Published in final edited form as:
Mov Disord. 2012 January ; 27(1): 72–78. doi:10.1002/mds.24003.

Rapid eye movement sleep behavior disorder and subtypes in autopsy-confirmed dementia with Lewy bodies

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Abstract

OBJECTIVE—To determine whether dementia with Lewy bodies with or without probable rapid eye movement sleep behavior disorder differ clinically or pathologically.

METHODS—Patients with dementia with Lewy bodies who have probable rapid eye movement sleep behavior sleep disorder (n=71) were compared to those without it (n=19) on demographics, clinical variables (core features of dementia with Lewy bodies, dementia duration, rate of cognitive/motor changes) and pathologic indices (Lewy body distribution, neuritic plaque score, Braak neurofibrillary tangle stage).

RESULTS—Individuals with probable rapid eye movement sleep behavior disorder were predominantly male (82% versus 47%), and had a shorter duration of dementia (mean 8 years versus 10 years), earlier onset of parkinsonism (mean 2 years versus 5 years), and earlier onset of visual hallucinations (mean 3 years versus 6 years). These patients also had a lower Braak neurofibrillary tangle stage (Stage IV versus Stage VI) and lower neuritic plaque scores (18% frequent versus 85% frequent), but no difference in Lewy body distribution. When probable rapid eye movement sleep behavior disorder developed early (at or before dementia onset), the onset of parkinsonism and hallucinations was earlier and Braak neurofibrillary tangle stage was lower compared to those who developed the sleep disorder after dementia onset. Women with autopsy-confirmed DLB without a history of dream enactment behavior during sleep had a later onset of hallucinations and parkinsonism and a higher Braak NFT stage.

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Financial Disclosures: Dr. Dugger reports no financial disclosures. Dr. Boeve has served as an investigator for clinical trials sponsored by Cephalon, Inc., and Allon Pharmaceuticals. He receives royalties from the publication of a book entitled Behavioral Neurology of Dementia (Cambridge Medicine, 2009). He has received honoraria from the American Academy of Neurology. Dr. Murray reports no financial disclosures. Dr. Parisi reports no financial disclosures. Dr. Fujishiro reports no financial disclosures. Dr. Dickson reports no financial disclosures. Dr. Ferman reports no financial disclosures.

Author Roles: Dugger: Research Project: conception, organization, execution; Statistical Analysis: execution, review and critique; Manuscript: writing of the first draft. **Boeve**: Research Project: organization, execution; Statistical Analysis: review and critique; Manuscript: review and critique. **Murray**: Research Project: execution; Statistical Analysis: review and critique; Manuscript: Review and Critique. **Parisi**: Research Project: execution; Manuscript: review and critique. **Fujishiro**: Research Project: execution; Manuscript: review and critique. **Dickson**: Research Project: conception, organization, execution; Statistical Analysis: review and critique; Manuscript: writing, review and critique. **Ferman**: Research Project: conception, organization, execution; Statistical Analysis: design, execution, review and critique; Manuscript: writing, review and critique.

CONCLUSIONS—Probable rapid eye movement sleep behavior disorder is associated with distinct clinical and pathologic characteristics of dementia with Lewy bodies.

Keywords

Parkinson's disease; REM sleep behavior disorder; Dementia with Lewy bodies; Lewy body disease; Alzheimer's disease

INTRODUCTION

Rapid eye movement sleep behavior disorder (RBD) is characterized by a loss of muscle atonia during rapid eye movement (REM) sleep and is associated with dream enactment behavior during REM sleep. The occurrence of RBD in Parkinson's disease (PD) and dementia with Lewy bodies (DLB) ranges from 38 to 83%[1–3] and, RBD often precedes the onset of parkinsonism and dementia by many years.[4–7] In patients with idiopathic RBD, the estimated 5-year risk of developing PD or DLB is 17.7%, and the 12-year risk is 52.4%.[8] In a cohort of 234 autopsy-confirmed dementia patients followed longitudinally, a history of definite or probable RBD was present in 76% of 98 with autopsy-confirmed DLB, indicating that it is frequent feature of DLB.[9] Moreover, a history of RBD improves clinical diagnostic accuracy and increases the odds of autopsy-confirmed DLB by 6-fold.[9] This growing literature indicates RBD is an essential clinical marker of Lewy body disease and may be the earliest clinical manifestation of an evolving neurodegenerative process. In order to guide early intervention and develop new therapies, it is necessary to identify DLB early and determine if there are subgroups of DLB with a specific clinical and pathologic characteristics.

Based on animal and lesion studies, RBD is associated with pathology in sleep-related brainstem nuclei, specifically those in the rostral pontine tegmentum.[4, 10, 11] These same areas are selectively vulnerable to α-synuclein immunoreactive Lewy-related pathology and neuronal loss in PD and DLB.[4, 12–14] In addition to Lewy-related pathologies, a subset of DLB and PD patients, especially PD with later developing dementia, have concomitant Alzheimer type pathology of varying degrees, including β-amyloid plaques and tau-positive neurofibrillary degeneration.[15] RBD is rare in Alzheimer's disease and more likely to occur in conditions with α-synuclein deposition.[16]

In PD, factors associated with RBD suggest a clinical phenotype that includes male predominance, dementia, visuoperceptual difficulties, autonomic dysfunction and decreased likelihood of tremor.[7, 17–23] Other features such as gait disturbance, fall frequency, visual hallucinations and disease duration have not shown a consistent relationship with RBD in PD.[7, 18, 20, 21, 24–26] There are no similar autopsy studies in DLB, and the goal of this study was to examine whether a history of RBD was related to the clinical or pathologic expression of DLB.

PATIENTS AND METHODS

Selection of cases

Patients were consecutively recruited from Mayo Clinic Behavioral Neurology and Movement Disorders clinics and followed longitudinally as part of the Alzheimer's Disease Research Center. Protocols were approved by the Institutional Review Board, and all subjects and their proxies provided written informed consent. All patients included in this study had a pathologic diagnosis of Lewy body disease (LBD), limbic or diffuse in type. Patients from this study were also included in a recent diagnostic validation study.[9] Furthermore, all patients had an antemortem consensus diagnosis of clinically probable

DLB, based upon the presence of dementia and two or more of the core features of visual hallucinations, parkinsonism and fluctuations[27] (see Figure 1). To avoid circularity, RBD was not included in the clinical diagnostic criteria for DLB in this study, even though it is considered a suggestive feature in the Consortium for DLB consensus criteria.[27] For analysis, patients meeting the above criteria were divided into two groups based on the presence or absence of clinically probable RBD (pRBD).

Clinical assessment

All patients met DSM-III-R criteria for dementia, having cognitive impairment that interfered with activities of daily living.[28] There was no statistically significant difference in the mean number of clinical visits for each group (RBD 4 ± 1.7, no-RBD 4 ± 1.6). Visual hallucinations were determined by an informant or patient report from clinical interview. Fluctuations were based on a score of three or four on the Mayo Fluctuations Scale (MFS),[29] and parkinsonism was based on 2 or more of the 4 cardinal clinical signs of Parkinson's disease (bradykinesia, tremor, postural instability and rigidity) based on neurologic examination. The presence of pRBD was based on informant report of dream enactment behavior during sleep from the Mayo Sleep Questionnaire (MSQ)[30] and corroborated by clinical interview. As a screen for RBD, the MSQ has 98% sensitivity and 74% specificity when confirmed with polysomnography.[30] A subset of patients in our sample (45% DLB with RBD, 11% DLB without RBD) underwent polysomnography to confirm the presence or absence of RBD, using established criteria by board-certified sleep specialists.[31] Polysomnography did not change the diagnosis in these patients, but two patients did not achieve REM sleep, making confirmation of RBD impossible for them. Global cognitive rating was assessed with Folstein Mini-Mental State Exam (MMSE).[32] Informants who were able to comment on daytime alertness completed the Epworth Sleepiness Scale, which is an 8-item scale that rates the patient's likelihood to fall asleep in everyday situations.[33] The severity of extrapyramidal signs was quantified using the motor subtest of the Unified Parkinson's Disease Rating Scale (UPDRS).[34] Annual interviews of informants and patients, and annual patient examinations were carried out. Information regarding temporal onset of clinical features was recorded. Consensus meetings with neurologists, neuropsychologists, and a social worker/gerontologist were held after each visit, and a consensus diagnosis was rendered using established criteria.[27]

Neuropathology

All cases underwent a standardized neuropathologic assessment for Lewy related and Alzheimer type pathologies according to published recommendations.[27] Subtypes of Lewy body pathology (diffuse vs. limbic) were assessed with antibodies to α-synuclein (polyclonal antibody NACP[35] used at 1:3000 or a monoclonal antibody, LB509 from Invitrogen, Carlsbad, CA used at 1:100) and classified according to scheme originally proposed by Kosaka and colleagues[36] as employed in the Consortium for DLB.[37] Neurofibrillary tangles (NFT) and senile plaques were detected using thioflavin S fluorescent microscopy or Bielschowsky silver stain, and a Braak NFT stage[38] and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque score[39] were assigned to each case, respectively. Cases were categorized based on the Consortium for Dementia with Lewy Bodies for the likelihood that the pathologic findings were associated with a DLB clinical syndrome.[27]

Statistical analyses

Mann-Whitney tests or Student's t-tests were used to analyze clinical and pathologic differences between groups. Chi-squared analyses and Fisher exact tests were used to compare group differences for categorical or ordinal data. Spearman rank correlations were used to compare the onset of clinical features with duration of dementing illness. Annualized

rate of change was calculated by subtracting the baseline score from the score at the last evaluation before death, then dividing it by the number of years between the first and last examination.

RESULTS

There were 71 DLB patients with pRBD and 19 patients without pRBD. Those with a history of pRBD included a higher proportion of men, an earlier onset of visual hallucinations and parkinsonism in relation to dementia onset, and a shorter duration of dementia (see Table 1). Compared to women without pRBD, women with pRBD had an earlier onset of visual hallucinations (pRBD 1.3 ± 1.8 years vs. no pRBD 5.9 ± 4.7 years, $t=3.2$, $p<0.005$), an earlier onset of parkinsonism (pRBD 0.9 ± 2.6 years vs. no pRBD 6.6 ± 5 years, $t=3.1$, $p<0.005$), and a trend towards a shorter duration of dementing illness (pRBD 7.8 ± 2.5 years vs. no pRBD 10.6 ± 4 years, $t=2.0$, $p=0.056$). Duration of dementia was correlated with visual hallucination onset ($r=0.55$, $p<0.001$) and parkinsonism onset ($r=0.58$, $p<0.001$) but not with pRBD onset ($r=0.19$, $p=0.11$). Thus, patients whose visual hallucinations and parkinsonism developed earlier in the dementia course also had a shorter duration of the dementing illness.

Patients with later developing pRBD (one or more years after estimated dementia onset) were compared to early developing pRBD (onset before or during the year of the estimated dementia onset). The early pRBD group developed visual hallucinations and parkinsonism earlier and had more severe baseline parkinsonism and a shorter duration of dementia (see Table 2). Braak NFT score was significantly lower in early pRBD compared to late pRBD. CERAD neuritic plaque density and Lewy body distribution subtype did not differentiate groups.

Baseline and annualized rates of change in UPDRS, MMSE, and ESS did not differ between DLB patients with and without pRBD (Table 1, Figure 2). There were no other group differences in other demographic or clinical features.

The pathologic findings of each group are summarized in Table 3. Probable RBD was associated with a lower median Braak NFT stage and a lower proportion of cases with frequent CERAD neuritic plaques. Diagnoses based on the Consortium for DLB assessments also differed according to pRBD. Cases without pRBD were more often in the “low likelihood DLB” category than cases with pRBD, most often due to cases with limbic Lewy body type and high Braak NFT stage (V–VI). There was no difference in frequencies of Lewy body type (limbic and diffuse) between groups. All differences remained significant after adjusting for age at death.

DISCUSSION

In our DLB cohort, patients with a history of clinically probable RBD were more likely to be male, had an earlier onset of parkinsonism and visual hallucinations relative to dementia onset, and a shorter duration of illness (based on dementia duration). The frequency of the core DLB clinical diagnostic features of parkinsonism, fluctuations and visual hallucinations, the rate of dementia progression, extrapyramidal severity, and severity of somnolence did not distinguish DLB patients with or without pRBD. Pathologically, DLB patients with pRBD had a lower Braak NFT stage and were less likely to have frequent neuritic plaques. Lewy body type (limbic versus diffuse) was not associated with the presence or absence of pRBD. That is, patients with pRBD were just as likely to have brainstem and limbic Lewy bodies as they were to have brainstem, limbic and neocortical Lewy bodies. This is the first autopsy study to show that pRBD may be a clinical marker of

a specific subtype in DLB. A history of pRBD is associated with the classic presentation of DLB characterized by early visual hallucinations, early parkinsonism, more rapid disease course and less AD pathology.

These results also reveal that women without a history of pRBD who have autopsy-confirmed DLB may present differently from men and women with pRBD. Specifically, women with a history of pRBD have an earlier onset of visual hallucinations and parkinsonism, and have less concomitant AD pathology, but the opposite is true for women with DLB who do not have pRBD. The later onset of these core clinical DLB features suggests women who do not have pRBD may pose a greater challenge for initial diagnosis of clinically probable DLB using existing criteria. Further investigation is needed to determine whether women without pRBD have other clinical or perhaps a specific baseline cognitive pattern that may improve our differential diagnosis of this group. It is unclear how the presence of concomitant AD pathology influences the clinical expression of DLB or if the AD pathology somehow takes precedence, at least in the beginning stages of the disease.

Furthermore, we divided cases based on early pRBD (before or within the year of estimated onset of dementia) to those with late pRBD (after the first year of estimated dementia onset), to understand if the temporal sequence of RBD in relation to dementia could demonstrate unique subtypes. We found early pRBD was associated with an earlier onset of the clinical features of visual hallucinations and parkinsonism, greater baseline parkinsonism severity, a shorter duration of dementing illness and a lower Braak NFT score. CERAD neuritic plaque density and Lewy body distribution subtype was not related to the temporal onset of pRBD. These data support a concept of a temporal aspect of a symptom, not just presence or absence, to produce clinical and pathologic subtypes.

The clinical subtypes of DLB are not dependent on whether the Lewy related pathology was limited to brainstem and limbic regions or if it was more diffuse and involved the neocortex. Patients develop dementia regardless of whether the patients have cortical Lewy pathology or not. Studies of idiopathic RBD with and without dementia have shown that patients have impairment of attention and visuoperceptual abilities.[19, 40–43] It is not known whether DLB without RBD harbor a different cognitive pattern and whether this may be related to the degree of co-occurring AD pathology. Clarifying the cognitive pattern and examining neuroimaging correlates in DLB with and without RBD may provide a useful window into the clinical expression of the disease.

If one considers the onset of RBD as an indication of early brainstem involvement in the DLB disease process, with later developing dementia and parkinsonism representing extension of the disease process to forebrain structures, then DLB patients with RBD may represent a proposed “bottom up” progression of DLB that follows the disease progression for PD.[13, 36] It is thus of interest that DLB with RBD shares demographic features with PD, such as male predominance. Given the hypothesized anatomical substrate of RBD within lower brainstem sleep related nuclei,[4] the Braak staging scheme for PD[13] fits with the evolution of clinical features of DLB in patients with RBD, with early onset of brainstem nuclei associated with RBD and parkinsonism prior to involvement of higher cortical regions associated with cognitive deficits.

It is possible DLB patients without RBD may not have a “bottom up” disease progression. Instead, these cases may be more in par with reports of early involvement of corticolimbic areas and later extension to brainstem nuclei.[44–46] In AD, Lewy-related pathologies are greatest in limbic structures with variable involvement of brainstem nuclei.[46] Further studies are needed to determine if neuronal loss and Lewy-related pathologies are greater in brainstem nuclei in DLB patients with RBD compared to DLB patients without RBD, and if

corticolimbic Lewy-related pathologies are greater in DLB without RBD compared to those with RBD. Our previous neuropathologic studies of a smaller subset of the cases (11 DLB with RBD and 10 DLB without RBD) included in the present study demonstrated no differences between DLB with and without RBD with respect to neuronal densities and α-synuclein and tau pathology in select brainstem sleep-related nuclei (i.e. locus ceruleus and pedunculopontine nucleus),[47] but cases and controls included in that study were matched for severity of Alzheimer pathology, which may have precluded our ability to find less Alzheimer type pathology in DLB with RBD. A future goal is also to determine biological markers that distinguish DLB with and without RBD, including possible genetic differences (e.g., variants in genes for apolipoprotein E, tau and α-synuclein).

While evidence from our study suggests DLB with RBD fits with a bottom-up disease progression described for PD, and while DLB without RBD has demographic and pathologic features consistent with early corticolimbic Lewy-related pathology, it is important to reiterate the frequency and severity of core clinical features of parkinsonism, fluctuations and VH did not differ between the two groups. On the other hand, this hypothetic subtyping of DLB disease progression may fit with other aspects of our findings. For example, previous studies have shown male predominance is common in both RBD and DLB,[7, 20, 48] but not in AD, which tends to be equally frequent amongst males and females.[49] Reports of PD with dementia with and without coexisting AD pathology found those with AD pathologies had a later age of onset of parkinsonism and longer duration of dementia.[50] These results are similar to our DLB cohort without RBD. Parkinsonism and VH, as well as longer disease duration, have less specificity in differential diagnosis in later stages of AD and are associated with non-Lewy-related pathologies, in particular, greater degree of neurofibrillary degeneration especially in catecholaminergic brainstem nuclei.[51–53]

A limitation to our study is the absence of polysomnography confirmation of RBD status in all cases. Despite its well-documented accuracy for true positives, polysomnography is seldom performed when RBD or other sleep disorders are not clinically suspected. This is clearly evident in our series, since there were significantly more patients with polysomnography in DLB with RBD compared to DLB without RBD. Another limitation is the small sample size of DLB patients without RBD. In our prospective sample, including those who have not come to autopsy, RBD is found in about 75% of DLB patients.[9] Although RBD appears to be a common feature of DLB that may define a clinicopathologically distinct subtype of DLB, it is important to confirm these findings in a larger sample.

In summary, our findings suggest the presence of RBD may reflect a distinct subtype of DLB, suggestive of a bottom-up disease progression, while DLB without RBD has additional features suggestive of a top-down progression. More work is needed to determine if RBD indeed defines clinicopathologic subtypes of DLB with distinct patterns of disease progression and treatment response and to develop biomarkers that may assist in differential diagnosis, early detection and prognosis of DLB.

Acknowledgments

The authors thank Monica Castanedes Casey, Linda Rousseau and Virginia Phillips their histopathological expertise and technical support, and Sonya Prescott for coordinating the annual visits and autopsy arrangements and for administering the assessment measures. We are grateful to our patients and their families who participated in annual evaluations and agreed to autopsy. This study was supported by grants from the National Institutes of Health (P50 AG16574, P50 NS72187 & R01 AG15866), Mangurian Foundation for Lewy Body Dementia Research, and Mayo Foundation for Education & Research.

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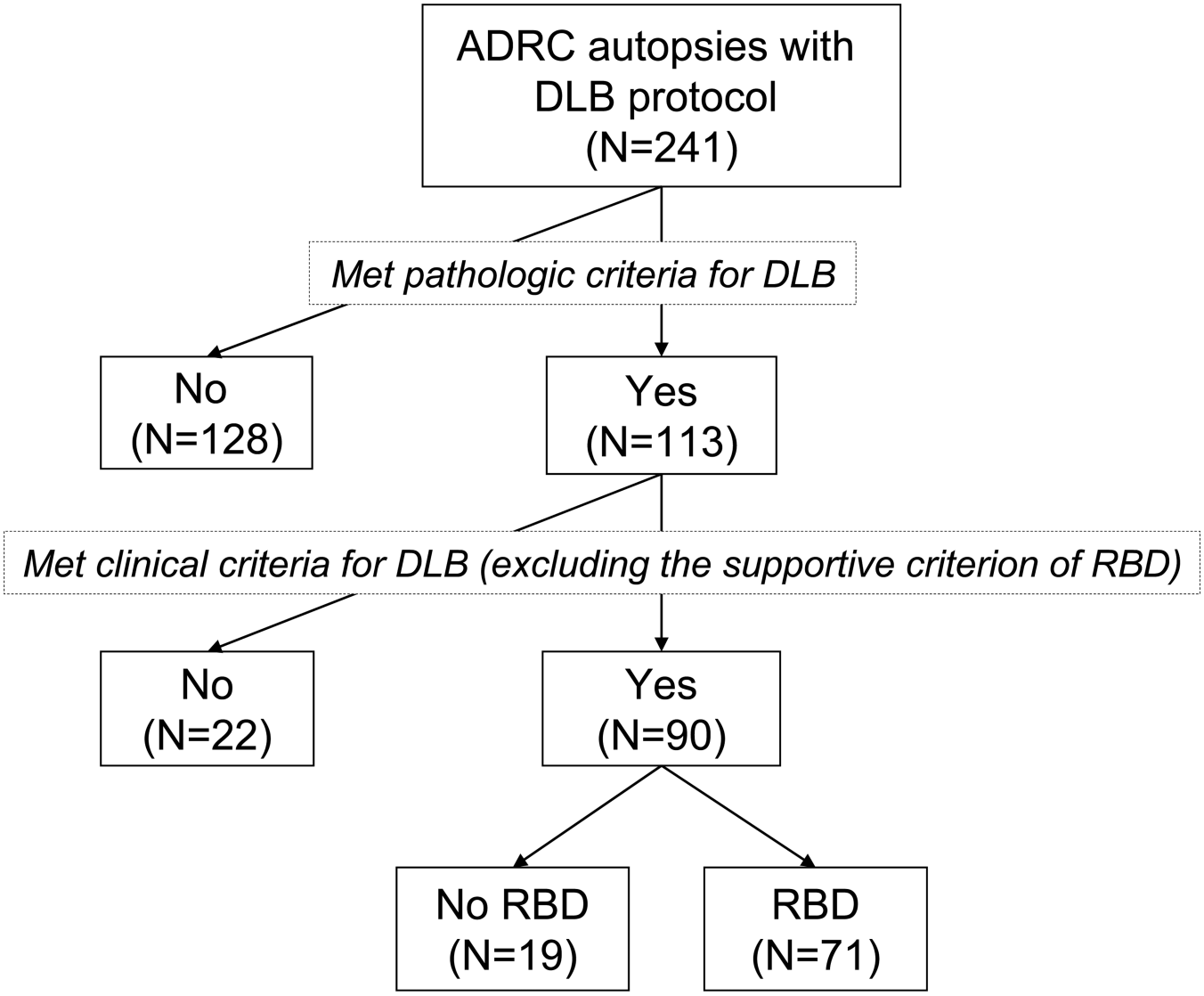

Figure 1.
Flow chart of study design illustrating inclusion criteria.

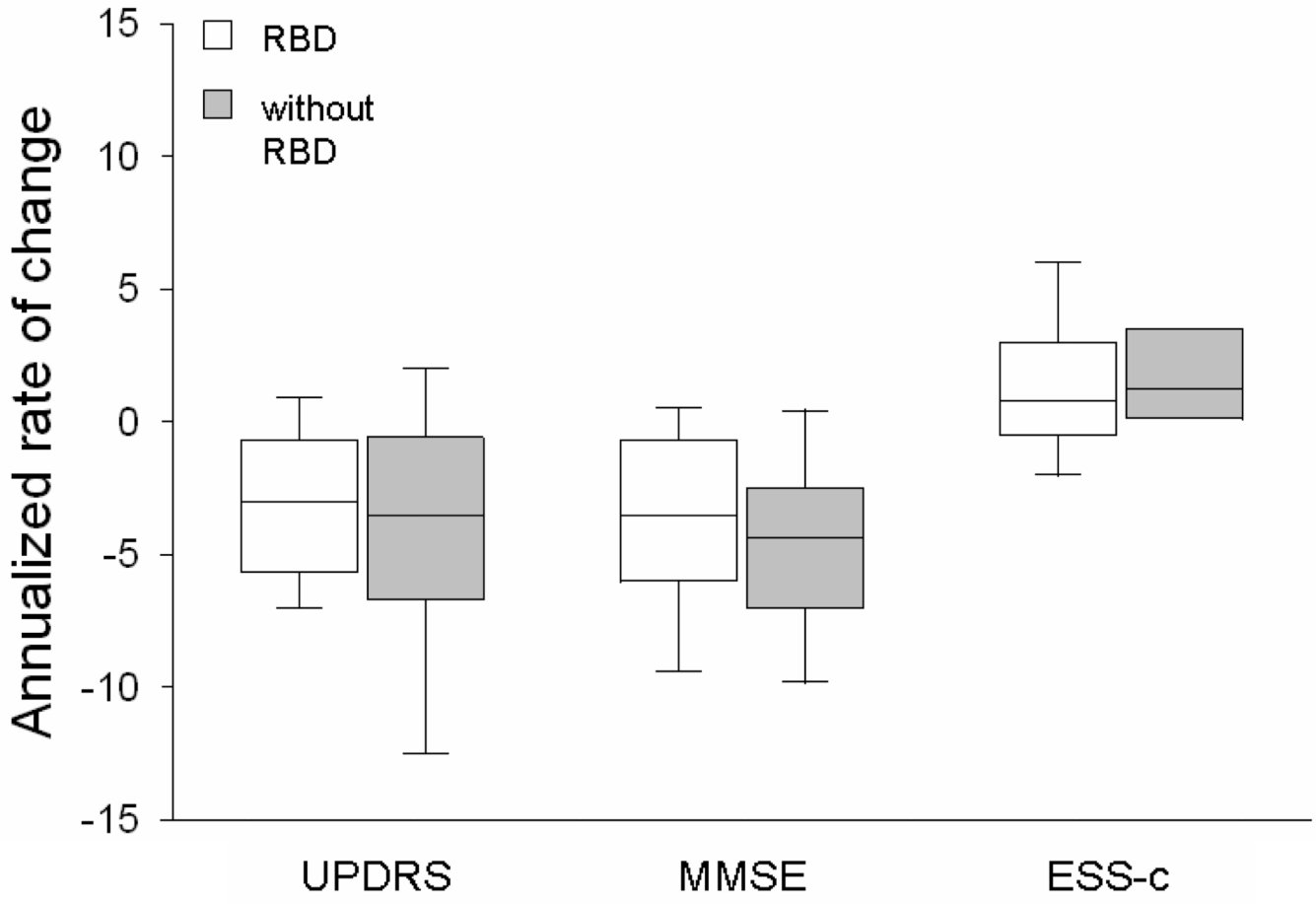

Figure 2.
Box plots of median, 25th and 75th percentile representing rate of change over time of UPDRS, MMSE, and ESS-c scores. Rates of change were calculated by subtracting the first examination score from the last examination before death, then dividing it by the time in years between the examinations.

Table 1

Clinical characteristics of pathologically confirmed DLB patients

	pRBD	No pRBD	P value
Number of patients	71	19	
RBD onset relative to dementia (mean years± sd)	−6.0 ± 12	-	
Polysomnography conducted (%)	45%	11%	0.01
Males (%)	82%	47%	0.006
Age of cognitive onset (mean years± sd)	69.3 ± 8.3	68.4 ± 11.6	0.56
Duration of dementia (mean years± sd)	7.9 ± 2.8	9.9 ± 4.3	0.045
Visual Hallucinations (%)	90%	74%	0.14
Onset relative to dementia (mean years± sd)	2.5 ± 2.5	5.5 ± 4.0	0.006
Extrapyramidal signs (%)	93%	100%	0.58
Onset relative to dementia (mean years± sd)	1.8 ± 2.9	4.5 ± 5.3	0.047
Fluctuations (%)	58%	53%	0.89
Baseline Scores			
Mini-Mental state Examination (mean ± sd)	24 ± 5	24 ± 6	0.46
Unified Parkinson Disease Rating Scale (mean ± sd)	9 ±7	8 ± 9	0.30
Epworth Sleepiness Scale – collateral (mean ± sd	11 ± 5	11 ± 7	0.72

Table 2

Clinical and pathologic differences in early versus late probable RBD

	Early pRBD	Late pRBD	P value
Number of patients	54	17	-
RBD onset relative to dementia (mean years± sd)	−8.5 ± 12	3.1 ± 2	0.001
Males (%)	82%	81.5%	0.94
Polysomnography conducted (%)	42.6%	52.9%	0.46
Duration of dementia (mean years± sd)	7.4 ± 2.8	9.4 ± 2.5	0.009
Visual Hallucinations (%)	94%	87%	0.42
Onset relative to dementia (mean years ± sd)	2.1 ± 2	3.6 ± 2	0.04
Extrapyramidal signs (%)	94%	93%	0.83
Onset relative to dementia (mean years± sd)	1.1 ± 2.9	3.7 ± 2	0.027
Baseline Unified Parkinson Disease Rating Scale (mean ± sd)	6.1 ± 6	10.2 ± 6	0.03
Braak NFT stage (mean ± sd)	3.2 ± 1.4	4.2 ± 1.7	0.02

Table 3

Pathologic characteristics of autopsy confirmed DLB patients.

		pRBD	No pRBD	P value
LB type n (%)	Limbic	20 (28%)	6 (32%)	0.99
	Diffuse	51 (71%)	13 (69%)	
CDLB assessment n (%)	Low	2 (3%)	5 (26%)	0.004
	Intermediate	20 (28%)	9 (47%)	0.100
	High	49 (69%)	5 (26%)	< 0.001
CERAD NP score n (%)	None	13 (19%)	0 (0%)	0.061
	Sparse	18 (27%)	0 (0%)	0.01
	Moderate	22 (32%)	4 (22%)	0.566
	Frequent	14 (21%)	14 (78%)	< 0.001
Braak NFT stage - median (range)		IV (0–VI)	VI (II–VI)	< 0.001

CDLB assessment = likelihood that the pathologic findings are associated with a DLB clinical syndrome; CERAD NP = Consortium to Establish A Registry for Alzheimer's Disease neuritic plaque score; NFT = neurofibrillary tangle