REVIEW

# Orthostatic hypotension and REM sleep behaviour disorder: impact on clinical outcomes in α-synucleinopathies

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## ABSTRACT

**Objective** Review the effect of orthostatic hypotension (OH) and rapid-eye-movement sleep behavioural disorder (RBD) on survival, cognitive impairment and postural stability, and discuss pathogenic mechanisms involved in the association of these two common non-motor features with relevant clinical outcomes in α-synucleinopathies.

**Methods** We searched PubMed (January 2007–February 2019) for human studies of OH and RBD evaluating cognitive impairment, postural instability, and survival in Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and pure autonomic failure (PAF). Included studies were analysed for design, key results and limitations as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

**Results** OH and RBD showed a positive association with cognitive impairment in PD and DLB, conflicting association in PAF, and no association in MSA. OH was correlated with incident falls and postural instability in PD and DLB but not in MSA. The association between RBD and postural instability was inconclusive; positive in five studies, negative in seven. OH, but not RBD, correlated with reduced survival in PD, DLB and MSA. The combination of OH and RBD was associated with cognitive impairment and more rapid progression of postural instability.

**Conclusions** OH and RBD yielded individual and combined negative effects on disability in α-synucleinopathies, reflecting a 'malignant' phenotype of PD with early cognitive impairment and postural instability. Underlying mechanisms may include involvement of selected brainstem cholinergic and noradrenergic nuclei.

## INTRODUCTION

Orthostatic hypotension (OH) and rapid-eye-movement (REM) sleep behaviour disorder (RBD) are frequent non-motor sources of disability in α-synucleinopathies including Parkinson's disease (PD), dementia with Lewy bodies (DLB), pure autonomic failure (PAF) and multiple system atrophy (MSA).[1–3] OH occurs in 20%–50% in PD, 30%–70% in DLB, 80% in MSA and, by definition, 100% in PAF[2]. RBD has a prevalence of 30%–50% in PD, 70%–80% in DLB and 80%–90% in MSA. In addition, 70%–90% of idiopathic RBD convert to alpha-synucleinopathies.[1]

OH is defined as a blood pressure (BP) drop of at least 20/10 mm Hg (systolic/diastolic) from supine to standing position, which results from cardiovascular dysfunction caused by the complex interplay between autonomic dysregulation in central (brainstem) and peripheral mechanisms, cardiac noradrenergic sympathetic denervation, peripheral norepinephrine deficiency and arterial baroreflex failure, ultimately leading to impaired arterial vasoconstriction and reduced compensatory cardiac output in response to hypotension.[4] The clinical manifestations of OH are typically insidious, ranging from non-specific symptoms such as dizziness, lightheadedness, and confusion, to potentially dramatic complications from syncope and falls,[5] with a 36% increased mortality risk among the elderly.[6]

RBD is a clinical disorder characterised by loss of the normal muscle atonia during the REM phase of sleep, which results in impaired suppression of movement generators and complex dream enactment behaviours.[7] Although the RBD-generating pathogenic mechanisms remain unclear, several lines of evidence suggest a dysregulation of specific brainstem areas, in particular, the REM-activating pre-coeruleus and sub-laterodorsal regions and the REM-inhibitory periaqueductal grey matter and lateral pontine tegmentum.[8] Clinically, RBD represents not only a primary cause of sleep quality disruption but also a major cause of secondary injuries due to punching, kicking, jumping or other involuntary motor behaviours occurring during sleep.[9]

Studies investigating the phenotypic heterogeneity of PD have identified OH and RBD as risk factors for early development of postural instability and dementia.[10–15] However, the clinical and pathological association of these two non-motor symptoms has never been properly analysed in α-synucleinopathies. We sought to systematically analyse and discuss data accumulated in support of the individual and combined effects of OH

and RBD on cognitive impairment, postural instability, and survival.

## METHODS

### Search methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] We searched PubMed for human studies published between January 2007 and February 2019 using combinations of the following terms: orthostatic hypotension, REM sleep behaviour disorder, cognition, dementia, postural instability, survival, Parkinson, multiple system atrophy, pure autonomic failure, DLB. Qualifying studies were categorised as documenting the individual versus combined effect of OH and RBD on at least one of the following endpoints: (a) cognitive impairment, (b) falls or postural instability and (c) survival. Imaging and pathological studies were included but analysed separately. To limit potential confounders, we excluded studies reporting outcomes on patients treated with deep brain stimulation or infusion therapies. No restrictions were applied to gender, age, ethnicity, disease duration, disease severity or language.

### Selection of studies and quality appraisal

Abstracts were independently reviewed for eligibility criteria by two investigators (AM and JAT). Quality appraisal and selection of pertinent full-text articles were conducted using the Wales Health Evidence Bulletin tools for cohort, case–control and cross-sectional studies.[17] Disagreements were settled by consensus among the authors. The reference lists of selected articles were additionally screened for additional pertinent studies.

### Data extraction

We used a standardised form to extract the following data from eligible studies: (a) study population (PD, DLB, PAF and MSA), (b) study design (longitudinal, cross-sectional, retrospective, pathologically proven, eg, autopsy, case series), (c) sample size, (d) key results, (e) measures of statistical association, and (f) possible bias and study limitations.

The level of diagnostic accuracy for OH, RBD, cognitive impairment and postural instability/falls was rated as follows:

*Diagnosis of RBD.* Level A: based on polysomnography; level B: based on RBD-specific validated questionnaires such as the REM Behavioural Screening Questionnaire[s1] or the Mayo Clinic RBD questionnaire;[s2] level C: based on non-specific questionnaires assessing sleep disturbances and other non-motor symptoms such as the Non-Motor Symptoms Questionnaire[s3] or the Non-Motor Symptoms Scale.[s4]

*Diagnosis of OH.* Level A: based on cardiovascular autonomic laboratory testing; level B: based on supine-to-standing BP measurements in a clinical setting; level C: based on clinical questionnaires.

*Diagnosis of cognitive impairment.* Level A: based on the Movement Disorder Society (MDS) level II criteria for mild cognitive impairment (MCI) [s5] or dementia;[s6] level B: based on MDS level I criteria for MCI[s5] or dementia;[s6] level C: based on clinical diagnosis of cognitive impairment not supported by formal neuropsychological testing.

*Diagnosis of falls and postural instability.* Level A: prospective assessment of the number of falls; level B: postural instability evaluated by validated clinical scales (ie, Tinetti and Berg balance scales [s7]) or posturography;[s8] level C: postural instability at the 'pull test'.[s9]

## RESULTS

Out of the 2601 records derived from the initial search strategy, 101 studies met full eligibility criteria and underwent data extraction[10–14 18–36][s10-s86]: 41 focused on OH; 43 on RBD; three on both OH and RBD and 14 on the association between OH and RBD (online supplementary figures 1-3).

### Individual impact of OH on clinical outcomes

*Cognition*. Three longitudinal studies found a 2.8-fold to 3.3-fold increased risk of cognitive impairment in patients having PD with OH,[10s10, s11] confirming the results from six cross-sectional studies in PD[s12-s17] and one in PAF.[s18] Negative data were reported by four cross-sectional studies in PD,[s19-s22] three in MSA[s23-s25] and one in PAF [s26] (online supplementary table 1).

*Postural stability and falls*. Six longitudinal,[s27-s32] one cross-sectional[s33] and two autopsy[18][S34] studies found an association between OH and incident falls in PD. OH was associated with number of falls in PD and DLB,[s35] and with increased postural sway in PD.[s36] Negative data were reported in one longitudinal and two cross-sectional studies in PD,[s37-s39] one autopsy series in DLB[s34] and two autopsy series in MSA (online supplementary table 2).[s34, 19]

*Survival*. Two longitudinal studies and one autopsy cohort demonstrated an independent association between OH and reduced survival in PD,[18 20 21] with a 10-year survival rate of 74% in patients having PD with OH compared with 93% in patients with PD without OH, 36% in MSA and 87% in PAF[20] (table 1). A reduced life expectancy was also documented in patients with DLB with OH,[21] and a trend towards reduced survival in MSA with early autonomic dysfunction.[19 22 23] Only one study did not find an association between OH and survival in PD.[24]

*Imaging and pathology*. OH correlated with cerebral atrophy involving the insular cortex,[s40] as well as with cholinergic alterations,[s17] subcortical microbleeds[s41] and white matter hyperintensities (WMH)[s42, s43] in PD (online supplementary table 3; figures 1 and 2). One study documented the association between OH and WMH in MSA,[s44] while two (one in PD and one in MSA) reported negative results.[s13, s24] In DLB, OH was correlated with hypoperfusion in the occipital-parietal cortex [s45] (online supplementary table 3).

### Individual impact of RBD on clinical outcomes

*Cognition*. Nine longitudinal studies reported an increased risk of cognitive impairment (OR=2–49) in patients having PD with RBD,[10 11 25 [s10, s46-s50]] confirming the results from 12 cross-sectional studies.[26–28 [s51-s59]] An autopsy series showed an association between RBD and more aggressive progression of dementia and hallucinations in DLB.[s60] Negative data were reported in one longitudinal [s61] and seven cross-sectional studies in PD,[29 30 [s62-s66]] and one longitudinal study in DLB (online supplementary table 4).[s67]

*Postural stability and falls*. One longitudinal [s31] and four cross-sectional studies showed that RBD is associated with falls[28 [s63, s68]] and postural instability [s66] in PD, whereas two longitudinal and five cross-sectional studies, all based on clinical questionnaires,[27 29 30 [s69-s72]] yielded negative results (online supplementary table 5).

*Survival*. A prospective population-based study found similar survival rates in patients having PD with and without RBD after adjusting for age, age at onset, sex and motor symptoms severity (table 1).[31]

**Table 1** Association between OH and RBD and survival in α-synucleinopathies

| Study | Study design | Study population | Diagnosis of OH | Diagnosis of RBD | Main results |
|---|---|---|---|---|---|
| **OH** | | | | | |
| **In support of an association** | | | | | |
| De Pablo Fernandez *et al* 2017[18] | AS | PD (n=100) | Level B | – | Association between OH, dysautonomia, and reduced survival rate |
| Stubendorf *et al* 2016[21] | L–3 y | PDD (n=14)<br>DLB (n=16) | Level B | – | Association between OH and reduced survival rate |
| Goldstein *et al* 2015[20] | L–10 y | PD (n=95)<br>PAF (n=26)<br>MSA (n=55) | Level B | – | Association between OH and reduced survival in PD |
| Coon *et al* 2015[23] | R | MSA (n=685) | Level A | – | Association between early autonomic dysfunction and reduced survival |
| Tada *et al* 2007[22] | AS | MSA (n=49) | Level B | – | Association between early autonomic dysfunction and reduced survival |
| O' Sullivan *et al* 2008[19] | AS | MSA (n=83) | Level A | – | Association between early autonomic dysfunction and reduced survival |
| **Not in support of an association** | | | | | |
| Gray *et al* 2009[24] | L–7 y | PD (n=109) | Level B | – | No association between OH and reduced survival |
| **RBD** | | | | | |
| **Not in support of an association** | | | | | |
| Forsaa *et al* 2010[31] | L–20 y | PD (n=230) | – | Level C | No association between RBD and reduced survival rate |

Diagnostic accuracy—OH: level A: diagnosis based on cardiovascular autonomic testing; level B: diagnosis based on laying-to-standing blood pressure measurements in a clinical setting; level C: diagnosis based on clinical questionnaires.
Diagnostic accuracy—RBD: level A: diagnosis based on polysomnography; level B: diagnosis based on RBD-specific validated questionnaires; level C: diagnosis based on non-specific questionnaires assessing sleep disturbances and other non-motor symptoms.
AS, autopsy series; DLB, dementia with Lewy bodies; L, longitudinal; MSA, multiple system atrophy; OH, orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson's disease; PDD, Parkinson's disease dementia; R, retrospective; RBD, REM sleep behavioural disorder; y, years.

*Imaging and pathology*. RBD was associated with WMH [s73, s74] and cerebral atrophy in the pedunculo-pontine nucleus, raphe, locus coeruleus/subcoeruleus,[26, s52, s75] thalamus,[s52, s76] medial amygdala, prefrontal, posterior cingulate and hippocampal cortex [s77] in PD (online supplementary table 6; figure 1). Functional and nuclear medicine studies found a correlation between RBD and reduced primary motor cortex activation on functional MRI,[s78, s79] reduced cortical metabolism,[s54] and extensive noradrenergic,[26] cholinergic [s68, s80] denervation, with still inconclusive data on nigrostriatal denervation.[s50, s54] Pathological data from two PD autopsy series documented an association between RBD and α-synuclein deposition in both cortical and subcortical regions.[s81, s82] In DLB, there was an association between RBD and lower cortical metabolic activity,[s83] greater nigrostriatal dopaminergic denervation[s84] and decreased amyloid or neurofibrillary tangles compared with α-synuclein pathology (increased DLB ratio) [s60, s85, s86] (online supplementary table 6).

## Combined impact of OH and RBD on clinical outcomes

The association between OH and RBD was examined in four longitudinal,[12–14 25] nine cross-sectional studies[26–30 32–35] and one autopsy series in PD.[36] The OH-RBD cluster correlated with cognitive impairment and postural instability in a cohort of drug-naïve patients with PD followed-up for a mean of 4.5 years,[14] and in analysis of the PPMI (Parkinson's Progression Markers Initiative) cohort,[12 36] which also demonstrated an association between OH-RBD and greater cerebral atrophy, lower dopamine uptake and lower β-amyloid levels in the cerebrospinal fluid (table 2). In drug-naïve PD, a cross-sectional study ascertained an association between OH-RBD and cognitive impairment, nigrostriatal denervation and electroencephalographic (EEG) alterations in the posterior cortical areas.[13]

## DISCUSSION

There was robust evidence supporting an association for OH and RBD with cognitive impairment in PD and DLB, as well as a significant negative effect of OH on postural instability and survival. The combination of OH and RBD ('OH-RBD cluster') was associated with a malignant phenotype of PD characterised by more rapid progression of cognitive deficits and postural instability.

In PD, OH strongly correlated with reduced survival, as well as with an increased risk of dementia, falls and postural instability. RBD was associated with increased risk of dementia and, to a lower extent, gait and postural impairment. Associations were more evident in studies employing a tilt table for the diagnosis of OH and a polysomnography for the diagnosis of RBD, casting doubts on the accuracy of clinical questionnaires for the screening of orthostatic symptoms and sleep disorders.[37] Similarly, we found that studies using screening measures of global cognition, such as the MMSE (Mini Mental State Examination) or Montreal cognitive assessment, frequently failed to find an association between RBD and OH or to predict the risk of incident dementia compared with those employing extensive neuropsychological testing.[s10]38 39

Similar data were also found in other α-synucleinopathies. In DLB, OH correlated with cognitive deficits,[s45] and RBD with Lewy body cortical pathology.[s60, s85] Also, idiopathic RBD showed higher risk of conversion to DLB than PD, possibly indicating an association between RBD and prodromal cognitive deficits.[40–43] In MSA, we did not find any associations between OH or RBD and cognitive deficits. While these findings might reflect lesser cortical involvement in this specific α-synucleinopathy,[44] the limited sample size of available studies should be taken into consideration due to the frequent finding of attentional, visual-spatial and executive deficits in patients with MSA.[45] In

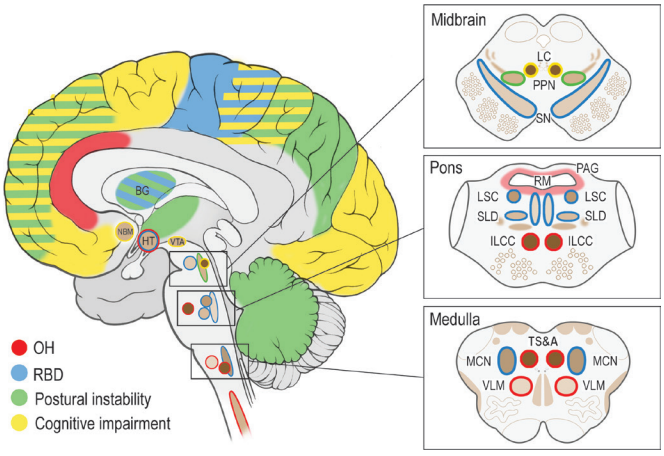


**Figure 1** Structures associated with OH, RBD, cognitive impairment and postural stability. OH-associated structures include the intermediolateral cell column (sympathetic), caudal and rostral ventrolateral medulla (sympathetic), tractus solitarius and nucleus ambiguous (parasympathetic), and paraventricular and supraoptic nuclei of the hypothalamus (production of oxytocin and ADH), anterior cingulate and insular cortex. RBD-associated structures include the magnocellularis nucleus of the medulla, pontine sublateral dorsal nucleus and dorsal raphe (serotonergic) nuclei, locus subcoeruleus (noradrenergic/sympathetic), and lateral pontine tegmentum, midbrain periaqueductal grey matter formation (GABAergic) and substantia nigra (dopaminergic), basal ganglia, hypothalamus, and motor cortex. Postural instability-associated structures include the pedunculopontine nucleus (glutamatergic/cholinergic) in the pontine tegmentum/midbrain, cerebellum, caudate nucleus (GABAergic), posterior thalamus, thalamic ventrolateral nucleus (GABAergic), and parieto-insular vestibular and prefrontal cortex. Cognitive-associated structures include the hippocampus, nucleus basalis of Meynert (cholinergic/parasympathetic) and the neocortex, especially prefrontal, temporo-parietal and occipital lobes. BG, basal ganglia; GABA, gamma-aminobutyric acid; HT, hypothalamus; ILCC, intermediolateral cell column; LC, locus coeruleus; LSC, locus subcoeruleus; MCN, magnocellularis nucleus; NBM, nucleus basalis of Meynert; OH, orthostatic hypotension; PAG, periaqueductal grey matter; PPN, pedunculopontine nucleus; RBD, REM-sleep behaviour disorders; RM, raphe medialis; SLD, sublateral dorsal nucleus; SN, substantia nigra; TS&A, tractus solitarius and ambiguous nuclei; VLM, caudal and rostral ventrolateral medulla; VTA, ventrotegmental area.

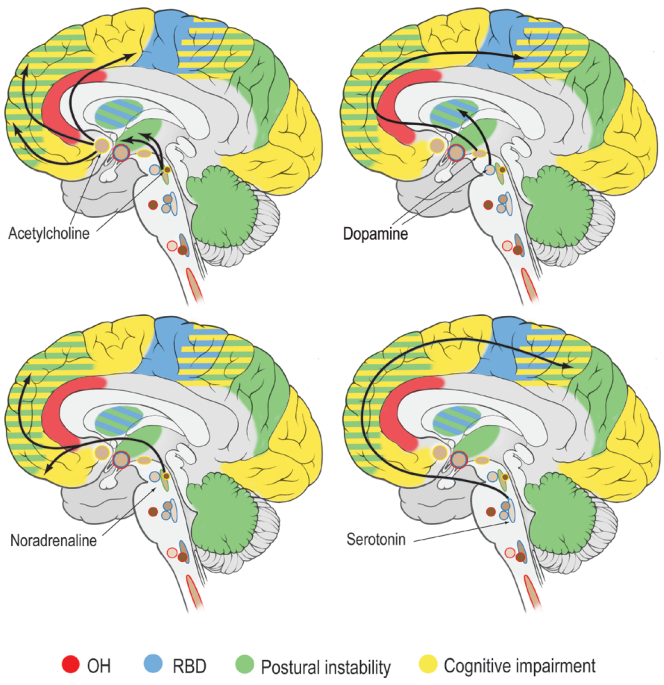


**Figure 2** Functional neurotransmission pathways connected to the regions linking OH, RBD, cognitive impairment and postural stability. Cholinergic pathways connect the pedunculopontine/lateral dorsal tegmental nuclei projections to thalamus and the nucleus basalis of Meynert with the neocortex. Dopaminergic pathways connect the substantia nigra in the ventral midbrain with the nigrostriatal system, and the ventrotegmental area to mesolimbic and mesocortical areas. Noradrenergic pathways connect the locus coeruleus with the cingulate and prefrontal cortex. Serotoninergic pathways connect the raphe nuclei with the frontal cortex. OH, orthostatic hypotension; RBD, REM-sleep behaviour disorders; REM, rapid-eye movement.

PAF, conflicting results were reported on the cognitive effect of cerebral hypoperfusion.[s18, s26]

Neuroimaging studies identified severe nigrostriatal denervation and EEG alterations in the posterior cortical areas of patients having PD with RBD and OH,[13] as well as an individual association of both conditions with cholinergic deficits.[s17, s68, s80] These data prove relevant when considering the pathological overlap in the anatomical and functional structures associated with OH and RBD, which involve critical brainstem regions modulating the cholinergic, serotoninergic and noradrenergic pathways (figures 1 and 2).

Neuropathological studies found an association between RBD and α-synuclein deposition in critical areas such as the locus coeruleus, raphe nuclei, paramammillary nuclei, amygdala, thalamus and entorhinal cortex. [s81, s82] The same regions are involved in the central autonomic network that extends from cortical and diencephalic structures (insular cortex, anterior cingulate and amygdala) to the brainstem periaqueductal grey, ventrolateral medulla, medullary raphe, dorsal motor nucleus of vagus, nucleus ambiguous, and pontine micturition centre.[2]

OH, in particular, is associated with degeneration in the pedunculopontine cholinergic nucleus, noradrenergic periacqueductal grey neurons, rostral ventrolateral medulla, dorsolateral vagal motor nucleus and nucleus ambiguous (figure 1). All of these structures participate in a subcortical network projecting to the thalamic areas and to the posterior insular cortex, which receives and integrate inputs from visceral, thermal and pain receptors and connect with the anterior cingulate cortex, amygdala and basal ganglia.[s40] While cholinergic and noradrenergic deficits due to the involvement of locus coeruleus, pontine reticular formation and lower raphe are likely to be involved in cognitive impairment,[26 46] mechanisms underlying the association between OH and falls remain unclear. It has been suggested that OH might cause falls due to orthostatic cortical hypoperfusion,[47] neurodegeneration of critical areas responsible for both postural instability and cardiovascular dysautonomia[s17] or a combination thereof.[48] Critically, the effect of peripheral hypotension and the frequently associated supine hypertension (SH) on the regulation of cerebrovascular perfusion remains to be clarified. A retrospective assessment of 204 subjects [s43] found that patients having PD with OH have a greater extent of deep and periventricular white matter lesions. However, the differential effect of OH and SH on white matter abnormalities remains unclear, as well as the impact of these two opposing haemodynamic conditions on cortical and subcortical areas involved in cognition and gait.

**Table 2** Association between OH and RBD

| Study | Study design | Study population | Diagnosis of OH | Diagnosis of RBD | Main results |
|---|---|---|---|---|---|
| **In support of an association** | | | | | |
| Nomura *et al* 2013[25] | L–2 y | PD (n=82) | Level B | Level A | Association between RBD and OH |
| Postuma *et al* 2011[34] | CS | PD (n=53) | Level A | Level A | Association between RBD and cardiac autonomic denervation |
| Sommerauer *et al* 2018[26] | CS | PD (n=30) | Level A | Level A | Higher prevalence of OH in patients with versus without RBD |
| Kim *et al* 2016[32] | CS | PD (n=94) | Level A | Level B | Association between RBD and OH |
| Postuma *et al* 2008[33] | CS | PD (n=36) | Level B | Level A | Association between RBD and OH |
| Nomura *et al* 2010[35] | CS | PD (n=49) | Level B | Level A | Association between RBD and cardiac autonomic denervation |
| Romenets *et al* 2012[28] | CS | PD (n=98) | Level B | Level A | Association between RBD and OH |
| Rolinski *et al* 2014[27] | CS | PD (n=475) | Level B | Level B | Higher BP drop at the tilt-test in patients with vs without RBD |
| Liu *et al* 2017[29] | CS | PD (n=141) | Level C | Level B | Association between RBD and OH symptoms |
| **Not in support of an association** | | | | | |
| Yoritaka *et al* 2009[30] | CS | PD (n=150) | Level C | Level B | No association between RBD and OH medication |
| **Clusters studies** | | | | | |
| Fehrestenehjad *et al* 2015[14] | L– 5 y | PD (n=76) | Level B | Level A | Worse motor, non-motor and cognitive (NPS) symptoms progression in the OH-RBD cluster |
| Fehrestenehjad *et al* 2017[12] | L–3 y | PD (n=421) | Level B | Level B | Worse motor and cognitive (UPDRS-I, MoCA) symptoms progression and worse ADL progression (UPDRS-II) in the OH-RBD cluster |
| Arnaldi *et al* 2017[13] | L–5 y | PD (n=54) | Level B | Level B | Worse cognitive (NPS) symptoms progression in the OH-RBD cluster |
| De Pablo Fernandez *et al* 2019[36] | AS | PD (n=111) | Level C | Level B | Malignant phenotype associated with falls, inability to walk, dementia and shorter survival |

Diagnostic accuracy—OH: level A: diagnosis based on cardiovascular autonomic testing; level B: diagnosis based on laying-to-standing blood pressure measurements in a clinical setting; level C: diagnosis based on clinical questionnaires.
Diagnostic accuracy—RBD: level A: diagnosis based on polysomnography; level B: diagnosis based on RBD-specific validated questionnaires; level C: diagnosis based on non-specific questionnaires assessing sleep disturbances and other non-motor symptoms.
ADL, activities of daily living; AS, autopsy series; BP, blood pressure; CS, cross-sectional; L, longitudinal; MoCA, Montreal cognitive assessment; NPS, neuropsychological testing; OH, orthostatic hypotension;PD, Parkinson's disease; RBD, Rem sleep behavioural disorder; UPDRS-I, unified Parkinson's Disease Rating Scale–section I; UPDRS-II, Unified Parkinson's Disease Rating Scale–section II; y, years.

Pathogenic mechanisms associated with RBD involve an extensive network of micro-circuits within the brainstem, forebrain and hypothalamus. In normal subjects, cholinergic inputs activate the subcoeruleus glutamatergic and gabaergic neurons, which promote REM sleep and muscle atonia.[49] The locus coeruleus activity is also modulated by the dorsal paragigantocellular reticular medullar nucleus, hypothalamic melanin-concentrating hormone neurons, dorsal raphe and periacqueductal grey matter (figures 1 and 2).[9] Pathologically proven case series have shown an association between RBD and α-synuclein deposition in the locus coeruleus and other brainstem nuclei participating to the thalamic modulation of the cortical activity.[s60, s81, s82][50] In addition, independent reports found evidence of cholinergic dysfunctions in patients with RBD,[s80] as well as signs of involvement of the pedunculopontine nucleus, which is a critical node in the locomotor mesencephalic area modulating gait and balance.[48]

Some limitations may affect the interpretation of our data. First, the studies assessing the combined effect of OH and RBD are relatively few. Second, the majority of studies focused on PD, with relatively limited data from other α-synucleinopathies. Third, substantial heterogeneity was detected in the inclusion criteria, as well as in the methodologies used to assess OH and RBD. Also, the variable number of available studies for each α-synucleinopathy inevitably limited comparisons between different pathologies. While OH and RBD showed a positive association with cognitive impairment in PD and DLB, conflicting results were reported in PAF and no association in MSA. To what extent these data reflect fundamental differences in pathological mechanisms remains to be clarified.

## CONCLUSIONS

Limitations notwithstanding, our systematic review highlights the importance of OH and RBD as markers suggestive of a distinctive subtype of α-synucleinopathies characterised by early cognitive impairment, pronounced postural instability and reduced survival rate. These data support the need for well-designed clinical and neuroimaging studies focusing on the management of non-dopaminergic symptoms,[38 51 52] critical to inform the development of innovative cholinergic and noradrenergic agents for cognitive impairment and postural instability in α-synucleinopathies.

Additional references are cited as supplementary materials (online supplementary references).

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