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## Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder

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## Abstract

**Objective**—To determine the pathologic substrates in patients with rapid eye movement (REM) sleep behavior disorder (RBD) with or without a coexisting neurologic disorder.

**Methods**—The clinical and neuropathologic findings were analyzed on all autopsied cases from one of the collaborating sites in North America and Europe, were evaluated from January 1990 to March 2012, and were diagnosed with polysomnogram (PSG)-proven or probable RBD with or without a coexisting neurologic disorder. The clinical and neuropathologic diagnoses were based on published criteria.

**Results**—172 cases were identified, of whom 143 (83%) were men. The mean  $\pm$  SD age of onset in years for the core features were as follows – RBD,  $62 \pm 14$  (range, 20–93), cognitive impairment ( $n = 147$ );  $69 \pm 10$  (range, 22–90), parkinsonism ( $n = 151$ );  $68 \pm 9$  (range, 20–92), and autonomic dysfunction ( $n = 42$ );  $62 \pm 12$  (range, 23–81). Death age was  $75 \pm 9$  years (range, 24–96). Eighty-two (48%) had RBD confirmed by PSG, 64 (37%) had a classic history of recurrent dream enactment behavior, and 26 (15%) screened positive for RBD by questionnaire. RBD preceded the onset of cognitive impairment, parkinsonism, or autonomic dysfunction in 87 (51%) patients by  $10 \pm 12$  (range, 1–61) years. The primary clinical diagnoses among those with a coexisting neurologic disorder were dementia with Lewy bodies ( $n = 97$ ), Parkinson's disease with or without mild cognitive impairment or dementia ( $n = 32$ ), multiple system atrophy (MSA) ( $n = 19$ ), Alzheimer's disease (AD) ( $n = 9$ ) and other various disorders including secondary narcolepsy ( $n = 2$ ) and neurodegeneration with brain iron accumulation-type 1 (NBIA-1) ( $n = 1$ ). The neuropathologic diagnoses were Lewy body disease (LBD) ( $n = 77$ , including 1 case with a duplication in the gene encoding  $\alpha$ -synuclein), combined LBD and AD ( $n = 59$ ), MSA ( $n = 19$ ), AD ( $n = 6$ ), progressive supranuclear palsy (PSP) ( $n = 2$ ), other mixed neurodegenerative pathologies ( $n = 6$ ), NBIA-1/LBD/tauopathy ( $n = 1$ ), and hypothalamic structural lesions ( $n = 2$ ). Among the neurodegenerative disorders associated with RBD ( $n = 170$ ), 160 (94%) were synucleinopathies. The RBD-synucleinopathy association was particularly high when RBD preceded the onset of other neurodegenerative syndrome features.

**Conclusions**—In this large series of PSG-confirmed and probable RBD cases that underwent autopsy, the strong association of RBD with the synucleinopathies was further substantiated and a wider spectrum of disorders which can underlie RBD now are more apparent.

## Keywords

REM sleep behavior disorder; Parasomnia; Lewy body disease; Dementia with Lewy bodies; Parkinson's disease; Multiple system atrophy; Synuclein; Synucleinopathy

## 1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by loss of normal skeletal muscle atonia during REM sleep with prominent motor activity and dreaming [1–5]. The parasomnia occurs more frequently in males, and usually begins manifesting after the age of 50 years [3–5]. RBD can occur without any coexisting neurologic disorders or findings (so-called idiopathic RBD or iRBD) and can be precipitated or aggravated by certain classes of medications, particularly selective serotonin or norepinephrine reuptake inhibitors [6,7]. RBD often is a manifestation of the state dissociation characteristic of narcolepsy [8]. Some cases of autoimmune and paraneoplastic encephalopathies, particularly in association with high titers of antibodies against proteins that form part of the voltage-gated potassium channel complex were identified over recent years [9]. RBD also can be triggered by structural brain lesions such as brainstem infarcts, tumors, vascular malformations, and demyelinating plaques associated with multiple sclerosis [10,11]; these accidents of nature have provided insights into the location of the networks implicated in human RBD. All structural lesions identified to date have been localized in the dorsal midbrain, pons, or medulla. Neuroimaging studies in the voltage-gated potassium channel complex-associated RBD cases show abnormalities in the mesial temporal lobe structures and usually not in the brainstem [12]. These unique cases underscore that the precise networks and neurotransmitter systems involved in human RBD remain unclear but most consistently relate to brainstem networks and their efferent or afferent connections.

RBD associated with neurodegenerative disease was first appreciated over 15 years ago [13], and because RBD often precedes the onset of a slowly evolving neurodegenerative syndrome by years or decades [3,5,10,13–28], international attention has turned to view iRBD as a potential early clinical manifestation and biomarker of sorts of neurodegeneration rather than a curious parasomnia. Other features on PSG also can suggest an evolving neurodegenerative disorder such as laryngeal stridor and slowing of electroencephalogram activity [29–31]. If iRBD is a harbinger of parkinsonism, cognitive impairment, autonomic dysfunction, or some combination of these, at least in some individuals, one would hope that an intervention could be commenced and potentially delay the onset of these disabling features or prevent them from occurring altogether. Therefore, attention is focused on iRBD representing a “window of opportunity” with a glimpse of the future like few other neurologic or medical disorders can offer [26,27,32–34]. However, many questions remain.

Most studies based on clinically diagnosed cases have found that some neurodegenerative disorders are commonly associated with RBD and thus the rule, while others infrequently are associated with RBD, and hence the exceptions. Those commonly associated with RBD include multiple system atrophy (MSA) [1,2,5,14,15,23,25,29,35–46], Parkinson’s disease (PD) with or without dementia [1,5,6,10,17,18,23,25,26,40,43,47–74], dementia with Lewy bodies (DLB) [10,21–27,75–85], and less commonly pure autonomic failure [40,86]. These disorders are collectively termed the *synucleinopathies* due to the presence of  $\alpha$ -synuclein-positive inclusions in neurons or glia [87–90]. Yet several nonsynucleinopathy disorders also have been reported in association with RBD, namely spinocerebellar atrophy type 3 (Machado–Joseph disease) [91–94], progressive supranuclear palsy (PSP) [5,40,95,96], Guadalupian parkinsonism [97], Huntington disease [98], and Alzheimer’s disease (AD) [26,99,100]. A single case of suspected corticobasal degeneration [101] was found to have REM sleep without atonia – the electrophysiologic substrate for RBD – but no history of dream enactment behavior. This case was considered representative of subclinical RBD. The clinically diagnosed cases therefore suggest that RBD often is (but not always associated with one proteinopathy – the synucleinopathies and less commonly associated with other proteinopathies; this is a phenomenon known in neurodegenerative disease circles as

selective vulnerability. As disease-modifying therapies are being refined in the transgenic mouse models of neurodegenerative diseases to target proteinopathy pathophysiology, it will be critical for clinicians to accurately predict during life which proteinopathy is likely underlying any patient's features. Although clinicians make syndromic diagnoses in the clinic every day and infer which disease (and hence which proteinopathy) is underlying each patient's syndrome, this is an imperfect science and numerous examples abound in the literature on clinicopathologic inaccuracies. Assumptions often are made when the gold standard of neuropathologic examination rarely is or is never performed. Herein we describe the value of clinicopathologic correlations and the purpose of this large collaborative clinicopathologic analysis.

## 2. Design and methods

### 2.1. Case ascertainment

The International RBD Study Group initially convened in 2007 led by Professors Moller, Oertel and Stiasny-Kolster from the University of Marburg and includes investigators from many sites in North American and Europe who are devoted to clinical practice and research issues pertaining to RBD. Investigators at each site were contacted in March of 2012 and asked to query their local databases or recall specific cases they had followed with RBD from January 1990 to March 2012 through to autopsy. Colleagues at other sites in North America, Europe, and Asia who were not formally part of the consortium but had previously published on RBD also were contacted. Previously published cases were not excluded from our analysis, as the intention was to be as inclusive and as up-to-date as possible.

### 2.2. Data collection

A site leader at each site was designated and asked to provide basic demographic and clinical data on each autopsied case as well as with the neuropathologic diagnoses rendered by their local neuropathologist. Additional information such as which routine and immunohistochemical stains were used in the diagnostic evaluation also was included. The following data was requested for each case from each site leader:

- sex
- onset age of RBD
- method of determining diagnosis of RBD (PSG, history of recurrent dream enactment behavior, or questionnaire)
- onset age of cognitive impairment, if applicable
- onset age of parkinsonism, if applicable
- onset age of autonomic dysfunction, if applicable
- final clinical diagnosis
- death age
- neuropathologic diagnosis
- additional details on pathology (eg, coexisting pathologies, stains used, criteria used).

### 2.3. Determination of RBD diagnosis

Three levels of RBD diagnosis status were decided *a priori*. The most desirable cases to include in any RBD analysis were those who fulfill the standard criteria for diagnosis, which requires PSG confirmation of increased electromyogram tone during tonic and/or phasic

REM sleep (stage R in the updated rubric) ± complex motoric behavior or vocalizations [102]. Such cases are considered PSG-confirmed RBD (PSG + RBD). Due to the inherent variability across centers in performing clinicopathologic analyses, some centers had hundreds of PSG + RBD cases but had few or none who had undergone autopsy. Others had brain banks with ample numbers of subjects who had consented to brain donation through various protocols, of whom some had undergone PSG antemortem and RBD was verified. Other patients were queried about RBD and had a classic history of recurrent dream enactment behavior but either had not undergone PSG, or did so but insufficient or no REM sleep was attained on the PSG. Therefore, the presence or absence of RBD could not be verified. These cases were classified as probable RBD due to the presence of recurrent dream enactment behavior (pRBD-DEB). Finally, some cases were identified by their completion of questionnaires during life intended to screen for RBD. A few of the questionnaires currently in use across some centers include the Mayo Sleep Questionnaire (MSQ), which has a sensitivity of 98% and a specificity of 74% for RBD based on PSG validation [103]; the RBD Screening Questionnaire [104], which is also highly sensitive and adequately specific; and the single-question screen of “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.)?” which is almost identical to the primary screening question in the MSQ. This single-question screen has a sensitivity of 94% and a specificity of 87% for RBD based on PSG validation [105]. Cases that screened positive for RBD based on a questionnaire were classified as probable RBD. Those who screened positive using the MSQ were classified as pRBD-MSQ; this measure has demonstrated utility in several patient populations [66,106–108].

#### 2.4. Polysomnography

All subjects who had undergone PSG did so for either clinical or research purposes. The diagnosis of RBD was confirmed by PSG if an experienced sleep medicine clinician diagnosed RBD based on published criteria [102,109].

#### 2.5. Neuropathologic assessment

All brains were processed, sectioned, stained, and assessed using local neuropathologic procedures. The neuropathologic diagnoses were requested based on the neuropathologist’s report or by the neuropathologist completing the standardized data request form sent to each team of investigators. Pathologic findings and diagnoses were characterized using standard stains and criteria [88,89,110,111]. For Lewy body disease (LBD), cases were classified as brainstem-, limbic-, or neocortical-predominant LBD as suggested by the consensus guidelines [111,112], but for the purpose of our analysis they were simply classified as LBD.

#### 2.6. Data analyses

Demographic, clinical, and neuropathologic data were tabulated and analyzed using descriptive statistics.

#### 2.7. Ethics

All subjects were evaluated and consented according to local ethics board policies at each respective institution.

### 3. Results

One hundred and seventy two cases were identified. Eight centers had one or more cases with adequate antemortem and pathologic data. The breakdown of contributed cases was as

follows, Mayo Clinic Rochester ( $n = 85$ ), Mayo Clinic Jacksonville ( $n = 44$ ), Mayo Clinic Arizona/Banner Sun Health ( $n = 27$ ), University of Miami ( $n = 6$ ), Hospital Clinic of Barcelona ( $n = 5$ ), Pitié-Salpêtrière Hospital ( $n = 2$ ), University of Minnesota ( $n = 2$ ), and University Hospital of Montpellier ( $n = 1$ ). Seventy-six of the 172 cases (44%) have been previously reported in various other clinicopathologic reports [16,24,27,82,83,113–116].

A summary of the demographic and clinical data are shown in Table 1. One hundred and forty three (83%) were men. The mean  $\pm$  standard deviations and range of onset ages, and death age also are shown in Table 1. For RBD, the age of onset was in the 50 to 69-year age range in  $95/172 = 55\%$ , and in the 50 to 79-year age range in  $137/172 = 80\%$ ; 11% had RBD onset prior to age 50. The RBD characteristics are shown in Table 2. Approximately half had RBD confirmed by PSG. A diagnosis of probable RBD based on a positive response to question 1 on the MSQ occurred in 15% of cases. The onset of RBD relative to the onset of other neurologic features also is shown in Table 2, with half of subjects developing cognitive impairment, parkinsonism, or autonomic dysfunction after the onset of RBD. Thirty (18%) of these cases had RBD precede the other neurologic features by 10 years or more, and five (3%) had an interval between RBD onset and other neurologic feature onset of over 40 years.

The breakdown of clinical diagnoses in subjects with PSG-proven and probable RBD who had undergone autopsy is presented in Table 3. As one would expect the vast majority (93%) of the neurodegenerative syndromes were in the presumed synucleinopathy group. Of note, one case with idiopathic RBD (iRBD) who died without any other neurologic signs or symptoms is included [114], and five cases from the Hospital Clinic of Barcelona and two from the University of Minnesota had been originally identified as iRBD and followed prospectively, as they developed DLB or PD several years after RBD diagnosis and underwent autopsy. A spectrum of cases with syndromes less commonly associated with RBD also were identified, including corticobasal syndrome (CBS,  $n = 3$ ), frontotemporal dementia ( $n = 1$ ), DLB with amyotrophic lateral sclerosis ( $n = 1$ ), MSA with mild cognitive impairment ( $n = 1$ ), AD with Binswanger disease ( $n = 1$ ), and neurodegeneration with brain iron accumulation type 1 (NBIA-1). Three cases with RBD associated with narcolepsy were identified – one who had narcolepsy with cataplexy for 61 years until developing classic DLB features, another with narcolepsy associated with voltage-gated potassium channel (VGKC) antibodies, and a 20-year-old man with an ill-defined hypothalamic lesion (the latter two cases represent secondary narcolepsy).

The primary neuropathologic diagnoses in this series are presented in Table 4. As expected among the neurodegenerative disorders, those with synucleinopathy pathology were most common (94%). Ten cases had nonsynucleinopathy pathology, six with AD (one PSG confirmed), two with PSP (one PSG confirmed), one with Creutzfeldt-Jacob disease (CJD) plus amyotrophic lateral sclerosis, and one with an indeterminate neurodegenerative disease. One of the LBD cases had a duplication of the gene encoding  $\alpha$ -synuclein (*SNCA*); he presented with RBD at age 45, then parkinsonism and autonomic dysfunction at age 49, cognitive decline at age 57, which evolved into frank dementia and death at age 63. The case with NBIA-1 had typical iron accumulation findings as well as Lewy bodies, Lewy neurites, and tau-positive tangles. The case with the VGKC antibody had an inflammatory lesion in the hypothalamus and no discernible pathology in the brainstem. The other case that had antemortem neuroimaging evidence of a hypothalamic lesion had marked gliosis and collagen deposition in the hypothalamus that could not be more distinctly classified.

Seven of the 29 women had MSA and 16 had LBD  $\pm$  AD. Considering the most frequently identified disorders in this series, the frequency of men was as follows: LBD (69/77; 90%),

LBD + AD (52/59; 88%), LBD ± AD (121/136; 89%), MSA (12/19; 63%), and AD (2/6; 33%).

The cases with clinicopathologic discrepancies are shown in Table 5. One could characterize the clinicopathologic findings as follows:

- PSG-proven or probable RBD plus presumed synucleinopathy and pathologically proven synucleinopathy = 152
- PSG-proven or probable RBD plus presumed synucleinopathy yet pathologically proven non-synucleinopathy = 7
- PSG-proven or probable RBD plus presumed nonsynucleinopathy yet pathologically proven synucleinopathy = 11
- PSG-proven or probable RBD plus presumed nonsynucleinopathy and pathologically proven nonsynucleinopathy = 2.

The timing of the onset of RBD relative to the onset of cognitive impairment, parkinsonism, and autonomic dysfunction also may have relevance for predicting synucleinopathy pathology. These data are addressed in Table 6, in which the clinicopathologic accuracy of a synucleinopathy disorder underlying the RBD-neurodegenerative disease association appears slightly higher among those who have RBD precede the other features, though this did not reach statistical significance (83/87, 95% vs 51/57 = 89%;  $p > 0.05$ ). This association appears slightly stronger for those with increasingly lengthy intervals from RBD to other neurologic features, realizing the <100% associations are driven by 1 to 3 patients depending on the interval.

## 4. Discussion

### 4.1. Overview

Our study is the largest series to date of PSG-verified and probable RBD who have undergone neuropathologic examination. The strong association of RBD with the synucleinopathies was further substantiated, and a wider spectrum of disorders that can underlie RBD now is more apparent.

### 4.2. Demographic and clinical considerations

The high frequency of RBD among males (83%) was present in this series, like in all other series. However, the frequency of RBD among men was lower in MSA (63%). These findings further support that the male predilection for RBD may be lower in MSA than in LBD [5,35,117], but a biologic explanation for this difference is not readily apparent. With only six cases with AD pathology, it is difficult to interpret the low frequency of men (33%) in this group.

While RBD may begin as early as the teens or twenties and as late in life as the nineties the mean age of onset was 62 years in this series with over half being in the 50 to 69-year age range and 80% in the 50 to 79-year age range. Eleven percent had RBD onset prior to age 50. These findings are consistent with other series showing that RBD is typically a disorder which begins in the 50 to 80-year age range.

When associated with an underlying neurodegenerative disorder, RBD usually begins prior to cognitive impairment, parkinsonism, or autonomic dysfunction (occurring in half of the subjects in this series), yet RBD can concurrently evolve or evolve after the onset of other neurologic features. The long interval between RBD onset and the onset of cognitive impairment, parkinsonism, or autonomic dysfunction in many cases was clearly present in

this series, with 30 cases having a 10 years or more interval and five having a 40-year or more interval.

#### 4.3. Neuropathologic considerations

Our findings underscore the point that when associated with dementia, parkinsonism, or autonomic dysfunction, RBD usually predicts an underlying synucleinopathy. Considering all cases in this series, the predictive accuracy of a synucleinopathy was 94% and this increased to 98% when considering only PSG-proven cases.

Considering only the PSG-confirmed cases, there were three cases (two AD and one CBS) in which a non synucleinopathy syndrome was diagnosed based on other neurologic features and a synucleinopathy (LBD) was found to be present with or without AD. There also were two cases with a presumed synucleinopathy that was suspected clinically (both PD) and a different synucleinopathy was identified at autopsy (both MSA). The two cases with non synucleinopathy pathology (one with AD and one with PSP) indicate that PSG-proven RBD is not 100% specific for the synucleinopathies in the setting of a neurodegenerative disorder. The RBD-synucleinopathy association appears increasingly stronger for those with increasingly lengthy intervals from RBD to other neurologic features.

These findings underscore several points. The presence of RBD in cases with otherwise typical features of AD or CBS should at least raise suspicion that LBD may be present, though it may be coexisting and not the primary pathology driving the other neurologic features. On the other hand, RBD can rarely be associated with a non synucleinopathy disorder, and the presence of probable or PSG-confirmed RBD could potentially dissuade the clinician from suspecting the correct underlying neurodegenerative disorder in rare instances. Such is the case in every clinicopathologic analysis in large series of neurodegenerative diseases – discrepancies will always be found – yet the strong association with the synucleinopathies is supported by these findings.

#### 4.4. Important points on key cases

Several cases warrant additional comments. The iRBD case with underlying LBD has been previously reported [114], as has another case [118]. While RBD typically is not associated with prion disease, features of state dissociation can clearly occur in prion disease – particularly in fatal familial insomnia [119]. Other phenomena such as oneiric stupor can also occur in fatal familial insomnia which shares some similarities to RBD [120]. Although the pathologically proven CJD case did not have RBD confirmed by PSG, additional cases of clinically suspected CJD and RBD warrant PSG. Three corticobasal syndrome cases had suspected RBD, with two PSG-confirmed, yet LBD pathology was present in two and AD pathology was present in all three. These cases underscore the variable pathologies which can underlie CBS, in which approximately 50% are due to corticobasal degeneration – a tauopathy [121]. The patient who presented with narcolepsy/cataplexy at age 14 and RBD at age 20 had a 61 year interval until classic DLB features evolved; the RBD in this case is more likely related to narcolepsy than LBD but interesting nonetheless. The two secondary narcolepsy plus RBD cases associated with structural changes in the hypothalamus but no obvious pathology in the brainstem suggests that rare instances of supratentorial pathology can contribute to RBD features, presumably via influences on brainstem structures, though specific pathways that are involved are not clear. The patient with NBIA-1 developed parkinsonism at age 20, cognitive decline at age 26, began exhibiting recurrent dream enactment behavior at age 30 but was unwilling to undergo PSG and died at age 38. His findings of NBIA, LBD, and tau-positive pathology indicate that another LBD spectrum disorder is associated with RBD. Finally, our case with PSG-proven RBD case associated with LBD pathology and a duplication in the gene encoding *SNCA* is noteworthy. One



would expect more reports of RBD among those with LBD associated with genetic alterations in *SNCA* than currently are published. PSG-confirmed RBD has not been previously reported in association with mutations, duplications, or triplications in *SNCA*.

#### 4.5. Limitations

Several limitations and qualifications must be acknowledged. While this was a multicenter collaborative study and additional sites and cases were sought from investigators in North America, Europe and Asia, these 172 cases surely do not represent near every case with RBD who has come to autopsy. The ages of onset for RBD, cognitive impairment, parkinsonism and autonomic dysfunction were largely based on patient and/or informant report, and the rigor with which the clinical features of interest were sought and recorded likely varied across patients and sites. The neuropathologic findings and diagnoses were based on the local neuropathologic reports, and no attempts were made to collect tissue and slides of all cases and assess the material in a standardized and blinded manner. The methods by which RBD was diagnosed varied, and one could argue that the diagnosis of probable RBD based on patient and informant report or on a screening questionnaire is not ideal. A sampling bias also could be suggested, because the RBD-synucleinopathy has been considered adequately supported by some investigators, as the original hypothesis was suggested over a decade ago [23]. Perhaps this bias might lead some investigators to not query patients and informants about RBD or seek autopsies if they had a presumed non-synucleinopathy disorder, or perhaps not seek autopsies in patients with RBD associated with presumed non synucleinopathy disorders. This latter point is not valid at least among most of the centers involved in our study, as the presence or absence of RBD is sought with some rigor in all patients with whom the investigators evaluate, and autopsies are sought in all subjects regardless of their clinical phenotype or suspected underlying neurologic disorder. This includes several hundred autopsied patients with AD, PSP, and other disorders evaluated by these investigators over the past two decades who had RBD specifically queried about and such a history was absent. Despite all of the potential limitations noted above, our findings further support the RBD-synucleinopathy association and also widen the spectrum of disorders associated with RBD.

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**Table 1**

Summary of demographic and clinical data on subjects with PSG-confirmed or probable RBD who underwent autopsy.

<b>Feature</b>		
Sex	<i>n</i> (%)	
Men	143 (83%)	
Women	29 (17%)	
Age of onset (y)	Mean ± SD	Range
RBD ( <i>n</i> = 172)	62 ± 14	20–93
Cognitive impairment ( <i>n</i> = 147)	69 ± 10	22–90
Parkinsonism ( <i>n</i> = 151)	68 ± 9	20–92
Autonomic dysfunction ( <i>n</i> = 42)	62 ± 12	23–81
Death age (years)	75 ± 9	24–96

*Abbreviations:* *n*, number of cases; PSG, polysomnogram; RBD, REM sleep behavior disorder; SD, standard deviation.

**Table 2**

RBD characteristics.

Characteristic	<i>n</i> (%)	
Diagnosis of RBD		
PSG-confirmed RBD	82 (48%)	
History of recurrent dream enactment behavior <sup>a</sup>	64 (37%)	
Questionnaire	26 (15%)	
Onset of RBD Relative to Onset of Other Features <sup>b</sup>	Mean ± SD <sup>c</sup>	Range <sup>c</sup>
RBD preceded other features ( <i>n</i> = 88 or 51%)	10 ± 12	1–61
RBD occurred concurrently ( <i>n</i> = 27 or 16%)	n/a	n/a
RBD evolved after other features ( <i>n</i> = 57 or 33%)	6 ± 5	1–20

*Abbreviations:* *n*, number of cases; n/a, not applicable; PSG, polysomnogram; RBD, REM sleep behavior disorder; SD, standard deviation.

<sup>a</sup>Includes 6 cases who underwent PSG for suspected RBD, but no REM sleep was attained.

<sup>b</sup>Other features refers to cognitive impairment, parkinsonism or autonomic dysfunction.

<sup>c</sup>Values are in years.

**Table 3**

Summary of primary clinical diagnoses in subjects with PSG-confirmed or probable RBD who underwent autopsy.

Clinical diagnosis	All cases <i>n</i> = 172	PSG confirmed <i>n</i> = 82	pRBD-DEB <i>n</i> = 64	pRBD-MSQ <i>n</i> = 26
<i>Neurodegenerative syndrome</i>				
Dementia with Lewy bodies	97	45	49	3
Multiple system atrophy	19	16	3	0
AD	9	2	1	6
Parkinson's disease	9	4	2	3
Parkinson's disease with MCI	2	1	1	0
Parkinson's disease with dementia	21	5	3	13
Corticobasal syndrome	3	2	0	1
Frontotemporal dementia	1	0	1	0
Idiopathic RBD	1	1	0	0
<i>Other/mixed</i>				
Combined DLB and AD	3	1	2	0
Combined DLB and ALS	1	1	0	0
Combined MSA and MCI	1	1	0	0
Combined AD and Binswanger	1	0	1	0
Narcolepsy, then DLB	1	1	0	0
NBIA-1	1	0	1	0
<i>Non-neurodegenerative syndrome</i>				
Narcolepsy plus RBD associated with brain lesion	1	1	0	0
Narcolepsy plus RBD associated with VGKC antibody	1	1	0	0
<i>Presumed synucleinopathy among the neurodegenerative syndromes</i>	158/170 = 93%	78/80 = 98%	61/64 = 73%	19/26 = 73%

*Abbreviations:* AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; DEB = history of recurrent dream enactment behavior; DLB = dementia with Lewy bodies; MCI, mild cognitive impairment; MSA, multiple system atrophy; NBIA-1, neurodegeneration with brain iron accumulation type 1; pRBD, probable REM sleep behavior disorder; PSG, polysomnogram; MSQ, screened positive for probable RBD on the Mayo Sleep Questionnaire; RBD, REM sleep behavior disorder; VGKC, voltage-gated potassium antibody.

**Table 4**

Summary of primary neuropathologic diagnoses in subjects with PSG-confirmed or probable RBD who underwent autopsy.

Primary neuropathologic diagnosis	All cases <i>n</i> = 172	PSG-confirmed <i>n</i> = 82	pRBD – DEB <i>n</i> = 64	pRBD – MSQ <i>n</i> = 26
<i>Neurodegenerative/prion</i>				
Lewy body disease <sup>a</sup>	77 (2)	34	32 (1)	11 (1)
Combined LBD and AD	59 (5)	25 (2)	22 (3)	12
Multiple system atrophy	19	16	3	0
AD	6 (2)	1	2	3 (2)
Progressive supranuclear palsy	2	1	1	0
<i>Other</i>				
Combined LBD and MSA	3	2	1	0
Combined LBD and ALS	1	1	0	0
NBIA-1 + LBD + tauopathy	1	0	1	0
CJD and ALS	1	0	1	0
Indeterminate degenerative	1	0	1	0
<i>Inflammatory/other</i>				
Hypothalamic inflammatory lesion associated with VGKC antibody	1	1	0	0
Indeterminate hypothalamic lesion	1	1	0	0
<i>Synucleinopathy among neurodegenerative diseases</i>	160/170 = 94%	78/80 = 98%	58/64 = 91%	23/26 = 88%

Values in parentheses represent the number of cases with coexisting cerebrovascular disease likely contributing to some of the antemortem features.

*Abbreviations:* AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CJD, Creutzfeldt-Jacob disease; DEB, history of recurrent dream enactment behavior; LBD, Lewy body disease; MSA, multiple system atrophy; NBIA-1, neurodegeneration with brain iron accumulation type 1; pRBD, probable REM sleep behavior disorder; PSG, polysomnogram; MSQ, screened positive for probable RBD on the Mayo Sleep Questionnaire; RBD, REM sleep behavior disorder; VGKC, voltage-gated potassium antibody.

<sup>a</sup>One LBD case was found to have a duplication of the gene encoding alpha-synuclein (*SNCA*).

**Table 5**

Clinicopathologic discrepancies among subjects with PSG-confirmed or probable RBD who underwent autopsy.

Clinical diagnosis	Neuropathologic diagnosis	All cases $n = 22$	PSG-confirmed $n = 7$	pRBD – +DEB $n = 8$	pRBD – MSQ+ $n = 7$
AD	LBD ± AD	8	2	2	4
CBS	LBD + AD	2	1	0	1
CBS	AD	1	1	0	0
FTD	AD	1	0	1	0
PD	MSA	2	2	0	0
PDD	AD	2	0	0	2
MSA	PSP	1	1	0	0
DLB	AD	1	0	1	0
DLB	CJD + ALS	1	0	1	0
DLB	Indeterminant	1	0	1	0
DLB	PSP + AD	1	0	1	0
Bins/AD	Bins/AD/LBD	1	0	1	0

*Abbreviations:* AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; Bins, Binswanger disease; CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; LBD, Lewy body disease; MSA, multiple system atrophy; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PSG, polysomnogram; PSP, progressive supranuclear palsy.

**Table 6**

Clinicopathologic correlations based on the timing of the onset of RBD relative to the onset of other neurologic features among subjects with PSG-confirmed or probable RBD who underwent autopsy.

Onset of RBD relative to onset of other features <sup>a</sup>	Synucleinopathy pathology
RBD preceded other features	83/87 = 95%
RBD preceded other features by 5 y	51/53 = 96%
RBD preceded other features by 10 y	29/30 = 97%
RBD preceded other features by 15 y	16/17 = 94%
RBD preceded other features by 20 y	10/10 = 100%
RBD occurred concurrently with other features	26/27 = 96%
RBD evolved after other features	51/57 = 89%

<sup>a</sup>Other features refers to cognitive impairment, parkinsonism and/or autonomic dysfunction.