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Duration and Pathologic Correlates of Lewy Body Disease

Jonathan Graff-Radford, MD; Jeremiah Aakre, MPH; Rodolfo Savica, MD, PhD; Bradley Boeve, MD; Walter K. Kremers, PhD; Tanis J. Ferman, PhD; David T. Jones, MD; Kejal Kantarci, MD; David S. Knopman, MD; Dennis W. Dickson, MD; Walter A. Kukull, PhD; Ronald C. Petersen, MD, PhD

IMPORTANCE Although patients with dementia with Lewy bodies (DLB) have shorter disease duration than patients with Alzheimer disease dementia, little is known about which factors influence disease duration among patients with DLB.

OBJECTIVE To identify pathologic correlates of disease duration in participants with Lewy body disease (LBD).

DESIGN, SETTING, AND PARTICIPANTS This observational study, performed from September 1, 2005, to June 1, 2015, using the National Alzheimer's Coordinating Center database included 807 participants with transitional or diffuse LBD.

MAIN OUTCOMES AND MEASURES The study used Braak neurofibrillary tangle (NFT) stage, frequency of neuritic plaques, and LBD stage to determine whether pathologic variables are associated with disease duration.

RESULTS This study included 807 participants with transitional or diffuse LBD (mean [SD] age, 70.0 [9.9] at the onset of cognitive decline and 79.2 [9.8] years at death; 509 male [63.1%]). Shorter disease duration from cognitive symptom onset to death was observed in men (β, −0.73; 95% CI, −1.33 to −0.14; $P = .02$) and in those with a later age at onset (β, −0.11; 95% CI, −0.14 to −0.08; $P < .001$). Diffuse (neocortical) LBD was associated with shorter disease duration compared with transitional LBD (β, −1.52; 95% CI, −2.11 to −0.93; $P < .001$). Braak NFT stage and the presence of neuritic plaques were not significantly associated with differences in disease duration.

CONCLUSIONS AND RELEVANCE Diffuse LBD was associated with shorter disease duration compared with transitional LBD, and this effect is independent of Braak NFT stage or extent of neuritic plaque disease. Identifying antemortem biomarkers of LBD stage may provide important prognostic information to patients with DLB.

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Author Affiliations: Department of Neurology, Mayo Clinic, Rochester, Minnesota (Graff-Radford, Savica, Boeve, Jones, Knopman, Petersen); Department of Health Sciences Research, Mayo Clinic and Foundation, Rochester, Minnesota (Aakre, Kremers); Department of Psychiatry and Psychology, Mayo Clinic, Jacksonville, Florida (Ferman); Department of Radiology, Mayo Clinic, Jacksonville, Florida (Jones, Kantarci); Department of Pathology and Laboratory Medicine, Mayo Clinic, Jacksonville, Florida (Dickson); National Alzheimer's Coordinating Center, Department of Epidemiology, University of Washington, Seattle (Kukull).

Corresponding Author: Ronald C. Petersen, MD, PhD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (peter8@mayo.edu).

Dementia with Lewy bodies (DLB) is the second most common cause of degenerative dementia after Alzheimer disease (AD).[1-4] Prognosis in DLB is worse than in AD dementia. Patients with DLB may have a shorter survival[5] than patients with AD dementia; in addition, patients with DLB are admitted to nursing homes earlier in the disease course and have a more rapid cognitive decline than patients with AD dementia.[6,7] On the other hand, subsets of patients with DLB have a notable response to acetylcholinesterase inhibition[8] that is associated with increased occipital cerebral blood flow.[9]

The sensitivity of the clinical diagnosis of DLB to subsequent pathologic confirmation is suboptimal,[10] so any study that investigates disease course in DLB requires pathologically identified cases. Although DLB refers to a clinical syndrome, the pathologic substrate underlying DLB is Lewy body disease (LBD). In a small study[11] of 12 pathologically confirmed LBD cases, the degree of AD pathologic findings was associated with shorter survival. Confirmation of this finding in a larger autopsy series of patients with LBD is needed. At autopsy, most patients with clinically diagnosed DLB have diffuse (neocortical Lewy bodies) LBD, but a few have transitional (limbic Lewy bodies) LBD.[12,13] Whether the clinical course is different between participants with transitional or diffuse LBD is unknown. Our objective was to investigate pathologic correlates of disease duration among participants with pathologically confirmed LBD by focusing on the degree of coexisting AD pathologic findings and LBD type.

Methods

Study Participants

Using data from the National Alzheimer's Coordinating Center (NACC), we identified all participants with autopsy confirmation

of transitional or diffuse LBD regardless of clinical diagnosis from September 1, 2005, to June 1, 2015. Brainstem predominant LBD was excluded because brainstem-only LBD pathologic findings did not occur in 2 autopsy-confirmed series of patients with clinically diagnosed DLB,[12,13] and brainstem predominant LBD has a low likelihood of being associated with a DLB clinical syndrome according to the third report of the DLB Consortium.[14] Neuropathologists from AD centers follow consensus guidelines,[14-16] with the exact method of staining and sampling left up to each site. Institutional review boards approved the study procedures across the Alzheimer disease centers. Written informed consent was obtained from all participants or their surrogates. All data were deidentified.

Key Points

Question What are the pathologic correlates of disease duration in individuals with Lewy body disease?

Findings In this observational study of 807 individuals, diffuse Lewy body disease was associated with shorter disease duration compared with transitional Lewy body disease, whereas Braak neurofibrillary tangle stage and extent of neuritic plaque were not associated with disease duration.

Meaning From onset of cognitive symptoms, patients with diffuse Lewy body disease have a shorter disease duration.

Clinical Data

Clinical data were abstracted for all participants from the NACC database with transitional or diffuse Lewy body pathologic findings based on a June 2015 data freeze, including sex, age at onset of cognitive symptoms, age at death, United Parkinson Disease Rating Scale score, Mini-Mental State Examination (MMSE) score, neuropsychologic test scores, and the presence of core DLB features (hallucinations, fluctuations, parkinsonism, and probable rapid eye movement [REM] sleep behavior disorder).

Statistical Analysis

For group comparison, 2-tailed unpaired *t* tests were performed for continuous variables and χ^2 tests for categorical variables. We calculated the disease duration from cognitive onset, using age of symptom onset subtracted from the age of death. We used Braak neurofibrillary tangle (NFT) stage, frequency of neuritic plaque (none, sparse, moderate, or frequent), LBD type (transitional or diffuse), and the presence or absence of vascular pathologic findings (microinfarcts, large artery infarcts, and lacunar infarcts) to determine whether pathologic variables are associated with disease duration. Linear regression models were used to evaluate associations of pathologic variables adjusting for sex, apolipoprotein E ε4 (*APOE*-ε4) status, and age at cognitive onset. We performed a sensitivity analysis on the subset of participants who were diagnosed as having DLB as a primary or contributing clinical diagnosis to determine whether there were any differences with the tier of diagnosis. We also performed a secondary analysis to determine whether any DLB core clinical features (visual hallucinations, fluctuations, parkinsonism, or probable REM sleep behavior disorder[17]) were associated with disease duration. Finally, mixed-effect models allowing for random intercepts and slopes with unstructured correlation structure were used to model the changes in MMSE scores, adjusting for age at cognitive onset, sex, and interval between last test point and death. $P < .05$ was considered statistically significant.

Results

This study included 807 participants with transitional or diffuse LBD (mean [SD] age, 70.0 [9.9] at the onset of cognitive decline and 79.2 [9.8] years at death; 509 male [63.1%]). **Table 1** summarizes the demographic characteristics of the cohort. Among participants with LBD, 126 (15.6%) of 806 had microinfarcts, 94 (14.3%) of 656 had lacunar infarcts, and 39 (6.0%) of 654 had large artery infarcts at autopsy. A total of 188 (73.7%) of 255 participants with transitional and 291 (72.6%) of 401 with diffuse LBD met National Institute on Aging–Reagan criteria for high or intermediate likelihood of dementia being caused by AD. Participants with transitional LBD were older at the time of death, less likely to present with parkinsonism, and less likely to have neuritic plaques compared with participants with diffuse LBD.

Disease Duration in Pathologic LBD

A total of 766 participants with LBD had information on disease duration. **Table 2** summarizes the linear regression models for disease duration. Among all participants with transitional and diffuse LBD, in univariate analysis, older age (β, −0.11; 95% CI, −0.14 to −0.08; $P < .001$) and male sex (β, −0.73; 95% CI, −1.33 to −0.14; $P = .02$) were associated with shorter disease duration from cognitive symptoms onset. The presence of an *APOE*-ε4 allele was not associated with disease duration (β, 0.11; 95% CI, −0.51 to 0.73; $P = .72$).

After adjustment for age at onset, sex, and *APOE*-ε4 status, higher Braak NFT stage (IV-VI vs 0-III) (difference in mean disease duration, 0.35 years; 95% CI, −0.37 to 1.06 years; $P = .34$) and the presence of moderate or frequent neuritic plaques (difference in mean disease duration, 0.04 years; 95% CI, −0.75 to 0.83 years; $P = .92$) were not associated with disease duration. On the other hand, the presence of diffuse compared with transitional LBD was associated with shorter disease duration (difference in mean disease duration, −1.52 years; 95% CI, −2.11 to −0.93 years; $P < .001$). These results were unchanged after adjusting for AD center to account for possible intercenter rating differences.

The association between diffuse LBD stage and shorter disease duration remained after including the presence of baseline parkinsonism in the model (difference in mean disease duration, −1.80 years; 95% CI, −3.37 to −0.22 years; $P = .03$). No statistically significant interactions were found among LBD type, Braak NFT stage, or the presence of neuritic plaques with regard to disease duration.

After adjustment for age at onset, sex, *APOE*-ε4 status, Braak NFT stage, presence of neuritic plaques, and LBD stage, large artery infarcts (difference in mean disease duration, −1.21 years; 95% CI, −2.70 to 0.28 years; $P = .11$) and microinfarcts (difference in mean disease duration, 0.56 years; 95% CI, −0.25

Table 1. Demographic Characteristics[a]

Characteristic	Transitional LBD (n = 344)	Diffuse LBD (n = 463)	Total (N = 807)	*P* Value
Males	206 (59.9)	303 (65.4)	509 (63.1)	.11
Age, mean (SD), y				
Onset of cognitive decline	70.0 (11.0)	70.0 (9.1)	70.0 (9.9)	>.99
Death	80.2 (10.5)	78.5 (9.2)	79.2 (9.8)	.01
APOE-ε4 allele present	148 (51.2)	216 (56.8)	364 (54.4)	.15
Level of education, mean (SD), y	15.2 (3.3)	15.3 (3.2)	15.3 (3.2)	.67
Parkinsonism during disease	76 (44.4)	193 (69.7)	269 (60.0)	<.001
Braak NFT stage ≥IV	260 (75.8)	337 (72.8)	597 (74.1)	.33
Disease duration, mean (SD), y	9.7 (4.2)	8.3 (3.8)	8.8 (4.0)	<.001
Neuritic plaques present	289 (84.0)	425 (91.8)	714 (88.5)	<.001

Abbreviations: *APOE*-ε4, apolipoprotein E ε4; LBD, Lewy body disease; NFT, neurofibrillary tangle.

[a] Data are presented as number (percentage) of patients unless otherwise indicated. The *t* test was used assuming equal variance for continuous variables and the χ^2 test for categorical variables. Because of missing data, sample sizes varied according to the feature: n = 669 for *APOE*-ε4 data, n = 806 for Braak NFT stage data, n = 448 for parkinsonism data, n = 804 for educational data, and n = 766 for disease duration data.

Table 2. Association of Disease Duration With Pathologic Variables

Variable	Effect Size, %[a]	Difference in Mean Disease Duration (95% CI)	*P* Value
Males	8.3	−0.73 (−1.33 to −0.14)	.02
Age	1.2	−0.11 (−0.14 to −0.08)	<.001
APOE-ε4 status	1.3	0.11 (−0.51 to 0.73)	.72
Braak NFT stage[b]	4	0.35 (−0.37 to 1.06)	.34
Frequency of neuritic plaques[b]	0.5	0.04 (−0.75 to 0.83)	.92
LBD stage (diffuse)[b]	17.2	−1.52 (−2.11 to −0.93)	<.001

Abbreviations: *APOE*-ε4, apolipoprotein E ε4; LBD, Lewy body disease; NFT, neurofibrillary tangle.

[a] Change in mean survival years divided by mean survival years among all patients with LBD.

[b] Model adjusted for age at onset, sex, and *APOE*-ε4 status.

to 1.36 years; *P* = .18) were not associated with disease duration, but lacunar infarcts (difference in mean disease duration, 0.98 years; 95% CI, −1.91 to −0.05; *P* = .04) were associated with shorter disease duration.

Disease Duration According to the DLB Consortium Neuropathologic Criteria

Compared with those with low-likelihood DLB, those with intermediate-likelihood (difference in mean disease duration, −1.66 years; 95% CI, −2.38 to −0.93 years; *P* < .001) and high-likelihood (difference in mean disease duration, −1.97 years; 95% CI, −2.71 to −1.22 years; *P* < .001) DLB had shorter disease duration after adjusting for age at onset, sex, and *APOE*-ε4 status.[14]

Disease Duration of Subset With Clinically Diagnosed DLB

We selected participants with a clinical diagnosis of probable DLB during life (n = 238) to focus on that clinical phenotype. This approach is relevant because participants with transitional LBD and a high Braak NFT stage may be more likely to present with an AD clinical phenotype and, as such, may exhibit disease trajectories that are more similar to AD than LBD. Covariates were modeled such that the β estimates refer to the adjustment in disease duration associated with each unit increase in the covariate. In the univariate model, older age (difference in mean disease duration, −0.09 years; 95% CI, −0.15 to −0.04 years; *P* < .001) continued to be associated with shorter disease duration; however, men were not more likely to have a shorter disease course (difference in mean disease duration, 0.55 years; 95% CI, −0.48 to 1.58 years; *P* = .29). Unlike the analysis of the larger group, the presence of an *APOE*-ε4 allele was associated with shorter disease duration (difference in mean disease duration, −1.41 years; 95% CI, −2.46 to −0.36 years; *P* = .009) among participants with clinically diagnosed DLB. After adjustment for age, sex, and *APOE*-ε4, shorter disease duration was more likely in those with diffuse LBD compared with transitional LBD (difference in mean disease duration, −1.65 years; 95% CI, −2.90 to −0.39 years; *P* = .01). Braak NFT stage (difference in mean disease duration, −0.29 years; 95% CI, −1.39 to 0.82 years; *P* = .61) and the presence of neuritic plaques (difference in mean disease duration, −0.33 years; 95% CI, −1.83 to 1.17 years; *P* = .66) were not associated with disease duration.

Differences Between Diffuse and Transitional LBD at Initial and Final Clinical Visits

Because the disease course was different between transitional and diffuse LBD, we performed a secondary analysis comparing the clinical differences at baseline and last follow-up. Not surprisingly, we observed that participants with diffuse LBD had more core features of DLB compared with transitional LBD (**Table 3**). In addition, participants with diffuse LBD had a faster rate of decline on the MMSE compared with participants with transitional LBD (**Figure**). On neuropsychologic testing, participants with diffuse LBD performed worse on the Category Fluency Test (animals), Wechsler Adult Intelligence Scale–Revised Digit Symbol subtest, and pentagon subscore on the MMSE compared with participants with transitional LBD, but there was no difference on the Logical Memory IIA–Delayed test (story units recalled) and Boston Naming Test.

Clinical Features as a Predictor of Disease Duration

In univariate linear regression models, duration of illness was not associated with the presence or absence of visual hallucinations (difference in mean disease duration, −0.57 years; 95%

Table 3. Clinical Characteristics by Transitional and Diffuse LBD Status[a]

Characteristic	Baseline			Final Visit		
	Transitional LBD	Diffuse LBD	*P* Value	Transitional LBD	Diffuse LBD	*P* Value
UPDRS total score, mean (SD)	9.7 (12.8)	14.8 (15.7)	<.001	14.0 (15.3)	21.4 (17.8)	<.001
Hallucinations	52 (17.4)	142 (32.8)	<.001	64 (21.1)	169 (38.8)	<.001
Fluctuations	NA	NA	NA	60 (27.4)	114 (35.4)	.05
Probable REM sleep behavior disorder	NA	NA	NA	32 (14.6)	72 (22.6)	.02
Changes suggestive of parkinsonism	NA	NA	NA	67 (43.2)	170 (64.9)	<.001
Presence of ≥1 core DLB feature	78 (26.1)	192 (44.2)	<.001	132 (42.7)	295 (66.0)	<.001
No. of DLB core features present (range, 0-4), mean (SD)	NA	NA	NA	0.72 (1.1)	1.17 (1.2)	<.001
DLB as primary or contributing diagnosis	26 (7.6)	111 (24.0)	<.001	32 (9.3)	136 (29.4)	<.001
History of stroke	16 (4.8)	22 (4.8)	.98	18 (6.8)	28 (7.7)	.68
MMSE score, mean (SD)	19.5 (8.5)	19.3 (8.2)	.76	15.8 (8.8)	14.5 (8.6)	.07
Category Fluency Test (animals) score, mean (SD)	11.4 (6.3)	9.7(5.5)	<.001	8.7 (5.7)	6.9 (5.0)	<.001
WAIS-R Digit Symbol subtest score, mean (SD)	24.3 (15.5)	20.2 (13.9)	.002	21.0 (15.6)	13.9 (15.4)	<.001
Logical Memory IIA-Delayed (story units recalled) test score, mean (SD)	3.7 (4.5)	4.0 (4.5)	.38	3.1 (4.4)	3.1 (4.1)	.97
Boston Naming Test (30 odd-numbered items) score, mean (SD)	20.4 (8.3)	20.8 (7.5)	.49	18.0 (8.6)	17.7 (8.6)	.72
Normal pentagon subscore on the MMSE	NA	NA	NA	53 (34.2)	50 (23.1)	.02

Abbreviations: DLB, dementia with Lewy bodies; LBD, Lewy body disease; MMSE, Mini-Mental State Examination; NA, not applicable; REM, rapid eye movement; UPDRS, United Parkinson Disease Rating Scale; WAIS-R, Wechsler Adult Intelligence Scale–Revised.

[a] Data are presented as number (percentage) of patients unless otherwise indicated. Because of missing data, sample sizes varied among the different features analyzed. The numbers missing for each variable are as follows: for UPDRS total score, n = 52 for transitional LBD and 70 for diffuse LBD at baseline and n = 128 for transitional LBD and 181 for diffuse LBD at final visit; for hallucinations, n = 45 for transitional LBD and 30 for diffuse LBD at baseline and n = 41 for transitional LBD and 27 for diffuse LBD at final visit; for MMSE, n = 26 for transitional LBD and 44 for diffuse LBD at baseline and n = 104 for transitional LBD and 138 for diffuse LBD at final visit; for Category Fluency Test (animals), n = 70 for transitional LBD and 97 for diffuse LBD at baseline and n = 146 for transitional LBD and 213 for diffuse LBD at final visit; for WAIS-R Digit Symbol subtest, n = 121 for transitional LBD and 193 for diffuse LBD at baseline and n = 227 for transitional LBD and 319 for diffuse LBD at final visit; for Logical Memory IIA-Delayed test score, n = 82 for transitional LBD and 104 for diffuse LBD at baseline and n = 152 for transitional LBD and 219 for diffuse LBD at final visit; for Logical Memory IIA-Delayed (story units recalled), n = 82 for transitional LBD and 108 for diffuse LBD at baseline and n = 158 for transitional LBD and 224 for diffuse LBD at final visit; for the Boston Naming Test (30 odd-numbered items), n = 78 for transitional LBD and 110 for diffuse LBD at baseline and n = 161 for transitional LBD and 224 for diffuse LBD at final visit; for DLB as a primary or contributing diagnosis, none missing; for history of stroke present, n = 9 for transitional LBD and 6 for diffuse LBD and n = 79 for transitional LBD and 97 for diffuse LBD at final visit; for presence of at least 1 core DLB feature, n = 45 for transitional LBD and 29 for diffuse LBD at baseline and n = 35 for transitional LBD and 16 for diffuse LBD at final visit; for changes suggestive of parkinsonism, n = 189 for transitional LBD and 201 for diffuse LBD at final visit; for probable REM sleep behavior disorder, n = 125 for transitional LBD and 144 for diffuse LBD at final visit; for normal pentagon subscore on the MMSE, n = 189 for transitional LBD and 247 for diffuse LBD at final visit; and for fluctuations, n = 125 for transitional LBD and 144 for diffuse LBD at final visit.

CI, −1.20 to 0.05 years; *P* = .07) or fluctuations (difference in mean disease duration, −0.44 years; 95% CI, −1.17 to 0.291; *P* = .23) reported at the final visit. In contrast, a shorter duration of illness was associated with the presence of parkinsonism (difference in mean disease duration, −1.11 years; 95% CI, −1.87 to −0.36 years; *P* = .004) or probable REM sleep behavior disorder (mean disease duration, −1.39 years; 95% CI, −2.25 to −0.52 years; *P* = .002) reported at the final visit.

Discussion

Using the NACC database, we examined whether the duration of illness in participants with transitional or diffuse LBD was associated with distribution of Lewy bodies, Braak NFT stage, frequency of neuritic plaques, or demographic features and core DLB features. The results reveal that participants with diffuse LBD have shorter disease duration from cognitive symptom onset to death compared with participants with transitional LBD. When the analysis was performed with the subgroup of participants with a primary or contributing clinical diagnosis of probable DLB, the relationship of shorter disease duration with diffuse LBD persisted. Among vascular lesions, the presence of lacunar stroke was also associated with shorter disease duration.

The ascending model of the synuclein spreading for Parkinson disease suggests that disease transitions from the brainstem to the limbic system and then to the cortex.[18] This staging scheme does not apply to all Lewy body disorders.[19] In fact, if the pathologic findings in all Lewy body spectrum disorders were similar, we would expect a spread from the brainstem to the cortex; therefore, those with diffuse LBD would be expected to have longer disease duration than those with transitional LBD. It is also probable that many transitional participants would become diffuse in time but die before progression to diffuse disease.

Most patients with DLB have coexisting AD pathologic findings.[1] Imaging features of AD pathologic findings predict treat-

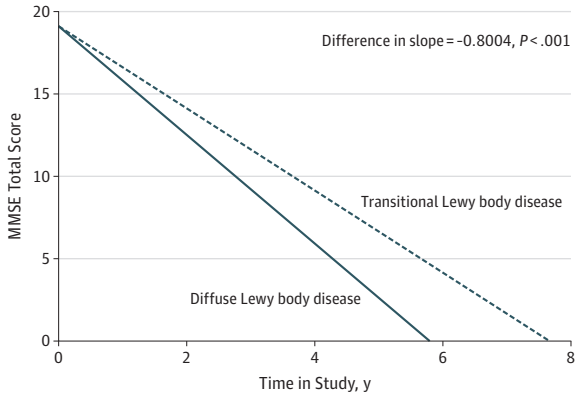
ment response,[8] and absence of significant coexisting AD pathologic findings at autopsy correlates with slower cognitive decline.[20] Thus, the presence of coexisting AD pathologic findings may be an important predictor of shorter disease duration in DLB. In the Hisayama study[11] among 12 participants with LBD, AD burden was associated with shorter disease duration. Contrary to these findings, among all participants with LBD pathologic findings, higher Braak NFT stage was not associated with disease duration. Most participants in the current study were diagnosed with AD dementia clinically and would be considered to have a low or intermediate likelihood of developing DLB according to the DLB Consortium pathologic criteria.[14] In fact, almost three-quarters of the participants in this study had Braak NFT stage IV or higher. Participants with diffuse or transitional LBD with high Braak NFT stage most often present clinically with AD dementia,[13] approximately 67% of the time for diffuse cases and 87% of the time for transitional cases. Therefore, to determine whether our pathologic findings were driven by cases presenting with a clinical AD dementia phenotype, we analyzed the subset who presented with DLB as the primary or contributing diagnosis. Among the subset of participants with probable DLB, the presence of diffuse LBD pathologic findings at autopsy remained associated with shorter disease duration, but Braak NFT stage was not associated with longer disease duration. Baseline hippocampal atrophy on magnetic resonance imaging predicts shorter disease duration in DLB.[21] Typically, hippocampal atrophy in DLB is associated with NFT pathologic findings. One possible explanation for the fact that hippocampal atrophy on magnetic resonance imaging predicts shorter disease duration but Braak NFT stage does not is that hippocampal atrophy on magnetic resonance imaging may be a surrogate marker of pathologic density of NFTs and synuclein pathologic findings that is not captured by Braak NFT stage alone. This study did not address the density of neuropathologic lesions that can be dissociated from stage. Therefore, it remains possible that density of AD pathologic findings (tau and amyloid) may be associated with disease duration.

In clinically diagnosed DLB, the presence of an *APOE*-ε4 allele is associated with shorter disease duration.[5] Among all participants with pathologically defined transitional or diffuse LBD, *APOE*-ε4 allele was not associated with disease duration. In the subgroup of participants with a primary or contributing diagnosis of DLB, *APOE*-ε4 was associated with shorter disease duration. The lack of association in the overall pathologic group is likely driven by the large number of participants with a low likelihood of developing DLB that represent cases with transitional LBD and high Braak NFT stage. *APOE*-ε4 is associated with the development of pure synucleinopathies even in the absence of significant AD pathologic findings.[22]

In AD dementia, a history of stroke is associated with shorter disease duration.[23] Similarly, lacunar stroke was associated with shorter disease duration in patients with LBD. Large artery stroke and microinfarction were not associated with disease duration, but additional studies are needed to determine whether they are associated with rate of cognitive decline in LBD.

Given the difference in disease duration between diffuse and transitional LBD, we performed a secondary analysis to determine whether there were any clinical differences between transitional and diffuse LBD at the initial and final clinical visits. Several patterns emerged: participants with diffuse LBD were more likely to be diagnosed with DLB and have core DLB features, including parkinsonism, probable REM sleep behavior disorder, fluctuations, and hallucinations. Although the baseline MMSE, Logical Memory IIA–Delayed test, and Boston Naming Test scores did not differ between participants with transitional and diffuse LBD, the Category Fluency Test and Wechsler Adult Intelligence Scale–Revised Digit-Symbol scores were lower in the diffuse LBD group. Although not available for the baseline evaluation, those with diffuse LBD performed worse on the pentagon subscale of the MMSE. These group differences in tests of processing speed, executive function, attention, and visual-spatial function support the notion that those with diffuse LBD are more similar in profile to participants with clinically diagnosed DLB. Whereas the MMSE was similar at baseline, participants in the diffuse LBD declined more rapidly.

Figure. Change in Mini-Mental State Examination (MMSE) Scores



Change in MMSE scores between transitional and diffuse Lewy body disease.

Because diffuse LBD was associated with disease duration, we explored which of the core features would be associated with disease duration. Similar to a prior study,[5] parkinsonism was associated with shorter disease duration, but hallucinations and fluctuations were not. Inclusion of parkinsonism in the model did not change the association between disease duration and LBD stage. Probable REM sleep behavior disorder was also associated with shorter disease duration, likely reflecting the shorter disease duration in participants who present with DLB vs AD clinically because REM sleep behavior disorder is present in approximately 80% of participants with DLB.[24] The natural history and sequence of clinical features to death may be important for disease duration and require further investigation.[24]

Limitations

This study has several limitations. The data were collected at AD centers, where the focus of research on Lewy body disorders may vary. Therefore, the findings cannot be applied broadly to persons with clinical DLB. In addition, because of the nature of this pathologic data collection, we are unable to determine the temporal ordering of pathologic changes that occurred many years earlier that influenced disease duration. Some pathologic changes, such as the presence of coexisting TAR DNA-binding

protein *43*, were not available, and the relevance of these pathologic elements should be the subject of future research.

Conclusions

Diffuse LBD is associated with shorter disease duration than transitional LBD among patients with pathologically verified LBD regardless of whether the clinical phenotype is AD dementia or DLB. Developing antemortem biomarkers that can identify transitional vs diffuse LBD will have clinical importance to predict the prognosis of the patients with DLB. Our findings support differences in prognosis between different patients with LBD according to the extent of Lewy body–related pathologic findings.

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Study concept and design: Graff-Radford, Kremers, Ferman, Jones, Dickson, Petersen.
Acquisition, analysis, or interpretation of data: All authors.
Critical revision of the manuscript for important intellectual content: Aakre, Savica, Boeve, Kremers, Ferman, Jones, Kantarci, Knopman, Dickson, Kukull, Petersen.
Statistical analysis: Graff-Radford, Aakre, Savica, Kremers, Jones.
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Study supervision: Savica.

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REFERENCES

1. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. *Alzheimer Dis Assoc Disord*. 2002;16(4):203-212.

2. Zaccai J, McCracken C, Brayne C. A systematic review of prevalence and incidence studies of dementia with Lewy bodies. *Age Ageing*. 2005;34(6):561-566.

3. Rahkonen T, Eloniemi-Sulkava U, Rissanen S, Vatanen A, Viramo P, Sulkava R. Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. *J Neurol Neurosurg Psychiatry*. 2003;74(6):720-724.

4. Savica R, Grossardt BR, Bower JH, Boeve BF, Ahlskog JE, Rocca WA. Incidence of dementia with Lewy bodies and Parkinson disease dementia. *JAMA Neurol*. 2013;70(11):1396-1402.

5. Williams MM, Xiong C, Morris JC, Galvin JE. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. *Neurology*. 2006;67(11):1935-1941.

6. Rongve A, Vossius C, Nore S, Testad I, Aarsland D. Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia. *Int J Geriatr Psychiatry*. 2014;29(4):392-398.

7. Olichney JM, Galasko D, Salmon DP, et al. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. *Neurology*. 1998;51(2):351-357.

8. Graff-Radford J, Boeve BF, Pedraza O, et al. Imaging and acetylcholinesterase inhibitor response in dementia with Lewy bodies. *Brain*. 2012;135(pt 8):2470-2477.

9. Mori T, Ikeda M, Fukuhara R, Nestor PJ, Tanabe H. Correlation of visual hallucinations with occipital rCBF changes by donepezil in DLB. *Neurology*. 2006;66(6):935-937.

10. Nelson PT, Jicha GA, Kryscio RJ, et al. Low sensitivity in clinical diagnoses of dementia with Lewy bodies. *J Neurol*. 2010;257(3):359-366.

11. Wakisaka Y, Furuta A, Tanizaki Y, Kiyohara Y, Iida M, Iwaki T. Age-associated prevalence and risk factors of Lewy body pathology in a general population: the Hisayama study. *Acta Neuropathol*. 2003;106(4):374-382.

12. Fujishiro H, Ferman TJ, Boeve BF, et al. Validation of the neuropathologic criteria of the Third Consortium for Dementia with Lewy bodies for prospectively diagnosed cases. *J Neuropathol Exp Neurol*. 2008;67(7):649-656.

13. Weisman D, Cho M, Taylor C, Adame A, Thal LJ, Hansen LA. In dementia with Lewy bodies, Braak stage determines phenotype, not Lewy body distribution. *Neurology*. 2007;69(4):356-359.

14. McKeith IG, Dickson DW, Lowe J, et al; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863-1872.

15. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement*. 2012;8(1):1-13.

16. Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *J Neuropathol Exp Neurol*. 1997;56(10):1095-1097.

17. Ferman TJ, Boeve BF, Smith GE, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. *Neurology*. 2011;77(9):875-882.

18. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003;24(2):197-211.

19. Toledo JB, Gopal P, Raible K, et al. Pathological α-synuclein distribution in subjects with coincident Alzheimer's and Lewy body pathology. *Acta Neuropathol*. 2016;131(3):393-409.

20. Nelson PT, Kryscio RJ, Jicha GA, et al. Relative preservation of MMSE scores in autopsy-proven dementia with Lewy bodies. *Neurology*. 2009;73(14):1127-1133.

21. Graff-Radford J, Lesnick TG, Boeve BF, et al. Predicting survival in dementia with Lewy bodies with hippocampal volumetry. *Mov Disord*. 2016;31(7):989-994.

22. Tsuang D, Leverenz JB, Lopez OL, et al. *APOE* ε4 increases risk for dementia in pure synucleinopathies. *JAMA Neurol*. 2013;70(2):223-228.

23. Larson EB, Shadlen MF, Wang L, et al. Survival after initial diagnosis of Alzheimer disease. *Ann Intern Med*. 2004;140(7):501-509.

24. Dugger BN, Boeve BF, Murray ME, et al. Rapid eye movement sleep behavior disorder and subtypes in autopsy-confirmed dementia with Lewy bodies. *Mov Disord*. 2012;27(1):72-78.