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Review

Autonomic impairment as a potential biomarker in idiopathic REM-sleep-behavior disorder

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A B S T R A C T

Autonomic dysfunction is common in REM-sleep behavior disorder (RBD). Several studies have demonstrated abnormalities in heart rate variability, cardiac scintigraphy, and cardiovascular autonomic reflex testing. In addition, the type and severity of these abnormalities may correlate with rate of phenoconversion from idiopathic RBD (iRBD) to manifest neurodegenerative disease. This article summarizes the current literature on autonomic impairment in iRBD, with specific focus on the role of autonomic impairment as a potential biomarker of disease progression. REM sleep physiology and relevant anatomy is also discussed in relation to the central autonomic network and autonomic neurodegeneration.

1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia characterized by loss of the normal skeletal muscle atonia that accompanies rapid eye movement (REM) sleep. Consequently, patients may talk, gesture, punch, kick, or perform other complex motor behaviors in association with dream content (Schenck et al., 1987). Much interest has arisen in the association between RBD and a group of neurodegenerative diseases involving abnormal aggregation of the protein α-synuclein (α-syn), collectively termed the α-synucleinopathies. These diseases include Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF). Several studies have documented that patients with idiopathic RBD (iRBD)— a diagnosis implying the absence of signs or symptoms of central nervous system (CNS) involvement—are at substantial risk of developing these diseases. Most longitudinal studies of patients initially diagnosed with iRBD have demonstrated a phenoconversion rate of > 80%, or approximately 10% per year from diagnosis, establishing iRBD as a clear and early marker of neurodegeneration (Iranzo et al., 2016; Postuma and Trenkwalder, 2017; Schenck, 2013; Li et al., 2017). The discovery and validation of prodromal markers of impending phenoconversion is pivotal for future neuroprotective drug trials. Certain features of autonomic impairment in this population may provide one such marker, as well as a potential marker of disease progression. In this article we will provide a brief review of the current knowledge of REM sleep anatomy, followed by a summary of the literature on autonomic impairment in iRBD and the α-synucleinopathies. Finally, the role of autonomic impairment as a biomarker of disease progression will be discussed.

2. Anatomy of REM sleep and central autonomic networks

REM sleep is one of the two states of human sleep, characterized by mixed-frequency electroencephalogram (EEG) activity, rapid eye movements, and active inhibition of spinal motor neurons, resulting in near complete skeletal muscle atonia. Multiple neurotransmitter systems are responsible for the muscle atonia of REM sleep (Boeve et al., 2007; Luppi et al., 2012) and include glycinergic and GABAergic premotor neurons that inhibit motor neurons (Ramaligam et al., 2013). The perilocus coeruleus, located in the rostral pons, exerts an excitatory influence on the medullary reticular formation through the lateral tegmentoreticular tract. These neuronal groups then hyperpolarize spinal motor neuron postsynaptic membranes through the ventrolateral reticulospinal tract (Fig. 1).

Much of the knowledge of RBD pathophysiology comes from lesion studies. All structural lesions identified to date have been localized in the dorsal midbrain, pons, or medulla. Neuroimaging studies of at least 20 cases of RBD have shown that lesions within or near the mesencephalic and pontine tegmentum can produce dream-enacting behaviors (Iranzo et al., 2016). More recent neuroimaging of the voltage-gated

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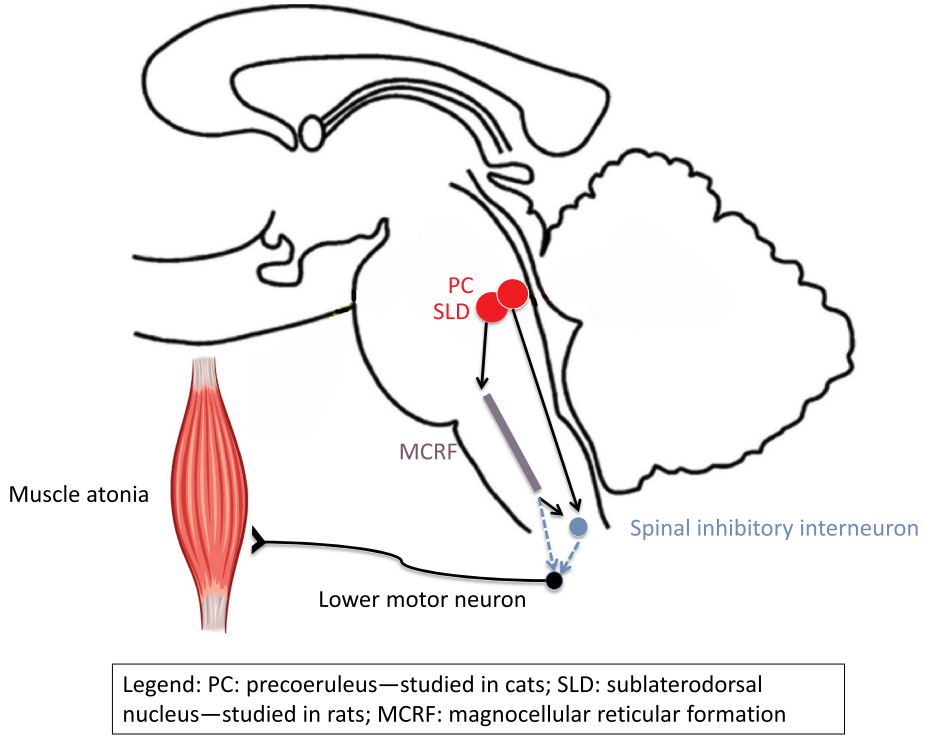

Fig. 1. Neuroanatomical structures involved in REM sleep.

potassium channel complex–associated iRBD cases have demonstrated abnormalities in the mesial temporal lobe structures and not exclusively in the brainstem (Thieben et al., 2004). These unique cases underscore the fact that the precise networks and neurotransmitter systems involved in iRBD remain unclear, however most consistently relate to brainstem networks and their efferent or afferent connections.

The relationship between iRBD and autonomic impairment is likely anatomical, however the exact pathophysiology remains unclear. In addition to REM control networks, the brainstem contains much of the neural circuitry responsible for the control of autonomic function. The central autonomic network (CAN), the internal regularory system of the brain involved in visceromotor, neuroendocrine, complex motor and pain-modulating control mechanisms, consists of a group of interconnected areas distributed throughout the neuraxis (Fig. 2). The periaqueductal grey in the midbrain, the parabrachial nucleus of the pons and several regions in the medulla, including the dorsal motor vagal nucleus and the nucleus ambiguous, are critical components of the CAN (Benarroch, 1993).

While α-syn-induced neurodegeneration of autonomic brainstem centers likely results in a significant portion of the autonomic impairment seen in patients with iRBD, peripheral autonomic nerves are also involved, as evidenced by many studies that have demonstrated postganglionic sympathetic denervation, although the timing of central vs. peripheral neurodegeneration remains unclear. In the staging systems of PD proposed by Braak (Braak et al., 2003) both parasympathetic structures (dorsal motor nucleus of vagus) and sympathethic structures (postganglionic neurons) show inclusion of Lewy bodies at early stages of PD pathology. However, the pattern and severity of α-syn-induced autonomic impairment is quite variable in patients with iRBD and RBD associated with CNS disease. Patients initially presenting with iRBD may go on to develop PD, DLB or MSA, and some may present with PAF and remain so (Miglis et al., 2017). Each of these diagnoses may manifest their own unique pattern of autonomic failure, and all have different prognoses. In addition, recent studies suggest that there may be different subtypes of PD with respect to disease onset, clinical phenotype, disease progression, and association with mild cognitive impairment or dementia (Kumru et al., 2007; Postuma et al., 2008a; Postuma et al., 2008b; Selikhova et al., 2009; Yoritaka et al., 2009; Jozwiak et al., 2017; Postuma et al., 2011; Gagnon et al., 2006). These subtypes seem to show different associations with RBD, another illustration that α-syn spread may be highly individual. In those patients with confirmed autonomic failure, the presence of RBD, especially early in the disease course, may suggest a greater risk of phenoconversion (Giannini et al., 2018).

3. Markers of autonomic impairment in patients with iRBD

3.1. Autonomic symptom severity

Autonomic symptoms are common in iRBD, and are reported in up to 94% of patients (Lee et al., 2015). In addition, the severity of autonomic symptoms may be correlated with an accelerated rate of phenoconversion (Li et al., 2017). An early multicenter case–control study examined and compared the presence of autonomic symptoms in 318 patients with iRBD and an equal number of sex- and age matched controls by means of the Scale for Outcomes in PD-Autonomic (SCOPA-AUT), a self-assessment measure that addresses autonomic symptoms in patients with PD (Ferini-Strambi et al., 2014). iRBD patients had substantially more symptoms of autonomic impairment when compared to controls, with the most severe symptoms in the gastrointestinal, urinary, and cardiovascular domains. In a similar study of patients with iRBD, those who converted to PD or DLB had higher baseline cardiovascular SCOPA-AUT scores than those who did not (Postuma et al., 2015).

Ferini-Strambi et al. reported that iRBD patients had significantly higher SCOPA-AUT scores when compared to controls, with the gastrointestinal domain being the most severely affected (Ferini-Strambi et al., 2014). Interestingly, constipation may be more common in PD patients with RBD than in those without RBD (Nihei et al., 2012), and it is well known that constipation is an early pre-motor symptom of PD. In an important longitudinal study, Li et al. administered the SCOPA-AUT to 43 patients with iRBD and followed them annually until the

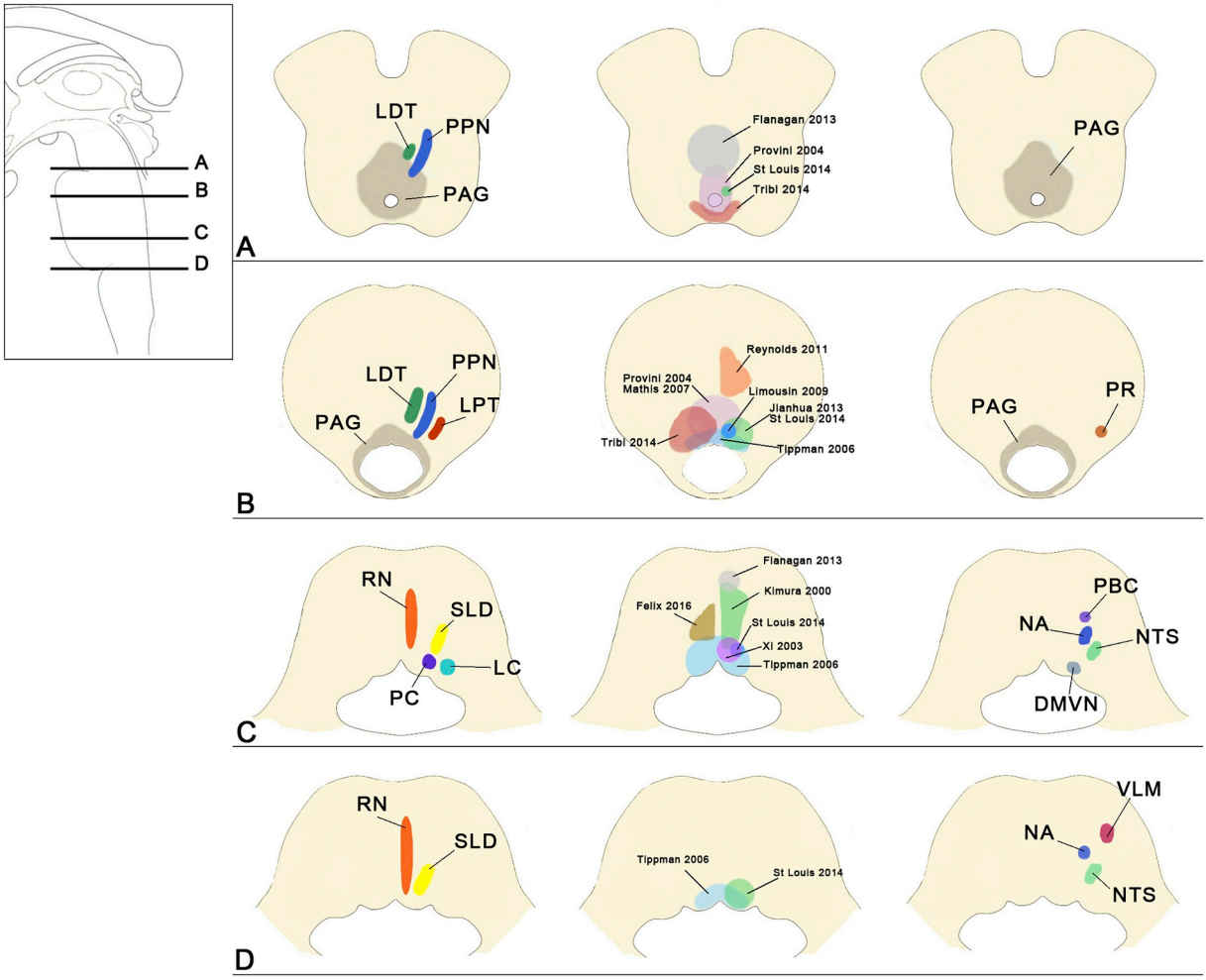

Fig. 2. Human brainstem templates showing (*left column*) the proposed nuclei involved in REM sleep control, (*central column*) published cases of RBD associated with brainstem lesions and their approximate locations of the lesions based on magnetic resonance imaging data, and (*right column*) the most important areas of the central autonomic network and their approximate location.
Letters represent cross-sectional views through the brain stem, with (A) corresponding to the ponto-mesencephalic junction, (B) to the upper/mid pons, (C) to lower/mid pons, and (D) just rostral to the ponto-medullary junction.
Abbreviations: LDT = laterodorsal tegmental nucleus; PPN = pedunculopontine nucleus; PAG = periaqueductal grey matter; LPT = lateral pontine tegmentum; PR = parabrachial region; RN = raphe nucleus; PC = precoeruleus; LC = locus coeruleus; SLD = sublaterodorsal nucleus; NA = nucleus ambiguus; PBC = Pre-Bötzinger complex; NTS = nucleus of the tractus solitaries; DMVN = dorsal motor vagal nucleus; VLM = ventrolateral medulla (*Inspired by Boeve et al., 2007 and integrated with Benarroch, 1993 with permissions, updated by the authors*).

development of parkinsonism or cognitive impairment. Eighteen patients in this cohort (41.9%) developed a synucleinopathy, and those with more severe autonomic symptoms had an accelerated rate of phenoconversion (Li et al., 2017).

Aguirre-Mardones et al. reported that iRBD patients scored higher than controls on the Non-Motor Symptoms Questionnaire (NMSQuest), a scale that does include some questions assessing autonomic function, though not specifically designed as an autonomic questionnaire. Patients in this study also had a trend to a higher total SCOPA-AUT autonomic score (Aguirre-Mardones et al., 2015). Schrempf et al. (Schrempf et al., 2016) found that when different domains in the NMSQuest were analyzed, iRBD patients scored highest in the cardiovascular domain (33%) urinary domain (50%), gastrointestinal domain (17%) and sexual function (22%) domain.

While the literature on autonomic symptom severity in iRBD is consistent, the literature on autonomic impairment in PD patients with RBD is less so. To help determine if the manifestations of PD are related to the presence of RBD, Postuma et al. assessed autonomic impairment with subjective (Unified Multiple System Atrophy Rating Scale [UMSARS]) and objective outcome measures (1-minute active stand test) in a cohort of patients with PD (Postuma et al., 2008a). Motor manifestations did not differ in patients with and without RBD, nevertheless the presence of RBD was strongly associated with orthostatic intolerance and an orthostatic BP fall at 1 min. There was however no association between RBD and other autonomic symptoms (constipation, urinary dysfunction or erectile dysfunction) on the UMSARS. In a later study, the authors noted that symptoms of urinary frequency were reported in iRBD patients up to 7 years before conversion to PD, with an extrapolated prodromal interval of 13 years, and erectile dysfunction was observed 7 years before disease conversion, with an extrapolated prodromal interval of 11 years (Postuma et al., 2013).

In support of the theory that autonomic functions are affected in a heterogeneous pattern in PD, and that the progression of autonomic dysfunction follows an erratic rather than stepwise progression, a more recent study in 45 PD patients found that axial motor impairment and RBD were related to neither autonomic symptoms (NMSQuest, SCOPA-AUT) or objective autonomic impairment (cardiovascular autonomic reflex testing) (Leclair-Visonneau et al., 2018). Furthermore, based on prospective investigations of RBD as a predictor of motor deterioration,

RBD has been associated with the progression of bradykinesia (Bugalho and Viana-Baptista, 2013) but not other motor symptoms, as measured by Hoehn and Yahr (HY) scores, conversion to postural instability gait disturbance (PIGD) subtype, worsening of tremor (Bugalho and Viana-Baptista, 2013), or the development of freezing of gait (FOG) or falls (Lavault et al., 2010).

However, others have reported greater autonomic symptom severity in PD patients with RBD compared to those without (Zhang et al., 2016). The discrepancies reported in patients with PD and RBD (as opposed to patients with iRBD only) may be due to several factors, including a more advanced disease state, greater cognitive impairment affecting self-reporting measures, and more confounding variables such as a polypharmacy and other medical comorbidities in this specific population. Nonetheless, it is clear that autonomic symptoms are highly prevalent in iRBD, the severity of which may be correlated with more rapid phenoconversion. The most common symptoms reported are those of gastrointestinal, genitourinary, sexual, and cardiovascular impairment. Of the scales employed in iRBD research, the SCOPA-AUT is the most widely reported, captures the scope of autonomic symptoms reported by patients, and thus should be considered in future prospective treatment trials.

3.2. Heart rate variability

It is difficult to measure autonomic fluctuations during sleep due to the uncomfortable and disruptive nature of most recording techniques. Heart rate variability (HRV) analysis of the RR interval offers an indirect, noninvasive alternative. Spectral analysis of heart rate variability (HRV) is often referenced as an estimate of sympathetic and parasympathetic tone during sleep, otherwise termed the sympathovagal balance. High-frequency RR signal (> 0.15 Hz) is associated with parasympathetic tone, due to the vagal respiratory sinus arrhythmia, where heart rate increases on inspiration and decreases on expiration. Conversely, low-frequency RR signal (0.04–0.15 Hz) may be associated with sympathetic tone (Malliani et al., 1991). A greater LF/HF ratio is suggestive of greater sympathetic drive, while a lower LF/HF ratio is suggestive of greater parasympathetic drive, although this correlation is not universally accepted. While HRV analysis is non-invasive and easy to perform, it prone to artifact and is thus a non-specific marker of cardiac autonomic impairment. Nonetheless, HRV has been utilized in many studies of autonomic function in patients with iRBD as it can be easily obtained from overnight polysomnography (PSG).

Reduced HRV has been well-established in iRBD, and most studies have demonstrated results consistent with sympathetic impairment (Sorensen et al., 2013; Postuma et al., 2011; Sauvageot et al., 2011), while some have demonstrated results consistent with both sympathetic and parasympathetic impairment (Covassin et al., 2012; Palma et al., 2013), depending on sleep stage (Palma et al., 2013), or severity of motor dysfunction (Covassin et al., 2012). Some studies evaluated HRV only in the waking state (Postuma et al., 2011), while others assessed PSG data, finding abnormalities in both REM and non-REM stages (Covassin et al., 2012; Sauvageot et al., 2011; Sorensen et al., 2012). Reduction in the HR response to arousals or periodic limb movements has been documented in iRBD and PD, with the HR response in those with iRBD being intermediate with respect to controls and those with PD, with a lower LF/HF ratio in REM, suggestive of sympathetic impairment and the opposite of what is typically seen in normal, healthy sleep (Sorensen et al., 2012). In addition, reduced HRV itself may be an independent risk of developing PD. In one large population-based study, a reduction in variability was associated with a 1.5–3× increase in the risk of PD (Alonso et al., 2015). The mean interval between detection of the variability and onset of PD was 18 years, suggesting that this marker has a very long lead time. However, this finding was not replicated in a slightly smaller study with a 14-year follow-up interval (Jain et al., 2012).

In 1996, it was first reported that patients with iRBD not only have a reduced tonic and phasic heart rate variability during sleep, but that the majority of these patients also have an impairment in one or more tests assessing cardiovascular reflex testing during wakefulness (Ferini-Strambi et al., 1996). However, no significant difference was found in autonomic function between iRBD and patients with diagnosed CNS synucleinopathy. Further supporting this notion, Lanfranchi et al. evaluated 10 subjects with iRBD and compared them to 10 age-matched controls, with the hypothesis that REM-related cardiorespiratory activation is altered in subjects with iRBD (Lanfranchi et al., 2007). They found that REM-related cardiac and respiratory responses were absent in subjects with iRBD, however were preserved in non-REM sleep, suggesting that iRBD preferentially affects the sympathetic control that is most active during REM sleep. In contrast, Rocchi et al. found autonomic impairment during wakefulness in iRBD that mainly arises under stress conditions (Rocchi et al., 2018). During head up tilt table testing (HUT) the LF HRV band was significantly higher in controls compared to those with iRBD, and the HF band was significantly higher in those with iRBD compared to controls. These findings suggest that the iRBD subjects have blunted sympathetic responses during orthostatic stress. Valappil et al. found that HRV during wakefulness was significantly decreased in patients with iRBD compared with control subjects, suggesting abnormalities of both sympathetic and parasympathetic function (Valappil et al., 2010). Some authors have suggested that HRV reduction could be specific for RBD and not PD (Postuma et al., 2011). Others, however, have found alterations in PD patients with and without RBD (Palma et al., 2013), and some have reported that circadian variation in LF spectra may accurately discriminate between PD patients with RBD and PD patients without RBD (Salsone et al., 2016).

Postuma et al. retrospectively assessed HRV from overnight PSG data in patients with iRBD to determine if cardiovascular autonomic dysfunction predicts eventual risk of neurodegenerative disease (Postuma et al., 2010). Patients with iRBD demonstrated clear evidence of cardiovascular autonomic dysfunction, as evidenced by reduction in RR-standard deviation, vLF and LF spectra, again suggestive of sympathetic impairment. However, this cardiovascular autonomic dysfunction, measured at baseline, did not predict phenoconversion to CNS disease. Barone et al. evaluated HRV in 20 patients with isolated rapid eye movement sleep without atonia (without dream enacting behaviors), or RSWA (Barone et al., 2015). Significant differences between groups were demonstrated in RR standard deviation, HRV power and LF spectra, suggesting that cardiovascular sympathetic impairment is present well-before before patients are noted to have their first RBD event.

In summary, many studies have demonstrated reduced HRV in patients with iRBD, most prevalent in the sympathetic power spectra, indicative of sympathetic cardiac impairment. However, the presence of this impairment may not correlate with disease severity or risk of phenoconversion, therefore its use in future trials is uncertain.

3.3. Cardiac scintigraphy

Metaiodobenzylguanidine (MIBG) scintigraphy is based on evidence that norepinephrine (NE) and MIBG have the same mechanisms for uptake, storage, and release (Yamashina and Yamazaki, 2007), thus an abnormal MIBG scan suggests post-ganglionic sympathetic denervation. This is often referenced as a decreased heart to mediastinum (H/M) ratio, which represents weakened capacity of MIBG uptake in the terminal post-ganglionic sympathetic fibers (Taki et al., 2000). Studies of cardiac MIBG scintigraphy in patients with iRBD have demonstrated abnormalities similar to those seen in PD (Miyamoto et al., 2006; Postuma et al., 2013). These findings have also been demonstrated in DLB with and without autonomic failure (Taki et al., 2000; Orimo et al., 2005), but less so in MSA. In these CNS diseases, pathology such as distal axonopathy or a decrease in the number of cardiac autonomic fibers due to Lewy body deposition been reported (Orimo et al., 2005;

Mitsui et al., 2006). These scintigraphy studies provide a direct neuroanatomical correlate of the cardiac sympathetic impairment seen in HRV studies.

Kashihara et al. performed MIBG scintigraphy in patients with iRBD and compared the findings to patients with PD and controls (Kashihara et al., 2010). The authors demonstrated that the H/M ratios were lower for patients with iRBD when compared to PD patients at Hoehn and Yahr stages 1 and 2, but equal to those at Hoehn and Yahr stages 3, 4 and 5, thus suggesting that the autonomic denervation responsible for reduced 123I-MIBG uptake may be more closely associated with the presence of RBD than with PD. They also reported that cardiac sympathetic denervation is more severe in iRBD than in early PD. This suggests that iRBD may not simply be a premotor form of PD, but that it may be associated with more widespread autonomic changes than are seen in mild PD.

In 2008, Oguri et al. reported on unique the cardiac scintigraphy results of two RBD patients with differing clinical progression. One 69-year-old patient had more than a 20-year history of iRBD and showed a decrease in myocardial 123I-MIBG radioactivity. The other 69-year-old patient began to manifest nocturnal behaviors at age 62, then mild parkinsonism at age 68, and showed a similar decrease in myocardial 123I-MIBG radioactivity both before and after the onset of parkinsonism. These cases suggest that RBD could develop in diverse patterns of clinical progression (Oguri et al., 2008).

Miyamoto et al. reported on the pattern of 123I-MIBG scintigraphy abnormalities in iRBD, DLB, and MSA, and compared them to progressive supranuclear palsy (PSP, a tauopathy) (Miyamoto et al., 2008). The cardiac radioactivity of 123I-MIBG was normal in the MSA, PSP and control groups, however markedly reduced in 93.5% of the patients with iRBD, 75.0% patients with PD, and 100% patients with DLB (Miyamoto et al., 2008). In most cases of iRBD, a marked reduction in 123I-MIBG accumulation occurred soon after the onset of the disease. In PD, on the other hand, the H/M ratio decreased with disease duration. Other studies have demonstrated a more marked reduction of MIBG cardiac uptake in iRBD compared to early PD (Kashihara et al., 2010), and also in PD with RBD compared to PD without RBD (Nomura et al., 2010; Miyamoto et al., 2011), again suggesting that cardiac postganglionic sympathetic denervation may be more closely associated with the presence of RBD than with PD.

More recently, in 2016, Kim et al. (Kim et al., 2016) demonstrated that RBD was closely associated with orthostatic hypotension (OH) and cardiac sympathetic denervation in patients with early and mild PD. To address the question of whether MIBG cardiac uptake differs in patients with iRBD that predates neurodegeneration and iRBD that does not, Barateau et al. performed MIBG in a population of 34 type 1 narcolepsy (NT1) with RBD and compared the results to 15 iRBD patients. He found that reduced cardiac MIBG uptake was associated with iRBD but not with NT1, suggesting that cardiac sympathetic impairment seen in RBD may be unique to the synucleinopathies (Barateau et al., 2018).

In summary, like HRV, many studies have demonstrated abnormal MIBG scintigraphy in patients with iRBD, indicative of sympathetic cardiac impairment. The presence of this impairment may not correlate with disease severity or risk of phenoconversion, however it may help to differentiate RBD due to α-synucleinopathy from other disease states, such as NT1.

3.4. Cardiovascular reflex testing and blood pressure analysis

Cardiovascular reflex testing has been validated as the most quantitative and comprehensive method of assessing autonomic function. Autonomic cardiovascular reflex testing can include many specialized tests, but at a minimum should include measures of HRV with deep breathing (cardiovagal parasympathetic), Valsalva maneuver (sympathetic adrenergic), Valsalva HR ratio (cardiovagal parasympathetic) and 70-degree HUT (sympathetic adrenergic) for a minimum of 10 min, all performed with continuous BP and HR monitoring. Testing is performed in the autonomic laboratory under controlled conditions, and patients should refrain from large meals, alcohol, nicotine, caffeine, or any medications that might alter the test results. To our knowledge there are only three such studies that have performed this comprehensive testing in patients with iRBD.

The first study to investigate cardiovascular reflex testing in iRBD was by Ferrini-Strambi et al. In that study they compared 10 iRBD, 1 PD, 2 MSA and 1 AD patient to controls and found that the blood pressure response to standing was abnormal in six patients (43%) (Ferini-Strambi et al., 1996). Frauscher et al. investigated autonomic function in iRBD by performing cardiovascular reflex testing in 15 iRBD patients and compered them to PD patients and controls (Frauscher et al., 2012). On HUT, BP changes were similar between iRBD patients and controls, however OH was present in 2 iRBD patients, the same frequency as in the PD group. Orthostatic BP changes were more pronounced in the PD group. Valsalva ratio was significantly lower in PD patients and iRBD patients compared to healthy controls.

In another small cohort, Lee et al. performed autonomic cardiovascular reflex testing on 17 patients with iRBD. 94% of these patients demonstrated sympathetic adrenergic and/or parasympathetic cardiovagal deficits (Lee et al., 2015). In contrast to the earlier work by Fraucher, in which the authors found relatively little OH, 10/17 (59%) of patients in this cohort had OH that appeared immediately after HUT and persisted throughout the tilt. Sympathetic cholinergic dysfunction was found in 7/17 (41%) of patients with iRBD, as evidenced by abnormal QSART sweat results (Lee et al., 2015), suggesting post-ganglionic sympathetic impairment. These results indicate widespread autonomic impairment in iRBD, with both central and peripheral autonomic involvement.

While the authors did not perform cardiovascular autonomic reflex testing, Postuma et al. did perform a 1-minute stand test on their cohort of 91 iRBD patients that they followed annually for an average of 3 years (Postuma et al., 2013). According to disease diagnosis, there were clear abnormalities in all autonomic symptoms and signs relative to controls, with the exception of orthostatic symptoms. Orthostatic symptoms were less common in patients even in the presence of a substantial orthostatic BP drop on 1-minute stand testing. The difference in orthostatic BP change between controls and patients with disease was statistically significant on logistic regression at least 5 years before disease onset (statistical testing at longer intervals was underpowered). However, when comparing patients who had a diagnosis of DLB with patients who had PD, there were no significant differences in any autonomic variable. It should be noted that OH may not be captured on a 1-minute orthostatic stand test, and a minimum of 3 min is now recommended to diagnose OH.

In summary, while studies are limited, cardiovascular autonomic reflex testing has demonstrated clear abnormalities in both central and peripheral autonomic function in patients with iRBD and provides the most comprehensive analysis of autonomic function in the waking state. A review of important autonomic studies in iRBD is presented in Table 1.

4. Conclusions

Autonomic dysfunction is common in iRBD, and symptoms may be present decades before a diagnosis of CNS synucleinopathy in made. The most salient and measurable symptoms, based on prior publications, include those of urinary, gastrointestinal, sexual (erectile dysfunction), and cardiovascular impairment. The severity of symptoms may correlate with phenoconversion rate. The SCOPA-AUT is a well-validated scale that captures the scope of these symptoms, and thus should be considered in future prospective treatment trials.

Patients with iRBD have clear evidence of post-ganglionic, cardiac sympathetic denervation, as evidenced by HRV and cardiac scintigraphy studies, and, like autonomic symptoms, this impairment is likely present decades prior to diagnosis. The severity of impairment,

Table 1
Summary of autonomic studies in patients with iRBD.

Study	Patient selection	Rating scales	Quantitative testing	Findings
Li et al. *Predictive markers for early conversion of iRBD to neurodegenerative synucleinopathy diseases.* Neurology, 2017.	- 43 iRBD	- NMSQ - RBD screening questionnaire - SCOPA-AUT - HAMD-17 - MMSE - MOCA - Olfactory testing (Sniffin Sticks 16-item test [SS-16])	- DAT-SPECT - PSG	- 10% phenoconversion rate
Postuma et al. *Manifestations of Parkinson Disease Differ in Association with REM Sleep Behavior Disorder.* Mov Disorders, 2008.	- 21 PD with RBD - 15 PD w/o RBD	- Motor manifestations (H & Y and UPDRS in on and off states) - UMSARs	- PSG - Active stand testing	- Motor manifestations did not differ in patients with and w/o RBD - The presence of RBD in PD was strongly associated with signs and symptoms of OH - No association between RBD and other autonomic symptoms (constipation, urinary dysfunction or erectile dysfunction)
Lee et al. *The Severity and Pattern of Autonomic Dysfunction in Idiopathic Rapid Eye Movement Sleep Behavior Disorder.* Mov Disorders, 2015.	- 17 iRBD	- MMSE	- Autonomic cardiovascular reflex testing - Plasma NE levels	- 13/17 iRBD (77%) exhibited sympathetic adrenergic dysfunction - 14/17 iRBD (82%) exhibited parasympathetic cardiovagal dysfunction - 7/17 iRBD (41%) exhibited sympathetic sudomotor dysfunction - 10/17 iRBD (59%) had OH
Ferini-Strambi et al. *Autonomic symptoms in idiopathic REM behavior disorder: a multicentre case–control study.* J Neurol, 2014.	- 318 iRBD - 137 community controls - 181 sleep center controls with other sleep diagnoses	- SCOPA-AUT	None	- Autonomic symptoms more common in iRBD, esp. gastrointestinal, urinary, and cardiovascular functioning
Aguirre-Mardones. *Prevalence and timeline of nonmotor symptoms in idiopathic rapid eye movement sleep behavior disorder.* J Neurol, 2015.	- 44 iRBD - 40 controls	- NMSQuest - UPSIT - SCOPA-AUT - Hospital Anxiety and Depression Scale (for depression) - Beck depression inventory - MOCA - ESS	None	- Autonomic symptoms more common in iRBD, esp. constipation - Hyposmia more common in iRBD - No difference in depression scores - No difference in ESS scores
Leclair-Visonneau et al. *Heterogeneous pattern of autonomic dysfunction in Parkinson's Disease.* Journal of Neurology, 2018.	- 30 PD with RBD - 15 PD w/o RBD	- MMSE - MOCA - MDRS - SCOPA-AUT - NMSQuest	- PSG - Pupillometry - Tear secretion (Schirmer's test) - Saliva production (Saxon test) - Heart rate variability - Orthostatic hypotension - Quantitative thermal sensory testing (QST) - Nerve conduction velocity (NCV) - Sudomotor function [sympathetic skin response (SSR)] - Skin biopsy	- 13 (29%) PD patients had reduced intraepidermal nerve fiber density on skin biopsy - Skin denervation was associated with quantitative thermal sensory testing, constipation and ocular dryness - Cognitive impairment was associated with cardiovascular symptoms and dysfunction (orthostatic hypotension), as well as with constipation and sexual dysfunction - Axial motor impairment and RBD disorder were not related to any subjective or objective finding
Sorensen et al. *Attenuated Heart Rate Response in REM Sleep Behavior Disorder and Parkinson's Disease.* Mov Disorders, 2012.	- iRBD - 14 PD with RBD - 16 PD w/o RBD - 17 controls	None	- PSG	- The heart rate response to leg movements for the iRBD group was intermediate between PD and controls

(*continued on next page*)

Table 1 (*continued*)

Study	Patient selection	Rating scales	Quantitative testing	Findings
Postuma et al. *Cardiac Autonomic Dysfunction in Idiopathic REM Sleep Behavior Disorder*. Mov Disorders, 2010.	- 21 iRBD - 11 PD with RBD - 1 MSA with RBD - 5 LBD with RBD - 4 AD with RBD - 21 controls		- PSG - Heart rate variability	- R-R standard deviation was reduced in patients with iRBD compared with controls - Total power was reduced in patients with iRBD compared with controls - VLF was lower in patients with iRBD compared with controls - LF was lower in patients with iRBD compared with controls - No differences on any measure between patients with iRBD who went on to develop disease and those who remained disease free was found
Lanfranchi et al. *Cardiac Autonomic Regulation During Sleep in Idiopathic REM Sleep Behavior Disorder*. Sleep, 2007.	- 10 iRBD - 10 controls	- None	- PSG - Heart rate variability	- No differences were observed between the 2 groups in any of the sleep variables considered
Bugalho et al. *Heart rate variability in Parkinson disease and idiopathic REM sleep behavior disorder*. Clinical Autonomic Research, 2018.	- 10 iRBD - 18 PD with RBD - 8 PD w/o RBD	None	- Heart rate variability	- No heart rate variability differences between PD and iRBD
Barone et al. *Autonomic dysfunction in isolated rapid eye movement sleep without Atonia*. Clin Neurophysiol, 2015.	- 21 RSWA - 21 controls	None	- PSG - Heart rate variability	- Significant differences between groups in RR standard deviation
Miyamoto et al. *Reduced cardiac 123I-MIBG scintigraphy in idiopathic REM sleep behavior disorder*. Neurology, 2006.	- 13 iRBD - 12 PD - 8 controls	None	- PSG - MIBG	- Delayed H/M ratio reduced in patients with both iRBD and PD compared to controls
Postuma et al. *Prodromal Autonomic Symptoms and Signs in Parkinson's Disease and Dementia with Lewy Bodies*. Mov Disorders, 2013.	- 59 iRBD - 17 PD - 15 LBD	- Autonomic symptom checklist (structured interview based on the MSA rating scale) - Standardized neuropsychological battery	- Orthostatic stand testing	- Estimated prodromal interval of 10–20 years on regression analysis (and at least 5 years according to direct observation)
Kashihara et al. *Cardiac 123I-MIBG uptake is reduced more markedly in patients with REM sleep behavior disorder than in those with early stage Parkinson's disease*. Parkinsonism and Relat Disord, 2010.	- 13 iRBD - 222 idiopathic PD - 50 controls with vascular parkinsonism or essential tremor w/o neurodegenerative disease	- MMSE	- Cardiac MIBG - Brain MRI - HUT	- Delayed H/M ratios significantly lower patients with iRBD and PD compared to the controls. - H/M ratios significantly lower in iRBD PD at H & Y stages 1 and 2 and equaled those with PD at H & Y stages 3, 4 and 5. - The MMSE score was significantly decreased in patients with IPD when compared with those with RBD
Kim et al. *Orthostatic hypotension and cardiac sympathetic denervation in Parkinson disease patients with REM sleep behavioral disorder*. J Neurol Sci, 2016.	- 53 PD with iRBD - 41 PD w/o RBD	None	- HUT - Ambulatory 24-hour blood pressure values - MIBG	- Patients with iRBD had higher systolic blood pressure changes during orthostasis (7.3% Px w/o RBD Vs 41.5% with RBD) - Patients with RBD (84.9%) had lower myocardial MIBG uptake than patients without RBD (58.5%) and controls - Patients with OH also had lower mean H/M ratios those in the non-OH group
Barateau et al. *Cardiac Sympathetic Activity differentiates Idiopathic and Symptomatic Rapid Eye Movement Sleep Behaviour Disorder*. Scientific Reports, 2018.	- 15 iRBD - 34 Type 1 narcolepsy w/RBD - 78 controls	None	- PSG - MIBG - CSF hypocretin	- Reduced H/M ratios were associated with iRBD, but not with NT1-RBD
Frauscher et al. *Investigation of autonomic function in idiopathic REM sleep behavior disorder*. J Neurol, 2012.	- 15 iRBD - 15 PD	- Marburg RBD screening questionnaire - COMPASS	- HUT - Orthostatic standing test - Valsalva maneuver	- Blood pressure changes at minute 3 and 10 were similar between iRBD and controls on HUT - On orthostatic standing testing, iRBD patients had higher systolic and diastolic blood pressure changes than controls - Valsalva ratio was significantly lower in PD patients and iRBD patients compared to controls
	93 iRBD	- UPDRS part III - MMSE		- 26/93 patients developed a neurodegenerative disorder

(*continued on next page*)

Table 1 (*continued*)

Study	Patient selection	Rating scales	Quantitative testing	Findings
Postuma et al. *Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder.* Neurology, 2009.				- The estimated 5-year risk of neurodegenerative disease was 17.7% - The 10-year risk was 40.6% - The 12-year risk was 52.4%

Abbreviations: iRBD = idiopathic REM-Sleep Behavior Disorder; NMSQ = Nonmotor Symptom Questionnaire; SCOPA-AUT = Scale for Outcomes in Parkinson Disease – Autonomic; HAMD-17 = Hamilton Depression Rating Scale-17; MMSE = mini-mental state exam; MOCA = Montreal cognitive assessment test; OH = orthostatic hypotension; DAT-SPECT = dopamine active transporter single photon emission computed tomography; PSG = polysomnography; UMSARS = unified multiple system atrophy rating scale; HUT = head up tilt; PD = Parkinson's disease; H & Y = Hoehn and Yahr; UPDRS = unified Parkinson's disease rating scale; NE = norepinephrine; UPSIT = University of Pittsburg smell identification test; ESS = Epworth Sleepiness Scale; MDRS = Mattis dementia rating scale; LF = low frequency; HF = high frequency; MIBG = metaiodobenzylguanidine; H/M = Heart to mediastinum ratio; COMPASS = Composite Autonomic Scoring Scale.

however, has not been consistently demonstrated to correlate with the severity of RBD or with phenoconversion rate. This may indicate that α-syn induced neurodegeneration is more constant throughout the disease course in patients with less aggressive synucleinopathies, however this is speculative. While HRV may serve as a supportive test in the diagnosis of RBD, it does not seem to correlate with disease progression, and its use in future trials is uncertain.

While the data on cardiovascular reflex testing are limited, we believe this testing has the greatest potential to measure subtle autonomic changes in individuals with iRBD and to follow these changes over time. Measures of sudomotor function (QSART) may help quantify sudomotor post-ganglionic denervation and small fiber neuropathy, which may correlate with peripheral α-syn deposition. Measures of HRV and Valsalva HR ratio during wake provide measures of cardiovagal tone, and Valsalva and HUT testing provide controlled measures of sympathetic tone and baroreceptor function. Thus, if available at enrollment centers, we recommend cardiovascular reflex testing in all patients for future clinical trials. If this equipment is not available, an active stand test should be performed to evaluate for OH, with BP and HR measurements performed after 5 min of rest in the supine position, and then again at minute 1 and minute 3 of standing.

A main concern for any neuroprotection study involving patients with iRBD is enrolling patients who are so early in their disease state that the risk of potential side effects from neuroprotective agents outweighs any potential disease-modifying benefit. Evidence of autonomic impairment may help with risk stratification in this population, with those demonstrating greater autonomic impairment having a potential greater risk of phenoconversion. However, numerous studies have suggested that the presence of nonmotor features, including RBD and autonomic abnormalities such as OH, are associated with a diffuse and malignant subtype of PD with a high rate of progression and high incidence of dementia (Fereshtehnejad and Postuma, 2017; Nomura et al., 2013; Anang et al., 2014; Postuma et al., 2012). One possible explanation proposed for this finding is that α-synuclein pathology is different and more diffuse in RBD-associated PD than in disease without RBD, not only in the CNS but also in peripheral autonomic networks. Therefore, enrolling only iRBD patients with autonomic impairment may lead to a selection bias creating a subgroup of patients with more aggressive disease. Nonetheless, it is clear that RBD and autonomic impairment are strongly correlated, and any future clinical trial should include autonomic outcome measures as a component of its efficacy analysis. Future longitudinal studies evaluating autonomic function over time in patients with iRBD are ultimately needed to help determine which measures are directly correlated with α-syn-induced neurodegeneration.

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Declarations

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