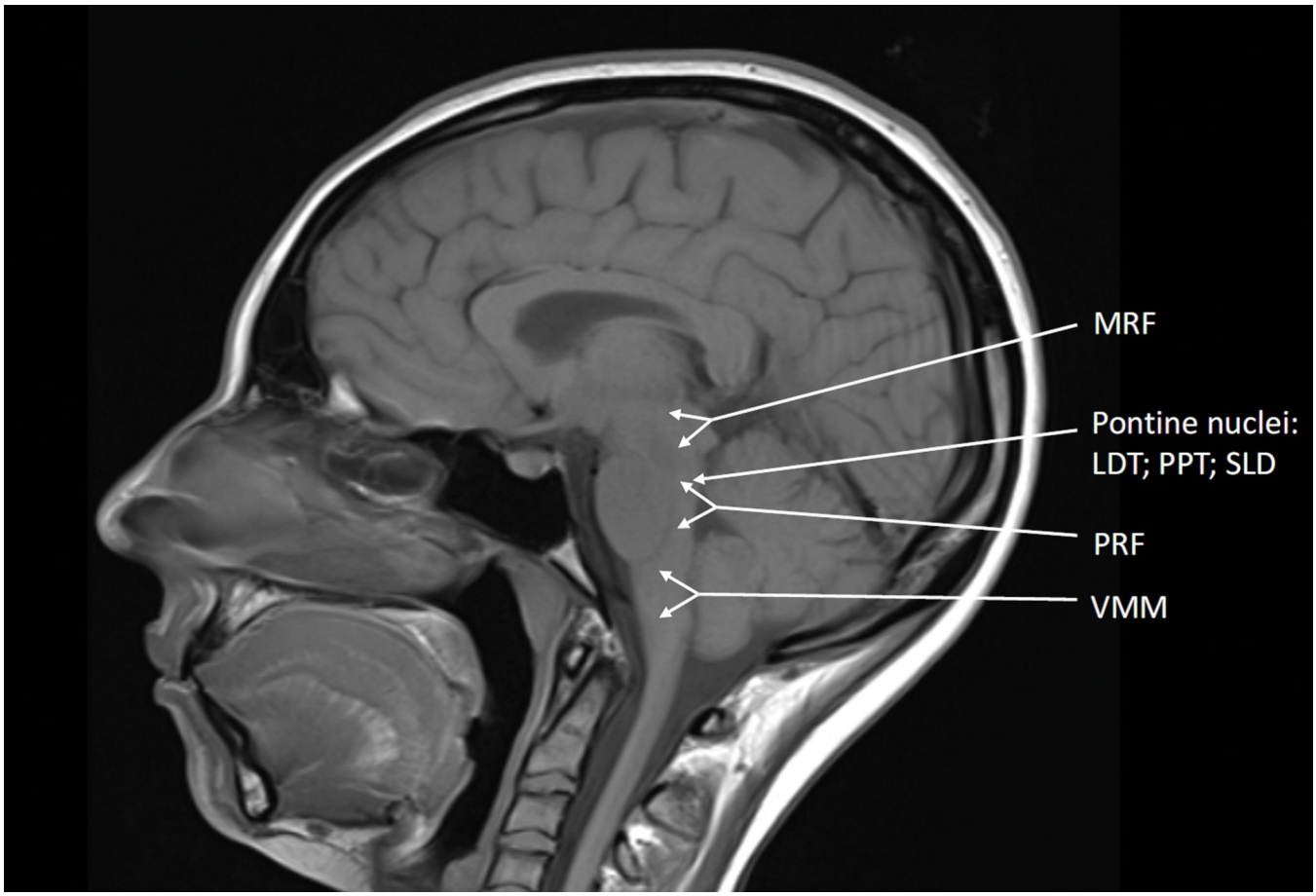

Figure 2:

A number of key structures within the brainstem are integrated into a network to produce REM sleep, and alterations in their activities may occur in RBD. Cholinergic signals from the LDT and PPT activating the PRF and MRF lead to cardinal features of REM sleep. The SLD contains neurons that are highly active in REM sleep, and contribute to muscle atonia via signals to the spinal cord (layer VII) and the VMM. MRF: mesencephalic reticular formation; LDT: laterodorsal tegmentum; PPT: pedunculopontine tegmentum; PRF: pontine reticular formation; SLD: sublaterodorsal tegmental nucleus; VMM: Ventromedial medulla

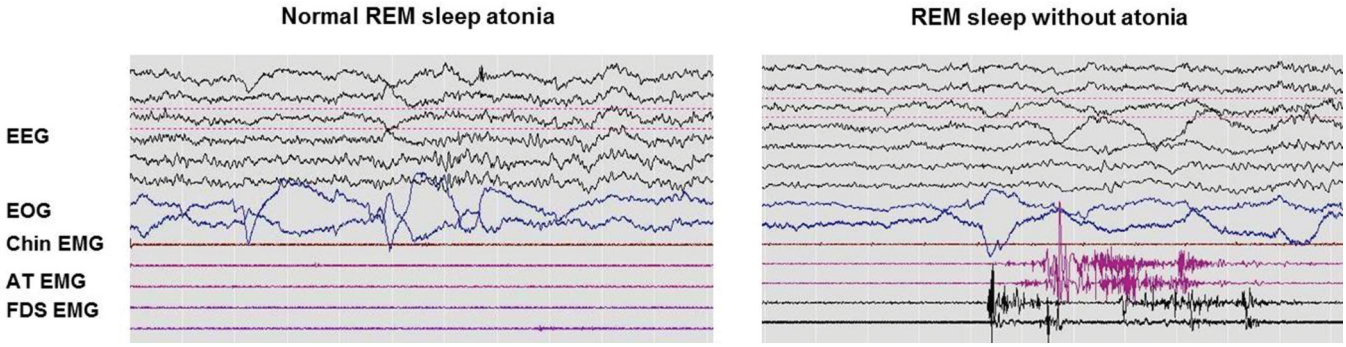

Figure 3:

A comparison between normal REM sleep and elevated muscle tone during REM sleep, taken from polysomnographic records. EEG: electroencephalography; EOG: electrooculogram; EMG: electromyogram; AT: anterior tibialis; FDS: flexor digitorum superficialis

Table 1:

Major clinical and pathological features of the alpha-synucleinopathies

Neurological disorder	Major clinical manifestations	Pathology
Parkinson's disease	Bradykinesia, muscle rigidity, rest tremor, postural instability	Alpha-synuclein-containing intracytoplasmic Lewy bodies in neurons and Lewy neurites
Dementia with Lewy bodies	Dementia, fluctuating clinical status, hallucinations, parkinsonism	Alpha-synuclein-containing intracytoplasmic Lewy bodies in neurons and Lewy neurites
Multiple system atrophy	Autonomic dysfunction, parkinsonism, cerebellar signs in some	Alpha-synuclein containing glial cytoplasmic inclusions
Pure autonomic failure	Autonomic dysfunction	Alpha-synuclein-containing intracytoplasmic Lewy bodies in neurons and Lewy neurites

Table 2:

Neurological disorders associated with RBD in adults

Neurological disorder	Nature of association	Reference
Parkinson's disease	Approximately 50% with PD have RBD May be associated with more rapid motor progression + cognitive dysfunction Bilateral cingulum and inferior occipital fasciculus alterations	(Iranzo, Molinuevo et al. 2006) (Gagnon 2002) (Sixel-Doring 2011)
Dementia with Lewy bodies	Cognitive deficits reported in RBD are seen mostly in patients with dementia risk Cognitive tests assessing attention and executive functions are useful in early detection of DLB in RBD patients	(Ferman TJ 2011) (Boeve, Silber et al. 1998)
Multiple system atrophy	Present in the majority of cases	(Iranzo 2005)
Pure autonomic failure	Possible association with risk of developing MSA	(Plazzi, Cortelli et al. 1998)
Progressive supranuclear palsy	Reported in a minority of cases	(De Cock, Lannuzel et al. 2007) (Munhoz and Teive 2014)
Guadeloupian atypical parkinsonism	Present in the majority of indivuduals (single small study)	(De Cock, Lannuzel et al. 2007)
Huntington's disease	Anecdotally reported: conflicting reports exist	(Lo Coco 2009)
Amyotrophic lateral sclerosis	Anecdotally reported: case study describing two siblings with familial ALS	(Ebben 2012) (Lo Coco 2009)
Alzheimer's disease	Anecdotally reported: rare RSWA may be more commonly seen	(Lo Coco 2009)
Guillain-Barre syndrome	Anecdotally reported: in some cases resolved with neurological recovery	(Schenck 1986) (Cochen 2005)
Stroke	Anecdotally reported: reported in brainstem infarcts	(Culebras 1989) (Kimura 2000) (Xi 2009) (Provini 2004)
Tumor	Anecdotally reported: reported in brainstem tumors	(Zambelis 2002) (Schenck 2002)
Demyelinating disorders	Anecdotally reported: seen in context of brainstem lesions RBD can be the first sign of multiple sclerosis	(Plazzi 2002) (Tippmann-Peikert 2006) (Gomez-Choco 2007)
Inflammatory lesions	Anecdotally reported: single case report Small MRI hypointensities found in pontine tegmentum and dorsal medulla, suggesting post-inflammatory lesions that persisted between acute episodes	(Limousin 2009)
Limbic encephalitis	Anecdotally reported. Data from animal studies suggest the limbic system may be involved in the pathogenesis of RBD, particularly the amygdala.	(Manni 2011) (Compta 2007) (Lin 2009)
PTSD	Anecdotally reported. Hypothesized that increased noradrenaline turnover can result from repeated traumas, which then may result in its depletion in locus coeruleus, which may, in turn, inhibit cholinergic laterodorsal tegmentum nucleus	(Husain 2001)
Narcolepsy with cataplexy	50% exhibit RSWA RBD in narcolepsy tends to occur at a much younger age than in idiopathic RBD	(Olson 2000) (Ferri 2008) (Mattarozzi 2008) (Nightingale 2005) (Schenck 1992) (Dauvilliers 2007)

Table 3

Signs and symptoms associated with RBD

Signs and symptoms	Description	Reference
Reduced heart rate variability	Index of beat to beat variability (RR standard deviation): 24.6 ± 2.2 msec in RBD vs 35.2 ± 3.5 msec in controls (p = 0.006)	(Postuma 2010)
Orthostatic hypotension	Systolic blood pressure drop 15.2 ± 2.1 mm Hg in RBD vs 3.7 ± 2.5 in controls (p = 0.003)	(Postuma, Gagnon et al. 2009)
Small fiber neuropathy	39% in RBD vs 4.5% in controls	(Schrempf, Katona et al. 2016)
Hyposmia	61.1% in RBD vs 16.6% in controls	(Fantini, Postuma et al. 2006) (Postuma, Gagnon et al. 2011)
Constipation	0.13 ± 0.092 constipation symptoms in controls vs 0.73 ± 0.11 in RBD (p < 0.01)	(Postuma, Gagnon et al. 2009)
Depression	28.8% in RBD vs 17.5% in controls (control subjects in this study were healthy and those with other sleep disorders)	(Frauscher, Jennum et al. 2014) (Vilas, Iranzo et al. 2015)
Cognitive dysfunction	43.7% impaired in visuospatial constructional tests in RBD; 82.3% impaired in visuospatial learning test in RBD MCI in 35% in RBD	(Ferini-Strambi, Di Gioia et al. 2004) (Terzaghi, Zucchella et al. 2013) (Youn, Kim et al. 2016)
Color vision impairment	Greater at baseline in individuals with RBD who subsequently developed neurodegenerative disease vs those who did not: adjusted Farnsworth Munsell −100 scores 153.0 ± 83.2 vs 129.1 ± 62 (p = 0.22)	(Postuma, Gagnon et al. 2011)
Subtle parkinsonian signs	Mean UPDRS score 6.0 ± 1.0 in RBD vs 3.0 ± 0.16 in controls (p = 0.023); 7/25 with RBD had detectable bradykinesia UPDRS part III (motor) score 5.8 ± 0.64 in RBD vs 2.70 ± 0.5 in controls (p < 0.001)	(Postuma, Lang et al. 2006) (Postuma, Gagnon et al. 2009) (Postuma, Lang et al. 2012)