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

The Article Processing Charge was funded by the Mayo Clinic.

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
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Title character count: 96
Running Head count: 37
Abstract word count: 236
Main text word count: 3502

Key Words: 123-I-FP-CIT SPECT; Amyloid PET; PiB; MCI; prodromal DLB

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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 Dekelboum Family Foundation, and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Program. Little Family Foundation; and LBD Functional Genomics Program.

Disclosures

Dr. Chen reports no disclosures relevant to the manuscript.
Dr. Lowe has consults 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 (NIA, NCI).

Dr. Boeve has served as an investigator for clinical trials sponsored by Biogen, Alector, and EIP Pharma. He receives royalties from the publication of a book entitled 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.

SA Przybelski reports no disclosures relevant to the manuscript.

Dr. Miyagawa receives research support from Japanese Society of Neurology, SENSHT Medical Research Foundation, and Mitsukoshi Health and Welfare Foundation.

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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.

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KW Kremers receives research funding from AstraZeneca, Biogen, Roche, DOD and NIH.

Dr. Fields receives research support from NIH.

Dr. Min reports no disclosures relevant to the manuscript.

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Dr. J. Graff-Radford receives research support from the NIH.
**Dr. Savica** reports no disclosures relevant to the manuscript.

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**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, 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; receives royalties from publishing Mild Cognitive Impairment (Oxford University Press, 2003). He also receives research support from NIH.

**Dr. Kantarci** serves on the Data Safety Monitoring Board for Takeda Global Research & Development Center, Inc.; Data Monitoring Boards of Pfizer and Janssen Alzheimer Immunotherapy. She receives research support from the Avid Radiopharmaceuticals, Eli Lilly. She is funded by the Alzheimer’s Drug Discovery Foundation and NIH.
ABSTRACT

**Objective:** To determine the clinical phenotypes associated with the amyloid-β PET and dopamine transporter imaging ($^{123}$I-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 one core clinical feature of DLB (n=34) were grouped into β-amyloid A+ or A- and $^{123}$I-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 $^{123}$I-FP-CIT SPECT. Individual MCI-LB patients fell into one of four 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%). Least common was A+D- biomarker profile (8.8 %). The A+ group was older, had a higher frequency of APOE ε4 carriers, and a lower MMSE score than the A- group. The D+ group was more likely to have probable rapid eye movement sleep behavior disorder. Lower putamen DATQUANT z-scores and lower PiB SUVRs were independently associated with higher Unified Parkinson Disease Rating Scale (UPDRS)-III scores.

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

Mild cognitive impairment (MCI) with one or more core features of dementia with Lewy bodies (DLB) represent 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-LB)\(^1\). The use of imaging biomarkers has facilitated the early detection of DLB\(^2\) 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 Lewy body disease; many patients also have varying degrees of amyloid-β pathology, which may synergistically contribute to the pathogenesis of DLB\(^3\)\(^-\)\(^5\). However, whether co-existing Lewy-related pathology and amyloid-β pathology influence the clinical presentation of the prodromal stage of DLB is currently unknown.

Elevated amyloid-β burden on Pittsburgh compound-B (PiB) PET\(^6\), was reported in more than half of patients with DLB\(^7\) and has been associated with greater cognitive impairment in DLB\(^8\). The quantitative analysis of antemortem\(^123\)I-FP-CIT SPECT demonstrated excellent discrimination between patients with and without autopsy-confirmed LB disease, supporting the utility of\(^123\)I-FP-CIT SPECT as a biomarker for the underlying Lewy-related pathology in MCI-LB\(^12\).

Our objective was to determine the clinical phenotypes associated with amyloid-β PET and\(^123\)I-FP-CIT SPECT in patients with MCI-LB who are at a higher risk for progression to probable DLB. We hypothesized that the two 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 one core feature of DLB (i.e. parkinsonism, fluctuations, visual hallucinations, or 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\(^1\). Evaluations included information obtained through clinical interview by a neurologist, neurologic examination, and the neuropsychological assessment. The Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Sum of Boxes (CDR-SOB) were used to determine cognitive and disease severity. Assessments for the clinical features of DLB were detailed in previous reports from the ADRC cohorts\(^13,14\). Briefly, the presence of parkinsonism was based on two of the four cardinal features (tremor, rigidity, bradykinesia, and postural instability) and the severity was quantified using the Unified Parkinson's Disease Rating Scale-III (UPDRS-III)\(^15\). A history of probable RBD was based on the International Classification of Sleep Disorders-II diagnostic criteria\(^16\). 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\(^17\).

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 Amyloid-β PET Acquisitions

MRI examinations were performed at 3T and a 3-D high resolution magnetization prepared rapid gradient echo (MPRAGE) acquisition with approximately 1 mm cubic resolution was obtained for anatomical segmentation and labeling. Amyloid-β PET was performed with $^{11}$C-Pittsburgh Compound B (PiB)\textsuperscript{6} on PET/CT scanners in 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).

Amyloid-β PET Image Analysis

Amyloid-β PET images were analyzed with our in-house fully automated image processing pipeline\textsuperscript{18}, where image voxel values are extracted from automatically labelled regions of interest propagated from the MRI template (Mayo Clinic Adult Lifespan Template, MCALT) using SPM12 and ANT's. Regional cortical uptake of PiB was determined using the MCALT_ADIR122 atlas. The global cortical PiB retention standardized uptake value ratio (SUVR) was calculated from the prefrontal, orbitofrontal, temporal, parietal, anterior cingulate, and posterior cingulate/precuneus regions of interest using grey plus white sharpened voxels that were normalized to the cerebellum crus as previously reported\textsuperscript{19}.

Dopamine Transporter Imaging Acquisitions

A $^{123}$I-FP-CIT SPECT (DaTscan, GE Healthcare, Chicago, IL) was performed according to previously published protocol for each participant\textsuperscript{12}. In brief, at least one hour before the injection of $^{123}$I-Ioflupane, a 100 mg Lugols solution was given, and then the recommended $^{123}$I-Ioflupane dose of 111 to 185 MBq (3 to 5 mCi) was administered slowly intravenously. SPECT imaging occurred 3-6 hours post injection. GE D670/D630 SPECT systems with ultra-high-resolution fan
beam collimators and an energy setting of 159 keV 20% window was used on all patients. Data were reconstructed using ordered subset expectation maximization method, and the planar images were pre-filtered using a Butterworth filter (power=10, cut-off = 0.6 cycles/cm), and no attenuation correction was used\textsuperscript{12}. Projection images were used for the quantitative analysis.

\textsuperscript{123}I-FP-CIT-SPECT Analysis

Semi-quantitative 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 three contiguous slices were used. Then, the left and right striatum-to-background ratio (SBR) 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 Lewy body disease from those without Lewy body disease based on a previous study\textsuperscript{12} for statistical analysis.

Definition of Abnormality

Abnormal amyloid-\(\beta\) PET was defined as PiB SUVR \(\geq 1.48\), as previous described\textsuperscript{20}. Abnormal minimum DaTQUANT z-score in putamen was defined as \(< -0.82\), which was validated in autopsy-confirmed Lewy body disease\textsuperscript{12}. Participants were assigned to an A and D biomarker group, with A-D- denoting low PiB SUVR and high putamen \textsuperscript{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 standard deviations for continuous variables, with counts and percentages used for categorical variables. The groups were compared using either a t-test for continuous variables or chi-squared test for categorical variables with age adjusted as appropriate. To investigate isolated and synergistic contributions of amyloid-β 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 AxD 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 MCI-LB patients with 1, 2, 3+ core clinical features of DLB using a test for trend in linear regressions. A p-value <0.05 (two-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, as well as the isolated effects of A+ and D+ biomarkers are demonstrated in Table 1. Most of the MCI-LB patients in this study were male (n=30, 88.2%). The mean (SD) MMSE score was 27.6 (1.7), and for CDR-SB 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%), fluctuations (41.2%), and VH were 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 or more core DLB features.

Positivity of amyloid-β 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 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), were more likely to have RBD (p=0.048) and less likely to have fluctuations (p=0.026) than the D- group. The difference of RBD between D+ and D- groups were not significant after age adjustment (p=1.00), while the difference in fluctuations remain significant after age adjustment (p=0.046).
Distribution of PiB PET and $^{123}$I-FP-CIT SPECT positivity

The dichotomized distribution of PiB PET and $^{123}$I-FP-CIT SPECT with individual data points is shown in Figure 1. The A-D+ was the largest group accounting for 38.2% of the MCI-LB patients (n=13), followed by A+D+ (n=9) and A-D- (n=9), each of which included 26.5% of the MCI-LB patients. A+D- was the smallest group, including 8.8% of the MCI-LB patients (n=3). The representative images of PiB PET and $^{123}$I-FP-CIT SPECT from the four A and D groups (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 PiB PET and $^{123}$I-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.

Amyloid-β PET and $^{123}$I-FP-CIT SPECT positivity and the number of core DLB clinical features

The rate of D+ was 57.1% in MCI-LB patients with 1 core feature, 75% in MCI-LB with 2 core features, and 54.5% in MCI-LB with 3 or 4 core features. The rate of A+ was 57.1% in MCI-LB with 1 core feature, 25% in MCI-LB with 2 core features and 36.4% in MCI-LB with 3 or 4 core features. No difference was observed in the global cortical PiB SUVRs or putamen
DaTQUANT z-scores among the MCI-LB patients and the number of core DLB features (Figure 4).

DISCUSSION

In this study that utilized amyloid-β PET and $^{123}$I-FP-CIT SPECT biomarkers in MCI-LB, we confirmed the presence, and in some the co-existence of amyloid-β pathology and Lewy-related pathology. The most common biomarker profile was A-D+ and the least common was A+D-. Approximately a quarter of the MCI-LB patients 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, 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 $^{123}$I-FP-CIT SPECT in distinguishing probable DLB from other dementias as well as high specificity, but relatively lower sensitivity in distinguishing MCI-LB from MCI-AD. Decreased striatal $^{123}$I-FP-CIT SPECT uptake is associated with lower dopaminergic activity due to nigrostriatal degeneration in Lewy body disease. Importantly, the A-D+ was the most common profile in this group of MCI-LB, and it likely represented pure Lewy-related pathology at the prodromal stage, while the A+D+ that was observed in slightly more than a quarter of MCI-LB represented co-existing Lewy body disease and amyloid-β pathology. Our data suggest that
decreased striatal $^{123}$I-FP-CIT SPECT uptake with low levels of amyloid-$\beta$ was the most common observation in this cohort of MCI-LB.

In the current study, most patients with MCI-LB were A- (64.7%), while the rate of A+ was 35.3%. The positivity of amyloid-$\beta$ in MCI-LB was relatively lower than the ratio reported in probable DLB, which was up to 60% in previous studies $^{14,24-26}$. This discrepancy might be due to different stages of brain amyloid-$\beta$ accumulation over time in patients with probable DLB. Our previous study of longitudinal amyloid-$\beta$ accumulation by PiB PET demonstrated the trajectories of change in PiB SUVR in patients with mild probable DLB $^{27}$. The trajectory of amyloid-$\beta$ accumulation is steeper during the earlier stages followed by a slower accumulation phase. Thus, we expect that many of the A- MCI-LB patients will become A+ in the short-term perhaps as they progress to probable DLB, which needs to be investigated in a future study. Furthermore, PiB, the amyloid PET tracer, is expected to bind to the $\beta$-pleated sheet of the amyloid-$\beta$ protein present in both neuritic plaques and diffuse plaques in the cortical gray matter as well as the vessel walls $^{28-30}$. However, in autopsy-confirmed pDLB patients, PiB SUVR was primarily associated with the severity of diffuse plaques $^{31}$ that are abundant in patients with LB disease $^{32}$. Our data confirmed that amyloid-$\beta$ deposition already existed in about one third of patients with MCI-LB, lower in frequency than the observations in probable DLB patients who continue to accumulate amyloid-$\beta$ as the disease progresses $^{27}$.

As expected, we found that 9 out of 12 A+ MCI-LB were also D+ (A+D+), suggesting the mixed amyloid-$\beta$ pathology and LB-related pathology accounts for the majority of A+ MCI-LB patients, and A+ alone is rare. The relationship between amyloid-$\beta$ and $\alpha$-synuclein pathologies has been investigated in post-mortem and in vitro studies $^{33,34}$, which suggested that amyloid-$\beta$ and $\alpha$-synuclein have the capacity to promote each other’s aggregation $^{34,35}$, and have synergistic
toxicity in cells and transgenic mice\textsuperscript{35, 36}. However, the amyloid-β PET and \textsuperscript{123}I-FP-CIT SPECT biomarker profile is relatively less documented in patients with DLB\textsuperscript{37}. Our findings of A+D+ frequency in MCI-LB (26.5\%) is half of the frequency from a recent report (55.6\%) of 18 patients within the Lewy body disease spectrum (PD, DLB and PDD)\textsuperscript{37}. 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 mild cognitive impairment and one DLB core clinical feature and biomarker positivity (e.g. \textsuperscript{123}I-FP-CIT SPECT) to be sufficient to represent probable prodromal DLB, emphasizing the complementary role of the diagnostic information from clinical evaluation and biomarkers at the pre-dementia stage.

We note that a subset of MCI-LB patients had an A-D- (n=9) and another subset had an A+D+ (n=9) biomarker profile. This provides imaging evidence of the pathologic heterogeneity that can occur in DLB. It is unclear if the A-D- represent a subgroup without Lewy body disease, if this represents a very early stage of MCI-LB, or if this represents the subgroup of DLB that does not develop parkinsonism\textsuperscript{23}. In a longitudinal \textsuperscript{123}I-FP-CIT SPECT study, the initially negative \textsuperscript{123}I-FP-CIT SPECT became positive after 1.5 years in 5 of 7 patients with probable DLB\textsuperscript{38}. In addition, we note that one MCI-LB patient 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\textsuperscript{14, 37}. Taken together, although the global cortical PiB SUVR and \textsuperscript{123}I-FP-CIT SPECT uptake were classified as positive or negative in this study for diagnostic practicality, it is
important to note that amyloid-β and α-synuclein are continuous pathological processes in the patients with MCI-LB and so are PiB SUVR and $^{123}$I-FP-CIT SPECT uptake.

Patients with MCI-LB and an A+D- profile was the smallest group in our study. Only 3 patients were A+ alone and all were APOE ε4 carriers and older than 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 WM binding that can produce slightly suprathreshold SUVR values $^{31}$. One patient presented with only pRBD, one only with mild parkinsonism and one with pRBD and parkinsonism. In these patients, it is possible that amyloid-β 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 $^{123}$I-FP-CIT SPECT that was validated in an autopsy-confirmed LB disease, it is possible that the nigrostriatal Lewy body burden was too low in these A+D- MCI-LB patients to be detected by the $^{123}$I-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 $^{123}$I-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 MMSE. The association of amyloid-β and MMSE is a frequent finding in probable DLB $^{39}$ and MCI$^{40}$, although no relationships have also been reported$^{14,41,42}$. Furthermore, amyloid-β biomarkers in the CSF were reported to be associated with worse outcome in DLB patients $^{43}$. In addition, the coexistence of amyloid-β biomarkers indicated a poorer response to treatment in patients with DLB$^{44}$, suggesting that amyloid-β biomarkers may aid in predicting prognosis in DLB. Consistent with previous findings in DLB$^{45,46}$, D+ was associated with the severity of
parkinsonism in patients with MCI-LB. We found that D+ MCI-LB patients having a higher frequency of pRBD but the result is not significant after age adjustment, suggesting that the higher frequency of pRBD may be related to the relatively older of MIC-LB patients 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 amyloid-β deposition was associated with less motor impairment likely due to lower levels of nigrostriatal LB pathology in patients with high amyloid-β 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 high amount of amyloid-β and motor impairment due to LB to transition in to dementia rather than remain as MCI. However, we did not find that the global PiB SUVRs and putamen z-scores interacted in their association with the UPDRS-III scores and 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 amyloid-β 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 were 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 like to have mixed LB and AD-related pathology31. In addition, we used cut-off values of the A and D biomarkers that were previously validated by autopsy in probable DLB patients. LB pathology
may be too mild at the prodromal stage compared to that found at the dementia stage and 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 MCI patients may be predictive of progression to DLB vs AD \(^47\), MCI patients with preserved hippocampal volumes who progress probable DLB also survive longer \(^48\). 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 DLB patients are needed.

In conclusion, patients with MCI who have core clinical features of DLB have imaging biomarker abnormalities that are associated with clinical phenotypes. \(^{123}\)I-FP-CIT SPECT biomarker positivity was associated with the core clinical features of DLB, suggesting that \(^{123}\)I-FP-CIT SPECT biomarker is a strong predictor of DLB at the prodromal stage. Association of A+ with worse cognitive function suggests that targeting amyloid-\(\beta\) 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.
ACKNOWLEDGEMENTS

We are grateful to our patients and informants for their participation in our detailed annual assessments and for their involvement in current study. The staffs at GE Healthcare were not involved in the analysis, the interpretation of the data, nor in the preparation of this manuscript.

Appendix 1: Authors

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<td>Jeffrey L. Gunter</td>
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<tr>
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<tr>
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<tr>
<td>David Knopman</td>
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<tr>
<td>Name</td>
<td>Institution</td>
<td>Contributions</td>
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<tr>
<td>David Jones</td>
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<tr>
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<td>Mayo Clinic, Jacksonville</td>
<td>analysis or interpretation of the data, revising the manuscript, communicating with the research subjects, and study funding</td>
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<tr>
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<td>design or conceptualization of the study, data collection, analysis and interpretation of the data, drafting the manuscript, study funding</td>
</tr>
</tbody>
</table>
REFERENCES


38. van der Zande JJ, Booij J, Scheltens P, Raijmakers PG, Lemstra AW. [(123)]FP-CIT SPECT scans initially rated as normal became abnormal over time in patients with probable


FIGURE LEGEND

Figure 1. Distribution of MCI-LB patients based on global cortical PiB SUVR and putamen DaTQUANT z-scores.

Scatter plot showing the distribution of MCI-LB patients into the quadrants of global cortical PiB SUVR and putamen DaTQUANT z-scores with colored dots. Reference lines were 1.48 for global cortical PiB SUVR and -0.82 for putamen DaTQUANT z-score. The MCI-LB patients with PiB SUVR ≥ 1.48 are identified with abnormal amyloid-β PET (A+). The MCI-LB patients with putamen DaTQUANT z-score < -0.82 are identified with abnormal $^{123}$I-FP-CIT SPECT (D+). A- D- denote normal amyloid-β PET and normal $^{123}$I-FP-CIT SPECT in grey, A+D- denote abnormal amyloid-β PET but normal $^{123}$I-FP-CIT SPECT in blue, A-D+ denote normal amyloid-β PET but abnormal $^{123}$I-FP-CIT SPECT in orange, and A+D+ denote abnormal amyloid-β PET and abnormal $^{123}$I-FP-CIT SPECT in green.
Figure 2. Illustrative images. A-D-: normal amyloid-β PET and normal $^{123}$I-FP-CIT SPECT; A+D-: abnormal amyloid-β PET but normal $^{123}$I-FP-CIT SPECT; A-D+: normal amyloid-β PET but abnormal $^{123}$I-FP-CIT SPECT; A+D+: abnormal amyloid-β PET and abnormal $^{123}$I-FP-CIT SPECT. The bottom color bar represents cortical voxel-to-cerebellar retention ratio for amyloid-β PET. The right color bar represents normalized striatum-to-background ratio for $^{123}$I-FP-CIT SPECT.
Figure 3: Box-plots of UPDRS-III scores in A and D groups.

Box-plots show the UPDRS-III scores in patients with negative amyloid-β PET (A-) and positive amyloid-β PET (A+) (A), and negative 123I-FP-CIT SPECT (D-) and positive 123I-FP-CIT SPECT (D+) (B) in MCI-LB.
Figure 4: Box-plots of global cortical PiB SUVRs and putamen DaTQUANT z-scores across 3 groups.

Box-plots show the global cortical PiB SUVRs (A) and putamen DaTQUANT z-scores (B) in patients with mild cognitive impairment (MCI) with 1 core features (grey), with 2 core features (orange), and 3 or 4 core features (blue).
Table 1. Demographic and clinical characteristics of patients with MCI-LB and the isolated effects of amyloid-β and $^{123}$I-FP-CIT SPECT biomarkers.

<table>
<thead>
<tr>
<th></th>
<th>A- n = 22</th>
<th>A+ n = 12</th>
<th>P-value</th>
<th>D- n = 12</th>
<th>D+ n = 22</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.8 (8.5)</td>
<td>73.2 (6.8)</td>
<td>0.014*</td>
<td>66.8 (11.7)</td>
<td>69.4 (6.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>Males</td>
<td>21 (95%)</td>
<td>9 (75%)</td>
<td>0.077</td>
<td>12 (100%)</td>
<td>18 (82%)</td>
<td>0.12</td>
</tr>
<tr>
<td>$APOE \varepsilon 4$</td>
<td>2 (10%)</td>
<td>8 (67%)</td>
<td>&lt;0.001*</td>
<td>4 (36%)</td>
<td>6 (27%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Education</td>
<td>17.0 (2.6)</td>
<td>16.7 (2.6)</td>
<td>0.76</td>
<td>16.3 (3.0)</td>
<td>17.1 (2.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.0 (1.6)</td>
<td>26.8 (1.6)</td>
<td>0.046*</td>
<td>28.1 (1.8)</td>
<td>27.3 (1.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>CDR sum of boxes</td>
<td>1.8 (0.9)</td>
<td>1.4 (0.7)</td>
<td>0.15</td>
<td>1.8 (1.1)</td>
<td>1.6 (0.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>UPDRS-III score</td>
<td>10.8 (9.3)</td>
<td>7.2 (6.4)</td>
<td>0.24</td>
<td>5.0 (5.6)</td>
<td>12.0 (8.8)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Visual Hallucinations</td>
<td>3 (14%)</td>
<td>2 (17%)</td>
<td>0.81</td>
<td>1 (8%)</td>
<td>4 (18%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Fluctuations</td>
<td>11 (50%)</td>
<td>3 (25%)</td>
<td>0.16</td>
<td>8 (67%)</td>
<td>6 (27%)</td>
<td>0.026*</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>15 (68%)</td>
<td>9 (75%)</td>
<td>0.68</td>
<td>7 (58%)</td>
<td>17 (77%)</td>
<td>0.25</td>
</tr>
<tr>
<td>pRBD</td>
<td>21 (95%)</td>
<td>11 (92%)</td>
<td>0.65</td>
<td>10 (83%)</td>
<td>22 (100%)</td>
<td>0.048*</td>
</tr>
<tr>
<td>Number of core DLB features</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>1 feature</td>
<td>3 (14%)</td>
<td>4 (33%)</td>
<td></td>
<td>3 (25%)</td>
<td>4 (18%)</td>
<td></td>
</tr>
<tr>
<td>2 features</td>
<td>12 (55%)</td>
<td>4 (33%)</td>
<td></td>
<td>4 (33%)</td>
<td>12 (55%)</td>
<td></td>
</tr>
<tr>
<td>3 or 4 features</td>
<td>7 (32%)</td>
<td>4 (33%)</td>
<td></td>
<td>5 (42%)</td>
<td>6 (27%)</td>
<td></td>
</tr>
</tbody>
</table>

*P-values <0.05. Mean (SD) listed for continuous variables and count (%) for categorical variables. P-values comparing groups are from a t-test or chi-squared test. Abbreviations: A = amyloid-β; D = Dopamine transporter imaging; + = abnormal values; - = normal values; $APOE$ = Apolipoprotein E; MMSE = mini-mental state examination; CDR = clinical dementia rating scale; UPDRS = unified Parkinson disease rating scale; pRBD = probable rapid eye movement sleep behavior disorder; DLB = dementia with Lewy bodies.
## Table 2. The association of clinical phenotypes with amyloid-β PET and 123I-FP-CIT SPECT in patients with MCI-LB

<table>
<thead>
<tr>
<th></th>
<th>Log Amyloid Estimate</th>
<th>Log Amyloid P-value</th>
<th>Putamen DaT Estimate</th>
<th>Putamen DaT P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>17.97 (6.96, 28.97)</td>
<td>0.002*</td>
<td>0.22 (-1.1, 1.55)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>-4.02 (-9.84, 1.81)</td>
<td>0.18</td>
<td>1.05 (-0.28, 2.37)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>APOE ε4</strong></td>
<td>9.35 (3.04, 15.65)</td>
<td>0.004*</td>
<td>-0.03 (-0.53, 0.48)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>-0.7 (-5.08, 3.67)</td>
<td>0.74</td>
<td>-0.27 (-0.72, 0.18)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>MMSE score</strong></td>
<td>-2.13 (-4.66, 0.39)</td>
<td>0.095</td>
<td>0.12 (-0.14, 0.39)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>CDR sum of boxes</strong></td>
<td>-0.28 (-1.65, 1.09)</td>
<td>0.68</td>
<td>-0.06 (-0.2, 0.09)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>UPDRS-III score</strong></td>
<td>-12.11 (-23.43, -0.8)</td>
<td>0.037*</td>
<td>-2.31 (-3.48, -1.14)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Visual Hallucinations</strong></td>
<td>5.15 (-0.88, 11.19)</td>
<td>0.094</td>
<td>-0.33 (-0.9, 0.25)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Fluctuations</strong></td>
<td>-0.12 (-3.72, 3.48)</td>
<td>0.95</td>
<td>0.21 (-0.16, 0.58)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Parkinsonism</strong></td>
<td>0.91 (-2.91, 4.73)</td>
<td>0.64</td>
<td>-0.33 (-0.72, 0.07)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>pRBD</strong></td>
<td>-7.76 (-19.86, 4.34)</td>
<td>0.21</td>
<td>-2.1 (-5.41, 1.22)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*P-values <0.05. Regression coefficients and associated confident interval, and p-values are from either a linear regression or logistic regression model age adjustment where appropriate.

Abbreviations: A = amyloid-β; D = Dopamine transporter imaging; + = abnormal values; - = normal values; APOE = Apolipoprotein E; MMSE = mini-mental state examination; CDR = clinical dementia rating scale; UPDRS = unified Parkinson disease rating scale; aMCI = amnestic mild cognitive impairment; pRBD = probable rapid eye movement sleep behavior disorder; DLB = dementia with Lewy bodies.
Mild Cognitive Impairment at Risk for Lewy Body Dementia
Neurology published online January 6, 2021
DOI 10.1212/WNL.0000000000011454

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