β-Amyloid PET and 123I-FP-CIT SPECT in Mild Cognitive Impairment at Risk for Lewy Body Dementia

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Neurology® 2021;96:e1180-e1189. doi:10.1212/WNL.0000000000011454

Abstract

Objective

To determine the clinical phenotypes associated with the β-amyloid PET and dopamine transporter imaging (123I-FP-CIT SPECT) findings in mild cognitive impairment (MCI) with the core clinical features of dementia with Lewy bodies (DLB; MCI-LB).

Methods

Patients with MCI who had at least 1 core clinical feature of DLB (n = 34) were grouped into β-amyloid A+ or A− and 123I-FP-CIT SPECT D+ or D− groups based on previously established abnormality cut points for A+ with Pittsburgh compound B PET standardized uptake value ratio (PiB SUVR) ≥1.48 and D+ with putamen z score with DaTQUANT <−0.82 on 123I-FP-CIT SPECT. Individual patients with MCI-LB fell into 1 of 4 groups: A+D+, A+D−, A−D+, or A−D−. Log-transformed PiB SUVR and putamen z score were tested for associations with patient characteristics.

Results

The A−D+ biomarker profile was most common (38.2%), followed by A+D+ (26.5%) and A−D− (26.5%). The least common was the A+D− biomarker profile (8.8%). The A+ group was older, had a higher frequency of APOE ε4 carriers, and had a lower Mini-Mental State Examination score than the A− group. The D+ group was more likely to have probable REM sleep behavior disorder. Lower putamen DaTQUANT z scores and lower PiB SUVRs were independently associated with higher Unified Parkinson’s Disease Rating Scale-III scores.

Conclusions

A majority of patients with MCI-LB are characterized by low β-amyloid deposition and reduced dopaminergic activity. β-Amyloid PET and 123I-FP-CIT SPECT are complementary in characterizing clinical phenotypes of patients with MCI-LB.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the Mayo Clinic.

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Mild cognitive impairment (MCI) with ≥1 core features of dementia with Lewy bodies (DLB) represents an interim phase that may be present years before a diagnosis of clinically probable DLB, and recently, this was formulated as the key prodromal DLB phenotype (MCI with Lewy bodies [LB]). The use of imaging biomarkers has facilitated the early detection of DLB and identification of patients in the MCI-LB stage provides an opportunity for early intervention. In addition to the deposition of α-synuclein pathology that constitutes LB disease, many patients have varying degrees of β-amyloid pathology, which may synergistically contribute to the pathogenesis of DLB. However, whether coexisting Lewy-related pathology and β-amyloid pathology influence the clinical presentation of the prodromal stage of DLB is currently unknown.

Elevated β-amyloid burden on Pittsburgh compound B (PiB) PET was reported in more than half of patients with DLB and has been associated with greater cognitive impairment in DLB. The quantitative analysis of antemortem 123I-FP-CIT SPECT demonstrated excellent discrimination between patients with and those without autopsy-confirmed LB disease, supporting the utility of 123I-FP-CIT SPECT as a biomarker for the underlying Lewy-related pathology in MCI-LB.

Our objective was to determine the clinical phenotypes associated with β-amyloid PET and 123I-FP-CIT SPECT in patients with MCI-LB who are at a higher risk for progression to probable DLB. We hypothesized that the 2 imaging modalities that are sensitive to different pathologic processes associated with DLB would provide complementary information for characterizing the clinical phenotype in patients with MCI-LB.

Methods

Participants

The current study included patients with MCI-LB (n = 34) with at least 1 core feature of DLB (i.e., parkinsonism, fluctuations, visual hallucinations, or REM sleep behavior disorder [RBD]) who were enrolled in the Mayo Clinic Alzheimer’s Disease Research Center (ADRC) between January 2012 and January 2020. Diagnosis of MCI was made according to the published criteria. Evaluations included information obtained through clinical interview by a neurologist, a neurologic examination, and the neuropsychological assessment. The Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Sum of Boxes were used to determine cognitive and disease severity. Assessments for the clinical features of DLB were detailed in previous reports from the ADRC cohorts.

Briefly, the presence of parkinsonism was based on 2 of the 4 cardinal features (tremor, rigidity, bradykinesia, and postural instability), and the severity was quantified with the Unified Parkinson’s Disease Rating Scale Part III (UPDRS-III). A history of probable RBD was based on the International Classification of Sleep Disorders-II diagnostic criteria. Visual hallucinations were characterized by being fully formed and not restricted to a single episode or related to another medical issue, advanced dementia, or treatment. The presence of fluctuations was based on the 4-item Mayo Fluctuations Scale scores of 3 or 4.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Mayo Clinic Institutional Review Board. Informed consent was obtained from all participants and/or their proxies for participation in this study.

MRI and β-Amyloid PET Acquisitions

MRI examinations were performed at 3T, and a 3-dimensional high-resolution magnetization prepared rapid gradient echo acquisition with 1-mm cubic resolution was obtained for anatomic segmentation and labeling. β-Amyloid PET was performed with PiB PET on PET/CT scanners in the 3-dimensional mode. The PiB scans consisted of four 5-minute dynamic frames acquired from 40 to 60 minutes after injection with an average of 576 MBq (range 448–673 MBq).

β-Amyloid PET Image Analysis

β-Amyloid PET images were analyzed with our in-house fully automated image processing pipeline in which image voxel values are extracted from automatically labeled regions of interest propagated from the prefrontal, orbitofrontal, temporal, parietal, anterior cingulate, and posterior cingulate/precuneus regions of interest using gray plus white sharpened voxels that were normalized to the cerebellum crus, as previously reported.

Dopamine Transporter Imaging Acquisitions

A 123I-FP-CIT SPECT (DaTscan, GE Healthcare, Chicago, IL) was performed according to previously published protocol for each participant. In brief, at least 1 hour before the...
injection of $^{123}$I-ioflupane, a 100 mg Lugol solution was given, and then the recommended $^{123}$I-ioflupane dose of 111 to 185 MBq (3–5 mCi) was slowly administered intravenously. SPECT imaging occurred 3 to 6 hours after injection. GE D670/D630 SPECT systems with ultrahigh-resolution fan beam collimators and an energy setting of 159 keV 20% window were used on all patients. Data were reconstructed with ordered subset expectation maximization method; the planar images were prefiltered with a Butterworth filter (power 10, cutoff 0.6 cycles/cm); and no attenuation correction was used. Projection images were used for the quantitative analysis.

$^{123}$I-FP-CIT-SPECT Analysis

Semiquantitative calculations of striatal uptake were performed by DaTQUANT software (GE Healthcare). The volumes of interest (VOIs) of DaTQUANT fixed size were semi-automatically placed over the right and left putamen and caudate nucleus in the transaxial slice showing most intense tracer uptake. Another VOI was placed over the occipital lobe representing cortical background. The software automatically placed the same VOIs in the adjacent previous and following slices such that data from 3 contiguous slices were used. Then, the left and right striatum-to-background ratio and z scores on the caudate, putamen, and striatum were automatically calculated.

We calculated the minimum DaTQUANT z scores from putamen (right or left side) that showed the best discrimination between patients with autopsy-confirmed LB disease and those without LB disease based on a previous study for statistical analysis.

Definition of Abnormality

Abnormal β-amyloid PET was defined as PiB SUVR ≥1.48, as previous described. Abnormal minimum DaTQUANT z score in putamen was defined as <−0.82, which was validated in autopsy-confirmed LB disease. Participants were assigned to an A and D biomarker group, with A−D− denoting low PiB SUVR and high putamen $^{123}$I-FP-CIT SPECT uptake, A+D− denoting high PiB SUVR and high putamen $^{123}$I-FP-CIT SPECT uptake, A−D+ denoting low PiB SUVR and low putamen $^{123}$I-FP-CIT SPECT uptake, and A+D+ denoting high PiB SUVR and low putamen $^{123}$I-FP-CIT SPECT uptake.

Statistical Analysis

We report demographic and clinical characteristics for A and D groups using means and SDs for continuous variables, with counts and percentages used for categorical variables. The groups were compared with either a t test for continuous variables or a χ² test for categorical variables with age adjusted as appropriate. To investigate isolated and synergistic contributions of β-amyloid and $^{123}$I-FP-CIT SPECT biomarkers to the demographics and clinical phenotypes of MCI-LB, we used continuous A and D as predictors in a factorial modeling approach by fitting A, D, and A × D interactions in either linear regressions or logistic regression models while adjusting for age. Due to skewness, PiB SUVR was log transformed as a continuous measurement. In addition, we compared the group difference among the patients with MCI-LB with 1, 2, or ≥3 core clinical features of DLB using a test for trend in linear regressions. A value of $p < 0.05$ (2 tailed) was deemed significant in all of these analyses.

Data Availability

Anonymized data will be shared by request from a qualified investigator in accordance with the Mayo ADRC data-sharing protocol.

Results

Participant Characteristics

The demographic and clinical characteristics of patients with MCI-LB and the isolated effects of A+ and D+ biomarkers are demonstrated in table 1. Most of the patients with MCI-LB in this study were male (n = 30, 88.2%). The mean (SD) MMSE score was 27.6 (1.7), and the mean (SD) score for Clinical Dementia Rating Sum of Boxes was 1.7 (0.8), consistent with the MCI status of study patients. In this MCI-LB sample, RBD was the most common core DLB feature (94.1%), followed by parkinsonism (70.6%) and fluctuations (41.2%), with visual hallucinations the least common core DLB feature (14.7%). In terms of number of core DLB features, 20.6% of the patients with MCI-LB presented with 1 core DLB feature, about half (47.1%) presented with 2 core DLB features, and 32.4% had ≥3 core DLB features.

Positivity of β-Amyloid PET

In this MCI-LB sample, more patients were classified as A− (n = 22, 64.7%) than A+ (n = 12, 35.3%), as shown in table 1. The A+ status was strongly modulated by APOE ε4 status ($p < 0.001$) and age ($p = 0.014$), and A+ individuals had lower MMSE scores ($p = 0.046$) than the A− group.

Positivity of $^{123}$I-FP-CIT SPECT

In our MCI-LB sample, more patients were classified as D+ (n = 22, 64.7%) than D− (n = 12, 35.3%). The D+ subgroup had higher UPDRS-III scores ($p = 0.019$) and were more likely to have RBD ($p = 0.048$) and less likely to have fluctuations ($p = 0.026$) than the D− group. The difference in RBD between D+ and D− groups was not significant after age adjustment ($p = 1.00$), while the difference in fluctuations remained significant after age adjustment ($p = 0.046$).

Distribution of β-amyloid PET and $^{123}$I-FP-CIT SPECT Positivity

The dichotomized distribution of β-amyloid PET and $^{123}$I-FP-CIT SPECT with individual data points is shown in figure 1. The A−D+ group was the largest group, accounting for 38.2% of the patients with MCI-LB (n = 13), followed by A+D+ (n = 9) and A−D− (n = 9), each of which included 26.5% of the patients with patients with MCI-LB. A+D− was the smallest group, including 8.8% of the patients with MCI-LB (n = 3). Representative images of β-amyloid PET and $^{123}$I-FP-CIT SPECT from the 4 A and D groups are shown in figure 2.
Association With the Demographic Characteristics and Clinical Features in MCI-LB
No significant interactions between A and D were associated with demographic or clinical variables. Table 2 shows the association of β-amyloid PET and 123I-FP-CIT SPECT biomarkers with the demographic characteristics and clinical features of patients with MCI-LB in models with no interactions. Age and APOE ε4 status were associated with the log of global cortical PiB SUVRs but not with putamen DaTQUANT z scores. When the clinical features were examined, higher UPDRS-III scores were associated with lower putamen DaTQUANT z scores (p < 0.001) and lower log of global cortical PiB SUVRs (p = 0.037) (figure 3). There were no other associations between these imaging variables and clinical features.

Table 1 Demographic and Clinical Characteristics of Patients With MCI-LB and the Isolated Effects of β-Amyloid and 123I-FP-CIT SPECT Biomarkers

| Age, y          | A− (n = 22) | A+ (n = 12) | p Value | D− (n = 12) | D+ (n = 22) | p Value |
|-----------------|-------------|-------------|---------|-------------|-------------|---------|
| Male sex, n (%) |             |             |         |             |             |         |
| APOE ε4, n (%)  |             |             |         |             |             |         |
| Education, y    |             |             |         |             |             |         |
| MMSE score      |             |             |         |             |             |         |
| CDR Sum of Boxes score |   |             |         |             |             |         |
| UPDRS-III score |             |             |         |             |             |         |
| Visual hallucinations, n (%) |   |             |         |             |             |         |
| Fluctuations, n (%) |             |             |         |             |             |         |
| Parkinsonism, n (%) |             |             |         |             |             |         |
| pRBD, n (%)     |             |             |         |             |             |         |
| No. of core DLB features, n (%) |   |             |         |             |             |         |

Abbreviations: CDR = Clinical Dementia Rating; DLB = dementia with Lewy bodies; MCI-LB = mild cognitive impairment with Lewy bodies; MMSE = Mini-Mental State Examination; pRBD = probable REM sleep behavior disorder; UPDRS-III = Unified Parkinson’s Disease Rating Scale Part III; + = abnormal values; − = normal values.

Mean (SD) listed for continuous variables and count (percent) for categorical variables. p Values comparing groups are from a t test or χ² test.

Discussion
In this study that used β-amyloid PET and 123I-FP-CIT SPECT biomarkers in MCI-LB, we confirmed the presence and, in some, the coexistence of β-amyloid pathology and Lewy-related pathology. The most common biomarker profile was A−D+ and the least common was A+D−. Approximately one-quarter of the patients with MCI-LB were both A+ and D+. Whereas A+ was associated with older age, APOE ε4, and lower MMSE scores, D+ was associated with the most common core clinical features of DLB (RBD, fluctuation, and parkinsonism). Furthermore, lower PiB SUVR and lower putamen DaTQUANT z score were additively associated with higher UPDRS-III scores.

In agreement with a previous study,21 there were more D+ (64.7%) than D− patients with MCI-LB. Our results are also consistent with reports on the high sensitivity and specificity of 123I-FP-CIT SPECT in distinguishing probable DLB from other dementias,9 as well as high specificity but relatively lower sensitivity in distinguishing MCI-LB from MCI with Alzheimer disease (AD).21 Decreased striatal 123I-FP-CIT SPECT uptake is associated with lower dopaminergic activity due to nigrostriatal degeneration in LB disease.22 A−D+ was the most common profile in this group of people with MCI-LB, and it likely represented pure Lewy-related pathology.21,23
Our previous study of longitudinal studies.7,14,24,25 This discrepancy might be due to di
reported in probable DLB, which was up to 60% in previous
(64.7%), while the rate of A+ was 35.3%. The positivity of
In the current study, most patients with MCI-LB were A
steeper during the earlier stages, followed by a slower accu-
Our data suggest that decreased striatal123I-FP-CIT SPECT
uptake with low levels of
β
-amyloid was the most common
β
-amyloid pathology. Our
fi
rmed that patients with probable DLB,
about one-third of patients with MCI-LB, lower in frequency
than the observations in patients with probable DLB who
continue to accumulate β-amyloid as the disease progresses.26
As expected, we found that 9 of 12 A+ individuals with MCI-
LB were also D+ (A+D+), suggesting the mixed β-amyloid
pathology and LB-related pathology account for the majority
of A+ patients with MCI-LB, and A+ alone is rare. The
relationship between β-amyloid and α-synuclein pathologies
has been investigated in postmortem and in vitro studies,32,33
which suggested that β-amyloid and α-synuclein have the
capacity to promote each other’s aggregation33,34 and have
synergistic toxicity in cells and transgenic mice.34,35 However,
the β-amyloid PET and 123I-FP-CIT SPECT biomarker profile
is relatively less documented in patients with DLB.36
Our finding of A+D+ frequency in MCI-LB (26.5%) is half
the frequency from a recent report (55.6%) of 18 patients
within the LB disease spectrum (Parkinson disease, DLB,
and Parkinson disease dementia).36 Whereas biomarker positivity
appears to increase with increasing disease severity from MCI
to dementia, patients with more core features did not have
greater biomarker abnormalities. Thus, the number of core
clinical features and imaging biomarkers were independent.
Accordingly, the current research criteria for prodromal DLB
considers MCI and 1 DLB core clinical feature and biomarker
positivity (e.g., 123I-FP-CIT SPECT) to be sufficient to rep-
resent probable prodromal DLB, emphasizing the comple-
mentary role of the diagnostic information from clinical
evaluation and biomarkers at the predementia stage.
We note that a subset of patients with MCI-LB had an A–D–
(n = 9) and another subset had an A+D+ (n = 9) biomarker
profile. This provides imaging evidence of the pathologic
derogeneity that can occur in DLB. It is unclear whether
A–D– represents a subgroup without LB disease, a very early
stage of MCI-LB, or the subgroup of DLB who do not develop
parkinsonism.23 In a longitudinal 123I-FP-CIT SPECT study,
the initially negative 123I-FP-CIT SPECT became positive
after 1.5 years in 5 of 7 patients with probable DLB.37
In addition, we note that 1 patient with MCI-LB with an A–D–
profile had a borderline PiB SUVR (global cortical PiB SUVR
1.48). The borderline PiB SUVR in patients with DLB was
thought to be a marker for sparse or moderate neuritic plaques
and low or intermediate likelihood of AD pathology.14,36
Taken together, although the global cortical PiB SUVR and
123I-FP-CIT SPECT uptake were classified as positive or
negative in this study for diagnostic practicality, it is important
to note that β-amyloid and α-synuclein are continuous path-
ologic processes in the patients with MCI-LB, and so are PiB
SUVR and 123I-FP-CIT SPECT uptake.
Patients with MCI-LB and an A+D− profile made up the smallest group in our study. Only 3 patients were A+ alone, and all were APOE ε4 carriers and >76 years of age. All had PiB SUVR >2.0, strongly above the positivity threshold (1.48), suggesting that their A+ status was not due to any artifacts such as bleed-in from off-target white matter binding that can produce slightly suprathreshold SUVR values.30 One patient presented with only probable RBD, 1 with only mild parkinsonism, and 1 with probable RBD and parkinsonism. In these patients, it is possible that β-amyloid pathology was present earlier in the evolution of LB-related pathologic processes and AD pathology was the underlying etiology for MCI, potentially with concomitant LB-related pathology at an early stage. Whereas we used a cut point for 123I-FP-CIT SPECT that was validated in an autopsy-confirmed LB disease, it is possible that the nigrostriatal LB burden was too low

| Table 2 Association of Clinical Phenotypes With β-Amyloid PET and 123I-FP-CIT SPECT in Patients With MCI-LB |
|-----------------------------------------------|
|                                | Log Amyloid Estimate | Log Amyloid p Value | Putamen DaT Estimate | Putamen DaT p Value |
| Age                            | 17.97 (6.96, 28.97)  | 0.002*              | 0.22 (–1.1, 1.55)    | 0.73               |
| Male sex                       | –4.02 (–9.84, 1.81) | 0.18                | 1.05 (–0.28, 2.37)   | 0.12               |
| APOE ε4                        | 9.35 (3.04, 15.65)  | 0.004*              | –0.03 (–0.53, 0.48)  | 0.92               |
| Education                      | –0.7 (–5.08, 3.67)  | 0.74                | –0.27 (–0.72, 0.18)  | 0.23               |
| MMSE score                     | –2.13 (–4.66, 0.39) | 0.095               | 0.12 (–0.14, 0.39)   | 0.35               |
| CDR Sum of Boxes score         | –0.28 (–1.65, 1.09) | 0.68                | –0.06 (–0.2, 0.09)   | 0.43               |
| UPDRS-III score                | –12.11 (–23.43, –0.8) | 0.037*             | –2.31 (–3.48, –1.14) | <0.001*            |
| Visual hallucinations          | 5.15 (–0.88, 11.19) | 0.094               | –0.33 (–0.9, 0.25)   | 0.26               |
| Fluctuations                   | –0.12 (–3.72, 3.48) | 0.95                | 0.21 (–0.16, 0.58)   | 0.26               |
| Parkinsonism                   | 0.91 (–2.91, 4.73)  | 0.64                | –0.33 (–0.72, 0.07)  | 0.10               |
| pRBD                           | –7.76 (–19.86, 4.34) | 0.21               | –2.1 (–5.41, 1.22)   | 0.22               |

Abbreviations: DaT = DaTQUANT; MCI-LB = mild cognitive impairment with Lewy bodies; MMSE = Mini-Mental State Examination; pRBD = probable REM sleep behavior disorder; UPDRS-III = Unified Parkinson’s Disease Rating Scale Part III. Regression coefficients, associated confidence interval, and p values are from either a linear regression or a logistic regression model with age adjustment when appropriate.* p < 0.05.
in these A+D− patients with MCI-LB to be detected by the 123I-FP-CIT SPECT. Longitudinal assessment of these patients may clarify the possible presence of early LB pathology.

Our data did not show evidence that PiB PET and 123I-FP-CIT SPECT interact with each other when modeling associations of these biomarkers with cognitive performance or core clinical features of DLB. We found that A+ was associated with worse cognitive impairment measured with the MMSE. The association of β-amyloid and MMSE score is a frequent finding in probable DLB38 and MCI,39 although no relationships have been reported.14,40,41 Furthermore, β-amyloid biomarkers in the CSF were reported to be associated with worse outcome in patients with DLB.41 In addition, the coexistence of β-amyloid biomarkers indicated a poorer response to treatment in patients with DLB,42 suggesting that β-amyloid biomarkers may aid in predicting prognosis in DLB. Consistent with previous findings in DLB43,44 D+ was associated with the severity of parkinsonism in patients with MCI-LB. We found that D+ patients with MCI-LB had a higher frequency of probable RBD, but the result is not significant after age adjustment, suggesting that the higher frequency of probable RBD may be related to the relatively older age of patients with MIC-LB with D+. A counterintuitive finding was that fluctuations were less common in D+ compared to D− patients. This finding requires further investigation in a larger sample.

As expected, lower putamen z scores were associated with higher UPDRS-III scores, suggesting that nigrostriatal dopaminergic deficits are directly associated with worse motor impairment. On the contrary, greater β-amyloid deposition was associated with less motor impairment, likely due to lower levels of nigrostriatal LB pathology in patients with high β-amyloid as they transition through MCI. In other words, this association we observed may be dependent on survivor bias, which may have led those with both a high amount of β-amyloid and motor impairment due to LB to transition to...
dementia rather than remain as MCI. However, we did not find that the global PiB SUVs and putamen z scores interacted in their association with the UPDRS-III scores; therefore, these relationships between biomarkers of AD and LB-related pathology with motor impairment were best described as additive.

Our study demonstrates the frequency of β-amyloid and 123I-FP-CIT SPECT biomarker positivity and several associating features with the biomarkers in prodromal DLB. The potential limitation of the study was a relatively small sample size. As expected, most of the patients in our study were men; therefore, the power to investigate the biomarker profiles was limited in women with MCI-LB. Nonetheless, most female patients with MCI-LB had an A+D+ profile, which is consistent with previous findings that women with LB-related pathology are more likely to have mixed LB and AD-related pathology.10 In addition, we used cutoff values of the A and D biomarkers that were previously validated by autopsy in patients with probable DLB. LB pathology may be too mild at the prodromal stage compared to that found at the dementia stage; therefore, we may have labeled those with low levels of LB pathology as D− in the MCI-LB cohort. Our data are cross-sectional and cannot provide information on the temporal evolution of biomarkers or cause and effect in patients with MCI-LB. In addition, other imaging biomarkers such as hippocampal volumes have been associated with clinical features in patients with MCI-LB. Whereas preserved hippocampal volumes in patients with MCI may be predictive of progression to DLB vs AD,45 patients with MCI with preserved hippocampal volumes who progress to probable DLB also survive longer.46 Further investigations in a larger cohort and a longitudinal design to investigate the trajectory of multiple imaging biomarkers in association with disease progression from very early stage to overt dementia stage in patients with DLB are needed.

Patients with MCI who have core clinical features of DLB have imaging biomarker abnormalities that are associated with clinical phenotypes.123I-FP-CIT SPECT biomarker positivity was associated with the core clinical features of DLB, suggesting that 123I-FP-CIT SPECT biomarker is a strong predictor of DLB at the prodromal stage. Association of A+ with worse cognitive function suggests that targeting β-amyloid deposition during the prodromal stage of DLB in a subset of patients who are A+ may be a potential strategy for slowing the progression from prodromal DLB to overt DLB.

**Acknowledgment**

The authors are grateful to their patients and informants for their participation in the detailed annual assessments and for their involvement in current study.

**Study Funding**

This work is supported by the NIH grants U01 NS100620, P50 AG016574, and P30 AG 062677; Foundation Dr. Corinne Schulerand; the Mangurian Foundation for Lewy Body Research; The Elsie and Marvin Dekelboun Family Foundation; the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Program; Little Family Foundation; and LBD Functional Genomics Program.

**Disclosure**

Dr. Chen reports no disclosures relevant to the manuscript. Dr. Lowe has consulted for Bayer Schering Pharma, Piramal Life Sciences, and Merck Research and receives research support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals, and the NIH (National Institute on Aging, National Cancer Institute). Dr. Boeve has served as an investigator for clinical trials sponsored by Biogen, Alector, and EIP Pharma. He receives royalties from the publication Behavioral Neurology of Dementia (Cambridge Medicine, 2009, 2017). He serves on the Scientific Advisory Board of the Tau Consortium. He receives research support from the NIH, the Mayo Clinic Dorothy and Harry T. Mangurian Jr. Lewy Body Dementia Program, the Little Family Foundation, and the Turner Family Foundation. S.A. Przybelski reports no disclosures relevant to the manuscript. Dr. Miyagawa receives research support from the Japanese Society of Neurology, SENSHIN Medical Research Foundation, and Mitsukoshi Health and Welfare Foundation. M.L. Senjem reports no disclosures relevant to the manuscript. Dr. Jack consults for Eli Lilly and serves on an independent data monitoring board for Roche, but he receives no personal compensation from any commercial entity. He receives research support from the NIH. T.G. Lesnick reports no disclosures relevant to the manuscript. W.K. Kremers receives research funding from AstraZeneca, Biogen, Roche, Department of Defense, and NIH. Dr. Fields receives research support from NIH. Dr. Min, Dr. Schwarz, and J.L. Gunter report no disclosures relevant to the manuscript. Dr. J. Graff-Radford receives research support from NIH. Dr. Savica reports no disclosures relevant to the manuscript. Dr. Knopman serves on the Data Safety Monitoring Board of the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) study; is a site principal investigator for clinical trials sponsored by Biogen, Lilly, and the University of Southern California; and is funded by NIH. Dr. Jones reports no disclosures relevant to the manuscript. Dr. Ferman receives funding from the Mangurian Foundation for Lewy Body Research and NIH. Dr. N. Graff-Radford receives royalties from UpToDate and has participated in multicenter therapy studies by sponsored by Biogen, TauRx, AbbVie, Novartis, and Lilly. He receives research support from NIH. Dr. Petersen serves on scientific advisory boards for Elan Pharmaceuticals, Wyeth Pharmaceuticals, and GE Healthcare and receives royalties from publishing Mild Cognitive Impairment (Oxford University Press, 2003). He also receives research support from NIH. Dr. Kantarcı serves on the Data Safety Monitoring Board for Takeda Global Research & Development Center, Inc and Data Monitoring boards of Pfizer and Janssen Alzheimer Immunotherapy. She receives research support from the Avid Radiopharmaceuticals and Eli Lilly. She is funded by the Alzheimer’s Drug Discovery Foundation and NIH. Go to Neurology.org/N for full disclosures.
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*Neurology* 2021;96:e1180-e1189 Published Online before print January 6, 2021
DOI 10.1212/WNL.0000000000011454

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