Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies

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ABSTRACT

Objective: To determine whether adding REM sleep behavior disorder (RBD) to the dementia with Lewy bodies (DLB) diagnostic criteria improves classification accuracy of autopsy-confirmed DLB.

Methods: We followed 234 consecutive patients with dementia until autopsy with a mean of 4 annual visits. Clinical diagnoses included DLB, Alzheimer disease (AD), corticobasal syndrome, and frontotemporal dementia. Pathologic diagnoses used the 2005 DLB consensus criteria and included no/low likelihood DLB (non-DLB; $n = 136$) and intermediate/high likelihood DLB (DLB; $n = 98$). Regression modeling and sensitivity/specificity analyses were used to evaluate the diagnostic role of RBD.

Results: Each of the 3 core features increased the odds of autopsy-confirmed DLB up to 2-fold, and RBD increased the odds by 6-fold. When clinically probable DLB reflected dementia and 2 or more of the 3 core features, sensitivity was 85%, and specificity was 73%. When RBD was added and clinically probable DLB reflected 2 or more of 4 features, sensitivity improved to 88%. When dementia and RBD were also designated as probable DLB, sensitivity increased to 90% while specificity remained at 73%. The VH, parkinsonism, RBD model lowered sensitivity to 83%, but improved specificity to 85%.

Conclusions: Inclusion of RBD as a core clinical feature improves the diagnostic accuracy of autopsy-confirmed DLB. *Neurology*® 2011;77:875-882

GLOSSARY

AD = Alzheimer disease; **ADRC** = Alzheimer's Disease Research Center; **CJD** = Creutzfeldt-Jakob disease; **DLB** = dementia with Lewy bodies; **DLBD** = diffuse Lewy body disease; **DSM-III-R** = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised; **ESS-c** = Epworth Sleepiness Scale-collateral version; **GDS** = Global Deterioration Scale; **LB** = Lewy body; **NFT** = neurofibrillary tangle; **PSG** = polysomnography; **RBD** = REM sleep behavior disorder; **TLBD** = transitional Lewy body disease; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Dementia with Lewy bodies (DLB) is considered the second most common cause of neurodegenerative disease after Alzheimer disease (AD), with an estimated prevalence of up to 30%.¹⁻³ Validation of older versions of the DLB criteria tend to show high specificity at the expense of poor sensitivity,⁴⁻⁸ though more acceptable ranges are found with the use of standardized measures.⁹ It is critical to properly diagnose DLB during life in order to optimize symptom management, reduce iatrogenic treatment complications, and develop new therapies designed to prevent or interfere with disease progression.

In 2005, the DLB diagnostic criteria were modified to include 3 new features in a category termed "suggestive features." With this revision, clinically probable DLB is represented by 2 or more core features (fluctuations, parkinsonism, or visual hallucinations), or by one core feature plus one suggestive feature.¹⁰ The suggestive features include severe neuroleptic sensitivity, reduced

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basal ganglia dopamine uptake on functional imaging, and an REM sleep parasomnia called REM sleep behavior disorder (RBD).

RBD involves the loss of normal muscle atonia during REM sleep and presents as limb movements with or without vocalizations that tend to mirror dream content. It is an early feature of DLB, PD, and multiple system atrophy,^{11–14} with an onset typically preceding the onset of dementia or parkinsonism by years and often decades.^{15–18} 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%.¹⁹ This study was designed to determine whether the diagnostic accuracy of DLB improves when RBD is added to the other 3 core clinical features of DLB.

METHODS Clinical assessment. We included 234 patients with autopsies followed annually as part of the Mayo Alzheimer's Disease Research Center (ADRC). The study was approved by the Institutional Review Board, and all subjects and their proxies provided written informed consent. Patients were recruited from Behavioral Neurology and Movement Disorders Clinics. We performed annual neurocognitive and neurologic evaluations, with annual informant questionnaires and interviews. All patients met *DSM-III-R* criteria for dementia.²⁰ We obtained the Global Deterioration Scale (GDS)²¹ score for a noncognitive rating of dementia severity, the Folstein Mini-Mental State Examination²² score for a cognitive rating, and the Functional Activities Questionnaire²³ score for data about activities of daily living. Clinically probable RBD was diagnosed using the Mayo Sleep Questionnaire,²⁴ and via clinical interview using the following query: "Have you ever seen the patient appear to act out his or her dreams while sleeping?" with additional inquiry about the nature of the movements and whether the movements matched dream content. A minimum of 3 events during the patient's lifetime was needed to be considered clinically probable RBD. The sensitivity of the Mayo Sleep Questionnaire as a screen for RBD is excellent at 98% and the specificity is reasonable at 74% with the majority of false-positives occurring in those with untreated obstructive sleep apnea.²⁴ To ensure that patients were appropriately diagnosed with RBD in this study, overnight polysomnography was carried out, when possible, using established criteria by board-certified sleep specialists.²⁵ The core features of DLB were considered present if they developed at any point in the disease. Fluctuations were deemed present with a score of 3 or 4 from the informant-completed 4-item Mayo Fluctuations Scale.²⁶ The informant completed the Epworth Sleepiness Scale—collateral version (ESS-c)^{26,27} to gauge excessive daytime somnolence. Parkinsonism was based on neurologic examination and required 2 of the 4 cardinal features of PD. The Unified Parkinson's Disease Rating Scale (UPDRS)²⁸ provided a rating of extrapyramidal severity. The presence of VH and temporal onset of VH were obtained from informant report using the Mayo Visual Hallucinations and Delusions Questionnaire and via clinician interview. Consensus meetings with neurologists, neuropsychologists, and a social worker/gerontologist were held after each visit, and a consensus

diagnosis based on clinical features for each condition was rendered using established diagnostic criteria.^{10,29–31}

Neuropathology. All cases underwent a standardized neuropathologic assessment with gross and microscopic evaluation, and were assigned a pathologic diagnosis. Neurofibrillary tangles (NFT) and corresponding Braak NFT stage were detected using thioflavin-S microscopy or Bielschowsky silver stain, and classified according to NIA–Reagan criteria which uses the Consortium to Establish a Registry for Alzheimer's Disease method for assessing neuritic plaques.³² The subtypes of Lewy body (LB) pathology (diffuse vs transitional) were determined based on LB counts using a polyclonal antibody to α -synuclein. The final neuropathologic diagnosis of DLB was made according to the Consortium on Dementia with Lewy Bodies criteria.^{10,33} Specifically, the high and intermediate likelihood DLB category included those with neocortical, limbic, and brainstem LBs (diffuse LB disease [DLBD]) with any Braak NFT stage, or LBs confined to the limbic and brainstem regions (transitional LB disease [TLBD]) with a Braak NFT stage $\leq$ IV. The low and no likelihood DLB category included those without LB pathology, those with TLBD and a Braak NFT stage $>$ IV, and those with LBs relatively confined to the amygdala (i.e., AD with amygdala-predominant LBs).³⁴ The placement of cases with limbic LBs and advanced AD pathology in the low likelihood DLB group was based on prior data indicating that this subgroup is clinically difficult to distinguish from AD.¹⁰ For ease of discussion, the high and intermediate likelihood groups are referred to as the "DLB" autopsy group and the low and no likelihood groups are referred to as the "non-DLB" autopsy group.

Statistical analysis. In order to examine differences between the DLB and non-DLB groups, simple comparisons of clinical and pathologic measures were performed using χ^2 tests for qualitative variables and t tests for quantitative variables. Logistic regression analyses were carried out to determine which variables were associated with pathologically defined DLB status after accounting for other features. Sensitivity, specificity, positive and negative predictive values were calculated to assess the diagnostic utility of differing combinations of clinical features in predicting pathologically confirmed DLB.

RESULTS Clinical and autopsy diagnoses. This prospective autopsy series included 234 patients and was comprised of clinically diagnosed DLB ($n = 119$), AD ($n = 84$), frontotemporal dementia ($n = 26$), and corticobasal syndrome ($n = 5$). The autopsy diagnoses and corresponding Braak NFT stage are presented in table 1. A Braak NFT stage $\leq$ IV was evident in 63/113 (56%) of the DLB cohort. Due to a Braak stage of V or VI, a subset of patients with TLBD ($n = 15$) were placed in the non-DLB (low likelihood DLB) group. Those with advanced AD with amygdala-predominant LBs ($n = 10$) were also included in the non-DLB autopsy group.

Demographics and clinical features. Compared to the non-DLB group, the DLB group had more males, a shorter duration of illness, greater baseline daytime somnolence, and greater parkinsonism severity (table 2). There were no group differences in baseline dementia severity. Fluctuations were more frequent in

Table 1 Pathologic diagnosis and corresponding proportion with Braak NFT stage

Pathology	No.	Braak $\leq$ IV	Braak $>$ IV
DLBD	77	42	35
TLBD	36	21	15
AD	57	7	50
AD with amygdala predominant LBs	10	0	10
AD with cerebrovascular disease	14	1	13
Cerebrovascular disease ^a	6	5	1
Corticobasal degeneration	5	4	1
Progressive supranuclear palsy	4	3	1
Frontotemporal lobar degeneration	17	17	0
Other (tumor, AGD, hippocampal sclerosis)	5	5	0
CJD	3	3	0
Total	234	108	126

Abbreviations: AD = Alzheimer disease; AGD = argyrophilic grain disease; CJD = Creutzfeldt-Jakob disease; DLBD = diffuse Lewy body disease; LB = Lewy body; NFT = neurofibrillary tangle; TLBD = transitional Lewy body disease.

^aCerebrovascular disease = single or multiple infarctions or hemorrhages.

the DLB compared to non-DLB autopsy group at baseline and by end of life. VH and parkinsonism were more common in the DLB autopsy group and occurred earlier in the disease compared to their non-DLB counterparts. Males were more likely to have DLB, and were also more likely to have RBD (males 82% vs females 54%, $p < 0.01$), but gender was equally represented across the other core DLB features.

RBD was reported in 74/98 of the DLB group compared to 5/136 in the non-DLB group, and preceded the estimated onset of dementia by an average of 6 years (see table 2). Moreover, the onset of RBD preceded VH by 8.4 ± 12 years, and parkinsonism by 7.6 ± 12 years. Two non-DLB patients had baseline histories suspicious for RBD, but overnight PSG showed normal REM atonia revealing one with severe obstructive sleep apnea and one with non-REM sleepwalking. The patients were successfully treated for these conditions, the symptoms that resembled RBD resolved, and as such, were not included in the RBD group. Overnight sleep studies using polysomnography (PSG) were carried out in 36/74 DLB cases, and in 2/5 non-DLB cases with a history of RBD. Of these, REM sleep without atonia was confirmed in 84% and it was impossible to confirm in 13% due to the absence of REM sleep during the PSG. The 2 non-DLB cases with a history of RBD did not achieve REM sleep during the PSG.

Diagnostic accuracy of DLB. Logistic regression modeling was carried out to determine which features were predictive of autopsy-confirmed DLB compared to the non-DLB group (see table 3). In a model including the 3 core features, each predictor was significantly associated with an approximate 2-fold increase in the odds of autopsy-confirmed DLB (odds ratio range = 1.83–2.29). When RBD was added to the model, there was a significant improvement in model fit, and RBD was associated with a 6-fold increase in the odds of autopsy-confirmed DLB, while fluctuations and VH were no longer significant predictors.

When probable DLB was represented by 2 of the 3 core features, sensitivity to pathologic DLB diagnosis was 85% and specificity was 73%. The addition of RBD (requiring 2 or more of 4 features for probable DLB) increased sensitivity to 88% without any loss of specificity. When the criteria were modified so that probable DLB reflected dementia plus RBD only or dementia plus 2 or more of the 4 features, diagnostic sensitivity increased to 90%, and specificity remained at 73%. When fluctuations were excluded and the model included VH, parkinsonism, and RBD, the specificity was 85% with sensitivity at 83% (table 4).

False-positive misclassified cases. The misclassified cases are presented in table 5 according to pathologic diagnosis and clinical features. The false-positives were not overwhelmingly in one diagnostic category, though AD and TLBD with a high Braak NFT stage were more likely to be misclassified as DLB than the other diagnoses. The exception is Creutzfeldt-Jakob disease (CJD), of which 2 of 3 cases met criteria for DLB.

Compared to the DLB group, the false-positive cases had a higher Braak NFT stage (DLB mean 3.6 ± 2 vs false-positive non-DLB mean 4.7 ± 2 , $p < 0.01$), and were more likely female (DLB females 22% vs false-positives 51%, $p < 0.01$).

Limbic LBs with advanced AD pathology. There were 7/15 TLBD with Braak NFT $>$ IV who met criteria for probable DLB, but were incorporated into the 37 false-positives. This is relevant, since these patients have LBs, but were rated as low likelihood of DLB due to advanced AD pathology. As a group, these 15 individuals with TLBD had a longer duration of illness than the intermediate/high DLB group (DLB 7.9 ± 3 years vs TLBD 11.3 ± 5 years, $p < 0.01$), and later onset of VH (DLB 2.6 ± 4 years vs TLBD 8.2 ± 4 years, $p < 0.01$), and parkinsonism relative to dementia onset (DLB 1.8 ± 3 years vs TLBD 7.3 ± 5 years, $p < 0.01$). A similar pattern was observed in the AD with amygdala-predominant LBs ($n = 10$), with a longer duration of illness (mean

Table 2 DLB features in pathologic groups

Clinical feature	DLB intermediate-high	DLB no-low	χ^2 or t	p Value
No.	98	136		
Males, %	76	51	14.7	<0.01
No. of annual evaluations, mean $\pm$ SD	3.6 $\pm$ 2	4.7 $\pm$ 3	4.0	<0.01
Duration of illness, y, mean $\pm$ SD	7.8 $\pm$ 3	9.2 $\pm$ 4	2.8	<0.01
Global Deterioration Scale, mean $\pm$ SD	3.9 $\pm$ 1	3.9 $\pm$ 1	0.6	0.56
Mini-Mental State Examination, mean $\pm$ SD	22.9 $\pm$ 5	22.6 $\pm$ 9	-0.3	0.76
Baseline UPDRS, mean $\pm$ SD	9.6 $\pm$ 7	4.2 $\pm$ 6	-6.1	<0.01
Baseline ESS-c, mean $\pm$ SD	11 $\pm$ 5	8.6 $\pm$ 5	-3.2	<0.01
Fluctuations, baseline only, %	50	29	10.3	<0.01
Fluctuations, during disease, %	82	40	38.6	<0.01
Visual hallucinations, %	75	24	59.8	<0.01
Parkinsonism, %	86	38	52.8	<0.01
REM sleep behavior disorder, %	76	4	128.8	<0.01
Visual hallucinations onset relative to estimated dementia onset, y, mean $\pm$ SD	2.6 $\pm$ 3	5.2 $\pm$ 4	3.5	<0.01
Parkinsonism onset relative to dementia onset, y, mean $\pm$ SD	1.8 $\pm$ 3	4.9 $\pm$ 4	4.6	<0.01
REM sleep behavior disorder onset relative to dementia onset, y, mean $\pm$ SD	-6.0 $\pm$ 12	0.6 $\pm$ 11	1.2	0.23

Abbreviations: DLB = dementia with Lewy bodies; ESS-c = Epworth Sleepiness Scale-collateral version; UPDRS = Unified Parkinson's Disease Rating Scale.

^aThe onset year of visual hallucinations, parkinsonism, and REM sleep behavior disorder were each subtracted by the estimated year of dementia onset.

12 $\pm$ 3 years), and a later onset of VH (mean 7 $\pm$ 4 years) and parkinsonism (mean 6 $\pm$ 4 years) compared to the DLB group (p < 0.01).

Non-DLB autopsy group with RBD. In the no/low likelihood DLB group, 5/136 patients had a history of probable RBD. Each of these 5 individuals had 3

or 4 DLB features, but none had PSG confirmation of RBD. The pathologic diagnoses revealed 2 with TLBD and a Braak NFT stage of VI, 1 with cerebrovascular disease (no REM sleep on PSG), 1 with progressive supranuclear palsy with hippocampal-sparing AD (no REM sleep on PSG), and 1 with CJD with amyotrophic lateral sclerosis.

Table 3 Logistic regression model as a predictor of DLB pathology

Variable	β Coefficient	Wald	Odds ratio	p Value
3-Factor model				
Constant	-2.83	52.21	0.59	<0.01
Fluctuations	0.61	11.0	1.83	<0.01
Visual hallucinations	0.71	16.2	2.03	<0.01
Parkinsonism	0.83	19.5	2.29	<0.01
4-Factor model				
Constant	-2.88	42.78	0.57	<0.01
Fluctuations	0.33	2.09	1.39	0.15
Visual hallucinations	0.23	0.93	1.26	0.34
Parkinsonism	0.64	7.71	1.90	<0.01
RBD	1.82	43.88	6.17	<0.01

Abbreviations: DLB = dementia with Lewy bodies; RBD = REM sleep behavior disorder.

False-negative misclassified cases. In the autopsy-confirmed DLB group, 12 patients did not meet criteria for DLB (see table 5), and 3 had none of the 4 clinical features. Duration of illness for this group did not differ from the symptomatic DLB cohort (DLB mean 7.9 $\pm$ 3 vs false-negative DLB mean 7.32 $\pm$ 3, p = 0.47). Of those with a single feature, 2 (DLBD with Braak NFT of V; DLBD with Braak NFT of III) presented with RBD and dementia only. Interestingly, these 2 patients had the shortest durations of illness (4 and 5 years) and had mild and mild to moderate dementia at death. This suggests that they may have died before other features could develop.¹⁸

DISCUSSION Patients with a history of RBD were 6 times more likely to have autopsy-confirmed DLB than other neurodegenerative dementia conditions. This is an improvement from the model that included 3 core features (fluctuations, parkinsonism,

Table 4 Diagnostic accuracy of clinical feature combinations

Dementia plus clinical features	DLB intermediate-high	DLB no-low	χ^2	p Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV, %	NPV, %
Two or more: visual hallucinations, parkinsonism, fluctuations								
Yes	83	37						
No	15	99	73	<0.01	85 (76-91)	73 (64-80)	69	87
Two or more: visual hallucinations, parkinsonism, fluctuations, RBD								
Yes	86	37						
No	12	99	82	<0.01	88 (79-93)	73 (64-80)	70	89
RBD as sole clinical feature or 2 or more: VH, parkinsonism, fluctuations, RBD								
Yes	88	37						
No	10	99	90	<0.01	90 (82-95)	73 (64-80)	70	91
Two or more: visual hallucinations, parkinsonism, RBD								
Yes	81	21						
No	17	115	102	<0.01	83 (73-89)	85 (77-90)	79	87

Abbreviations: CI = confidence interval; DLB = dementia with Lewy bodies; NPV = negative predictive value; PPV = positive predictive value; RBD = REM sleep behavior disorder.

and VH) that yielded a 2-fold increase in autopsy-confirmed DLB. Diagnostic sensitivity, the proportion of true positives, was 85% when clinically probable DLB was considered to reflect dementia plus at least 2 of the 3 core clinical features for a pathologic diagnosis of intermediate/high likelihood of DLB. When RBD is added and clinically probable DLB is represented by dementia plus at least 2 of 4 clinical features, then diagnostic sensitivity improved to 88%. If the model includes dementia and RBD as the sole clinical features or dementia plus 2 of the 4 clinical features, diagnostic sensitivity was further increased to 90%. Thus, adding RBD as a core clinical feature to the DLB diagnostic criteria improves the overall predictive value and diagnostic sensitivity of the criteria.

Diagnostic specificity, the identification of true negatives, remained at 73% in each of the above models. This dampening of specificity may be attributable to our assessment of fluctuations. Fluctuations, as measured by the Mayo Fluctuations Scale,²⁶ occurred in 80% of the autopsy DLB group, but also occurred in 40% of our non-DLB cohort with advanced disease and has been shown by others to be fairly common in advanced AD.³⁵ When fluctuations were excluded from the analysis, specificity improved to 85% (along with a concurrent improvement in positive predictive value), with a mild drop in sensitivity to 83%.

When considering the diagnostic utility of clinical criteria, the model to use will depend on the clinical

situation and the costs of a missed or false-positive diagnosis need to be considered. From a patient care standpoint, the model with the best sensitivity may be most appropriate because missing a DLB diagnosis when the disease is actually present may have considerable implications for treatment³⁶ and disease morbidity.³⁷ Alternately, the model with the highest specificity may be better for group classification if a new intervention carries a high risk of adverse effects for those without the condition.

A history of RBD was present in 76% of the autopsy-confirmed DLB group, and in 4% of the non-DLB autopsy group, but only 3/136 non-DLB autopsy cases had probable RBD in the context of non-LB brainstem pathology. Thus, when probable RBD is reported, it is a sensitive indicator of brainstem synucleinopathy. Although the exact brainstem nuclei responsible for RBD in humans have yet to be established, REM sleep without atonia in animals has been associated with damage to the dorsal pontine-medullary region,^{38,39} and this region is thought to be affected early in LB disease.⁴⁰

RBD is an early feature of DLB that may occur many years before the onset of dementia or parkinsonism and may become less frequent or less symptomatic as the dementia progresses.¹⁴ In our autopsy DLB sample, patients with probable RBD developed their dream enactment behavior during sleep an average of 6 years before the onset of dementia. Distinguishing RBD from obstructive sleep apnea,

Table 5 Pathologic diagnosis of patients clinically misclassified

Pathologic diagnoses	Missed/n ^a	Females	DLB features				Number with			
			One	Two	Three	Four	Fluctuations	RBD	Parkinsonism	VH
False-positives										
TLBD and Braak > IV	7/15	4	0	3	3	1	5	2	7	5
AD	9/57	6	0	6	3	0	8	0	6	7
AD and amygdala LBs	6/10	3	0	2	4	0	5	0	5	6
AD and CVD	4/14	1	0	4	0	0	3	0	2	3
CVD	1/6	0	0	0	1	0	0	1	1	1
CBD	1/5	1	0	1	0	0	1	0	1	0
PSP	2/4	0	0	1	0	1	2	1	2	1
FTLD	4/17	2	0	3	1	0	4	0	4	1
CJD	2/3	2	0	1	1	0	2	1	1	1
Other	1/5	0	0	1	0	0	0	0	1	1
Total	37/136	19	0	22	13	2	30	5	30	26
False-negatives										
DLBD and Braak ≤ IV	2/42	1	2	0	0	0	0	1	1	0
DLBD and Braak > IV	9/35	4	6	0	0	0	2	1	2	1
TLBD and Braak ≤ IV	1/21	0	1	0	0	0	0	0	1	0
Total	12/98	5	9	0	0	0	2	2	4	1

Abbreviations: AD = Alzheimer disease; CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; CVD = cerebrovascular disease (single or multiple infarctions or hemorrhages); DLB = dementia with Lewy bodies; DLBD = diffuse Lewy body disease; FTLD = frontotemporal lobar degeneration; LB = Lewy body; PSP = progressive supranuclear palsy; RBD = REM sleep behavior disorder; TLBD = transitional Lewy body disease; VH = visual hallucinations.

^aNumber of misclassifications over total number with the pathologic diagnosis.

sleepwalking, and sleep talking is critical and polysomnography is indispensable to help rule them out.

Compared to the non-DLB group, the autopsy-confirmed DLB group had a greater number of males, shorter duration of illness, and greater severity of baseline extrapyramidal signs. VH and parkinsonism began an average of 2 years after estimated dementia onset in the DLB group, compared to an average of 5 years after estimated dementia onset in the non-DLB cohort. Further study that examines if cutoffs for temporal onset of VH and parkinsonism improve diagnostic accuracy of autopsy-confirmed DLB is warranted.

The TLBD group included a subset of 15 patients who were categorized as low likelihood DLB, due to the presence of advanced AD pathology, despite the presence of limbic and brainstem LBs. Of those, about half (7/15) met criteria for DLB and the onset of parkinsonism and VH occurred later in the disease, about 7 and 8 years after dementia onset, respectively. A similar pattern was observed in AD with amygdala-predominant LBs, suggesting when the LB pathology is confined to limbic regions in the context of advanced AD, groups may be clinically more sim-

ilar to their AD counterparts than to DLBD with advanced AD pathology, or TLBD with a low Braak stage. It would be helpful to know whether this similarity extends to include treatment response and risk of iatrogenic complications.

The autopsy-confirmed AD group had the highest number of false-positives (19/81 or 23%), which emphasizes the need to distinguish DLB from AD during life. CJD was discovered at autopsy in 3 cases, 2 of whom met DLB criteria and 3/9 from the CBD/PSP group had false-positive DLB diagnoses. These data highlight the importance of keeping rare conditions in mind when considering a diagnosis of DLB.

In the false-negative group, 12 patients with autopsy-confirmed DLB were missed. A single DLB clinical feature was present in 9/12, and of those, 2 had RBD and 4 had parkinsonism. There is a need to determine if other clinical or cognitive features, or combinations, further improve our ability to diagnose DLB.

We tried to address methodologic limitations of prior studies by including a larger sample size, broader representation of the comparison group, prospective follow-up of early dementia until death,

and using standardized clinical and pathologic measurement tools. Nonetheless, this study is limited by the relatively few controls with non-LB-related parkinsonian conditions and overnight polysomnography was not available in every patient. Also, the referral patterns in our setting may differ from other sites, and as such, validation of the criteria in other clinical settings is needed.

AUTHOR CONTRIBUTIONS

Dr. Ferman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, obtaining funding. Dr. Boeve: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Smith: drafting/revising the manuscript, study concept or design, study supervision, obtaining funding. Dr. Lin: study concept or design, acquisition of data. Dr. Silber: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Pedraza: analysis or interpretation of data, statistical analysis. Dr. Wszolek: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Graff-Radford: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Uitti: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients. Dr. Van Gerpen: drafting/revising the manuscript, acquisition of data. Dr. Pao: analysis or interpretation of data, acquisition of data. Dr. Knopman: drafting/revising the manuscript. Dr. Pankratz: analysis or interpretation of data, statistical analysis, obtaining funding. Dr. Kantarci: drafting/revising the manuscript, obtaining funding. Dr. Boot: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Parisi: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. B.N. Dugger: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Fujishiro: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. Petersen: drafting/revising the manuscript, obtaining funding. Dr. Dickson: drafting/revising the manuscript, contribution of vital reagents/tools/patients.

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DISCLOSURE

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