Role of β-Amyloidosis and Neurodegeneration in Subsequent Imaging Changes in Mild Cognitive Impairment

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**IMPORTANCE** To understand how a model of Alzheimer disease pathophysiology based on β-amyloidosis and neurodegeneration predicts the regional anatomic expansion of hypometabolism and atrophy in persons with mild cognitive impairment (MCI).

**OBJECTIVE** To define the role of β-amyloidosis and neurodegeneration in the subsequent progression of topographic cortical structural and metabolic changes in MCI.

**DESIGN, SETTING, AND PARTICIPANTS** Longitudinal, observational study with serial brain imaging conducted from March 28, 2006, to January 6, 2015, using a population-based cohort. A total of 96 participants with MCI (all aged >70 years) with serial imaging biomarkers from the Mayo Clinic Study of Aging or Mayo Alzheimer’s Disease Research Center were included. Participants were characterized initially as having elevated or not elevated brain β-amyloidosis (A+ or A−) based on 11C-Pittsburgh compound B positron emission tomography. They were further characterized initially by the presence or absence of neurodegeneration (N+ or N−), where the presence of neurodegeneration was defined by abnormally low hippocampal volume or hypometabolism in an Alzheimer disease–like pattern on 18F-fluorodeoxyglucose (FDG)–positron emission tomography.

**MAIN OUTCOMES AND MEASURES** Regional FDG standardized uptake value ratio (SUVR) and gray matter volumes in medial temporal, lateral temporal, lateral parietal, and medial parietal regions.

**RESULTS** In the primary regions of interest (ROI), the A+N+ group (n = 45) had lower FDG SUVR at baseline compared with the A+N− group (n = 17) (all 4 ROIs; P < .001). The A+N+ group also had lower FDG SUVR at baseline (all 4 ROIs; P < .01) compared with the A−N− group (n = 12). The A+N+ group had lower medial temporal gray matter volume at baseline (P < .001) compared with either the A+N− group or A−N− group. The A+N+ group showed large longitudinal declines in FDG SUVR (P < .05 for medial temporal, lateral temporal, and medial parietal regions) and gray matter volumes (P < .05 for medial temporal and lateral temporal regions) compared with the A−N+ group (n = 22). The A+N+ group also showed large longitudinal declines compared with the A−N− group on FDG SUVR (P < .05 for medial temporal and lateral parietal regions) and gray matter volumes (all 4 ROIs; P < .05) compared with the A+N− group. The A−N+ group did not show declines in FDG SUVR or gray matter volume compared with the A+N− or A−N− groups.

**CONCLUSIONS AND RELEVANCE** Persons with MCI who were A+N+ demonstrated volumetric and metabolic worsening in temporal and parietal association areas, consistent with the expectation that the MCI stage in the Alzheimer pathway heralds incipient isocortical involvement. The A−N+ group, those with suspected non-Alzheimer pathophysiology, lacked a distinctive longitudinal volumetric or metabolic profile.
The clinical syndrome of mild cognitive impairment (MCI) when due to Alzheimer disease (AD) represents an inflection point at which the tempo of cognitive decline accelerates and expands. Clinical acceleration is likely to be preceded or accompanied by neurodegenerative changes outside of the medial temporal lobe. The neurodegenerative expansion that occurs at the MCI stage is assumed to require the presence of β-amyloidosis but antemortem demonstrations are infrequent and contradictory. The many studies in patients with MCI that examined region-specific declines with magnetic resonance (MR) imaging did not have amyloid imaging available. Our current model posits that both β-amyloid and neurodegenerative biomarkers must be abnormal for higher rates of neurodegeneration to occur. We aimed to test that hypothesis in persons with MCI.

We studied Mayo Clinic Study of Aging (MCSA) and the Mayo Alzheimer Disease Research Center (ADRC) participants who had undergone serial clinical evaluations as well as serial MR imaging, FDG-PET imaging, and Pittsburgh compound B (PiB) PET imaging. Our major aim was to determine the pattern of progression of regional volume loss and metabolic declines at the MCI stage as a function of β-amyloid and neurodegeneration biomarker status. We were interested both in those participants with elevated β-amyloid (those in the AD pathway) and those with nonelevated β-amyloid and neurodegeneration (the suspected non-Alzheimer pathophysiology [SNAP]).

Methods

Participants

We examined participants with MCI in the MCSA and ADRC who had serial imaging biomarkers and who were 70 years of age and older at the baseline imaging visit. Participants had to be diagnosed as having MCI at baseline but were not excluded if their diagnosis changed over the course of follow-up.

Consensus clinical diagnoses were made using previously described methods in the MCSA. A consensus diagnosis of MCI was made using these criteria: cognitive concern by a physician, patient, or nurse; impairment in 1 or more of the 4 cognitive domains; essentially normal functional activities; and not demented, as previously described. These criteria were identical to those proposed by the National Institute on Aging-Alzheimer Association workgroup. We allowed any neuropsychologically defined MCI subtype.

These studies were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards and written informed consent was obtained from all participants.

Imaging Methods

All participants underwent MR, FDG-PET, and PiB PET imaging following our previously described method. Magnetic resonance and PET imaging were done within 6 months of a participant’s clinical visit. Magnetic resonance scanning was performed at 3 T. Amyloid PET imaging was performed with PiB and consisted of 4 5-minute dynamic frames acquired from 40 to 60 minutes after injection of 292- to 729-MBq 11C-PiB. Pittsburgh compound B values were gray matter (GM) and white matter sharpened and partial-volume corrected; they were normalized to the cerebellum. A global PiB standardized uptake value ratio (SUVR) was calculated from a group of regions including the parietal, cingulate precuneus, prefrontal, orbitofrontal, temporal, and anterior cingulate regions normalized to the cerebellum. All regions were summed over both hemispheres. Fluorodeoxyglucose-PET was obtained on the same day as the PiB scan and consisted of 4 2-minute dynamic frames acquired from 30 to 38 minutes after injection of 366- to 399-MBq FDG. Computed tomographic scans were obtained for attenuation correction. Fluorodeoxyglucose values were non-sharpened and were not partial-volume corrected. Amyloid PET and FDG-PET images were analyzed with our in-house fully automated image processing pipeline where image voxel values were extracted from automatically labeled cortical regions of interest (ROIs).

Biomarker Characterization of Participants

Participants were characterized at baseline as having elevated or not elevated amyloid (A+ or A−, respectively) based on PiB SUVR greater than 1.40 and on having abnormal or normal neurodegenerative changes (N+ or N−, respectively) based on either hippocampal volume by MR or FDG hypometabolism in an AD signature meta-ROI. Hippocampal volume was measured with FreeSurfer software (version 5.3) and total intracranial volume (TIV) was measured using an in-house method. Each participant’s raw hippocampal volume was adjusted for TIV to create a TIV-adjusted hippocampal volume by calculating the residual from a linear regression of hippocampal volume vs TIV among 133 cognitively normal persons aged 30 to 59 years. The cut point for hippocampal volume adjusted for Statistical Parametric Mapping version 12 TIV (TIV-adjusted hippocampal volume) less than –2.40 cm³. The FDG AD signature meta-ROI was defined as the average of uptake in defined voxels in the angular gyrus, posterior cingulate gyrus, and left middle/ inferior temporal gyrus normalized to the cerebellum. A global FDG standardized uptake value ratio (SUVR) greater than 1.40 and having abnormal or normal neurodegenerative changes (N+ or N−, respectively) based on PiB SUVR and FDG SUVR was less than 1.32. Cut-point values were derived from 75 persons with AD dementia from the Mayo ADRC or MCSA, and they represented the 90th percentile for FDG and MR imaging measures and the 10th percentile for PiB SUVR.

Outcome Measures

Regional GM volume and FDG SUVR were the measures of change. They were computed for 15 cortical regions from an atlas modified in-house. Right and left hemisphere values for volumes were summed, and right and left hemisphere values for FDG ratios were averaged and weighted to the ROI size. Regional GM volumes were estimated using the TBM-Syn algorithm. For the regional FDG SUVR used as outcome measures, values were normalized to the pons. Volumetric- and glucose metabolic-annualized changes in 4 temporoparietal ROIs were of primary interest: medial temporal, lateral temporal, medial parietal, and lateral parietal. These were chosen based on prior work with MR imaging. See Figure 1 for their locations. Eleven other regions were designated as secondary ROIs.
 Statistical Analysis

Our principal goal was to assess the role of elevated β-amyloidosis (A+) on the progression of regional FDG SUVR and GM volume changes in the presence or absence of neurodegeneration (N+ or N−) defined at baseline. A secondary goal was to learn whether the A−N+ (SNAP) group differed from the other MCI groups.

Differences in baseline characteristics were assessed using either the Pearson χ² test for 2 × 2 table using N-1 method or Welch 2-sample t test. Linear mixed-effects regression models were fit to assess group differences in baseline FDG SUVR and GM volumes and to assess group differences in changes over time in FDG SUVR and GM volumes. One participant was excluded from all GM volume analyses owing to having invalid volumetric estimates. Each model included main effects of time, baseline age, sex, biomarker group and interactions for age by time and time by biomarker group, and allowed for a random intercept and slope. These models allowed for groupwise differences at baseline and in the rates of change and controlled for age-related baseline differences. All outcome measures were log-transformed to reduce skewness and to allow for interpretation of estimates on a percentage rather than absolute scale. We summarized baseline and annual percentage change estimates using the usual 95% CIs and also using 84% CIs. We chose 84% CIs because at that level, non-overlapping intervals correspond to a biomarker group difference that is significant at the P < .05 level. We did not correct for multiple comparisons. All analyses were performed using R Statistical Software (version 3.0.1; R Foundation for Statistical Computing).

Results

The baseline characteristics of the biomarker-defined groups are shown in the Table. The A+N+ and A+N− groups had a higher proportion of apolipoprotein E ε4 carriers and greater PIB SUVR levels compared with both A− groups, as expected. The A+N+ group had the lowest global and memory z scores of the biomarker-defined groups. The A+N+ group also had the greatest decline in Mini-Mental State Examination score over time. Nearly half of participants in the N+ groups had both of the defining neurodegeneration features, hippocampal atrophy and FDG hypometabolism in an AD-like pattern: 9 of 22 (41%) in the A−N+ group and 20 of 45 (44%) in the A+N+ group. The number of participants with only abnormal FDG was 9 of 22 (41%) in the A−N+ group and 14 of 45 (31%) in the A+N+ group, and the numbers with only abnormal TIV-adjusted hippocampal volume were 4 of 22 (18%) in the A−N+ group and 11 of 45 (24%) in the A+N+ group. Participants were followed up for an average of 2 years, and the duration of follow-up did not differ between the biomarker-defined groups.

Baseline

There were substantial baseline differences in regional FDG SUVR across the MCI groups that were largely a consequence of how group membership was defined. In the primary 4 temporal/parietal ROIs, the A+N+ and A−N+ groups had the lowest FDG SUVR (P < .001 for the comparison of A+N+ with A+N−), which significantly differed from either the A+N− or A−N− groups for all comparisons except for a borderline difference in the medial temporal region for the A−N+ vs A−N− groups (Figure 2; eTable 1 and eTable 2 in the Supplement). There were no significant differences in FDG SUVR between the A+N+ and A−N+ groups in these 4 regions. The A+N+ group had the smallest GM volumes in the medial temporal, lateral temporal, and lateral parietal regions, although not all differences were significant. See Figure 1 and its legend for the P values for between-group comparisons.

Among the secondary ROIs, the A+N+ group had significantly lower FDG SUVR in all ROIs compared with the A+N− group but not compared with the other 2 groups (eFigure 1 in the Supplement). The A−N+ group generally had lower FDG SUVR compared with the A+N+ group but not different FDG SUVR compared with the A−N− group, although there were some exceptions. Across the secondary ROIs, regional GM volumes were generally not significantly different across the 4 biomarker-defined groups, although a few regions in the A+N+ group compared with the A−N− and A+N+ groups showed lower volumes (eFigure 2 in the Supplement).

Annual Change

The A+N+ group generally showed greater declines in both FDG SUVR and GM volume in the 4 primary temporal/parietal ROIs compared with the A−N+ and A−N− groups, although not all of these differences were significant (Figure 3; eTable 1 and eTable 2 in the Supplement). For example, the A+N+ group showed greater declines in FDG SUVR compared with the A−N− group in the medial temporal (P = .007), lateral temporal (P = .03), and medial parietal (P = .04) ROIs. The change in FDG SUVR and GM volume did not significantly differ between the A+N+ and A+N− groups for any of these 4 regions. Although the A+N− group exhibited point estimates that were lower than the values for the 2 A− groups, none of the differences exceeded the nominal significance level of 0.05. See Figure 2 and its legend for the P values for between-group comparisons.

Across the secondary ROIs, there were very few significant differences in either change in FDG SUVR or change in GM volume.
The findings are summarized in Figure 4. The A+N+ group demonstrated low glucose metabolism and GM volumes in the 4 primary temporoparietal ROIs at baseline and large annual declines. In contrast, the A+N− group exhibited higher metabolisms and volumes at baseline but rates of decline that were not different from the A+N+ group. The A−N+ (SNAP) group had low glucose metabolism and smaller medial temporal GM volume at baseline but experienced no regional metabolic or volumetric declines that distinguished them from the A+N− or A−N− groups.

### Discussion

Our principal finding was that participants with MCI with elevated β-amyloidosis and neurodegeneration (A+N+) at baseline experienced worsening of FDG SUVR and cortical GM volume in the medial and lateral temporal regions and parietal ROIs compared with the MCI groups without elevated β-amyloid levels. Our findings support a model of AD pathophysiology that requires the combined presence of brain β-amyloidosis and neurodegeneration, which in turn signifies a high likelihood of worsening of neurodegeneration in synaptically connected extramedial temporal regions.

While some neurodegenerative changes arise independently of β-amyloid prior to MCI, neurodegeneration at the MCI...
stage was facilitated when β-amylloid was elevated. The changes in the MCI A+N+ group were far larger than any seen in our prior study of cognitively normal individuals.

The pattern of changes we observed in our A+N+ patients with MCI who were on the AD pathway is what one would expect for typical AD progression on clinical-pathological grounds. While others have shown extratemporal changes in cognitively normal individuals, analyses of ours using the same design as used here showed that structural and metabolic abnormalities in persons who are A+N+ but cognitively normal are focused in the medial temporal lobe. As overt cognitive impairment ensues, neurodegeneration spreads to the temporal and parietal cortices, paralleling the progression of neurofibrillary tangle burden. The A+N− participants had larger metabolic declines than either of the A−N+ or A−N− groups, but none of the differences were significant. The percentage of participants who progressed to dementia at the last follow-up visit in the A+N− group was 12% (2 of 17), in contrast to the A+N+ group in which the percentage of participants who progressed was 22% (10 of 45). The pattern was similar but not identical to what we and others have previously reported. A more detailed analysis of the relationship of imaging findings to cognition is beyond the scope of the current report and requires longer periods of observation and more dementia events than we had available. The more favorable clinical outcomes in the A+N− group (who had less neurodegeneration at baseline) is consistent with the idea that a certain threshold of neurodegeneration must be exceeded for progression of cognitive impairment to occur. Over the course of the current study, the worsening of GM volumes and FDG SUVR meant that many in our A+N− group (8 of 17) would have been reclassified as A+N+ at the end of the observation period.

The A−N+ group (SNAP) had significantly lower FDG SUVR at baseline in most of the cortical ROIs compared with the N− groups; however, except for the medial temporal lobe, the A−N+ group did not have concomitant lower GM volumes.
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Elsewhere at baseline. While a few of the A−N+ participants had PiB SUVr levels at baseline that approached the cut point for elevated β-amyloid, at the end of the current observation period, only 1 individual in the A−N+ group had transitioned to A+N+. Thus, most of the A−N+ group was not on an amyloid-dependent pathway. Longitudinally, the A−N+ group experienced less worsening in atrophy or metabolism compared with the A+N+ group, and in no region did the A−N+ group experience significantly worse declines than the N− groups. These observations suggest that prevalent medial temporal atrophy was a major feature of MCI A−N+, in a manner not distinguishable from the A+N+ group. However, the amount of decline in medial temporal volume in the A−N+ group was much less than the A+N+ group. Primary age-related tauopathy,40 cerebrovascular disease, or hippocampal sclerosis41 could account for the more indolent medial temporal volume loss in the A−N+ group. The A−N+ group had widespread hypometabolism at the baseline, and this also worsened less compared with the A+N+ group. It is possible that multiple nonmedial temporal nontauopathy pathophysiologies (eg, cerebrovascular or neurodegenerative) are driving the widespread hypometabolism. Such heterogeneity would tend to obscure any one distinct pattern of worsening. Visual inspection of the MR and FDG PET scans of the A−N+ group failed to reveal any cases in which an obvious etiological diagnosis (eg, frontotemporal degeneration) could be inferred from the scan. Biomarkers that are specific for non-AD degenerative processes are needed to address the progression of A−N+ cases. The proportion of A−N+ (SNAP) participants who progressed to dementia at the last follow-up was lower than in prior studies37-39 including our own36: 18% (4 of 22), about the same as the A+N− group (as described here) but more than the A−N− group (8%; 1 of 12). As noted here, the clinical progression data should be treated with caution because of the small numbers who progressed to dementia at last follow-up and because these numbers did not adjust for differences in demographics among the groups. However, the indolent anatomic progression in the A−N+ group was mirrored in the low number of participants who progressed to dementia at last follow-up.

Our observations support the claim that the presence of β-amyloidosis is required for anatomic and clinical progression, but that is not the same as claiming a causal role for β-amyloidosis at the MCI stage. Importantly, the increased risk for progression that elevated β-amyloid conferred does not clarify...
when in the sequence of events that the elevated β-amyloid actually mattered. As elevated β-amyloidosis has likely been present in these patients with MCI for at least 15 to 20 years, the point at which β-amyloid's presence was causal could have been any time in that window. Furthermore, neurodegenerative changes in the medial temporal lobe (such as in middle-aged cognitively normal individuals)—which we observed in participants with MCI without elevated β-amyloid imaging markers—are likely to be β-amyloid independent at least initially. It is hard to escape the conclusion that high levels of brain β-amyloidosis at some point play a facilitating role in the progression of neurodegeneration. It is beyond the scope of this study to speculate on the mechanism of the interaction of β-amyloidosis and neurodegeneration at the molecular pathway level.

Conclusions

We relied on prior MR imaging and FDG-PET studies of patients with MCI who progressed to dementia to allow us to focus our attention on progression in temporal and parietal isocortical regions. However, the prior studies lacked amyloid imaging and used quite different approaches than ours to characterize participants at baseline. In persons with AD dementia, progression of hypometabolism into lateral temporoparietal cortices occurs, a pattern that our findings confirmed. We extended the prior observations by showing that regional isocortical changes can be demonstrated at the MCI stage without preselecting those who progressed. We further clarified the role of elevated β-amyloidosis, after stratifying on baseline neurodegenerative status.

There were limitations to our analyses. We included all MCI neuropsychological subtypes; however, we were not able to perform syndrome-specific analyses owing to low numbers. Even so, the number of MCSA participants with MCI who have had serial imaging was small, particularly when subsets with specific imaging features were of interest. The number of participants available with serial imaging may have reduced our power to detect other smaller isocortical changes. In particular, the smaller sizes of the A+N−, A−N+, and A−N− groups reduced our ability to detect differences in those groups. Our choice of neurodegeneration biomarkers was limited and unlikely to thoroughly cover the multiple processes that comprise AD neurodegenerative pathophysiology. Because each neurodegeneration biomarker is unique, ones other than hippocampal atrophy and FDG AD−signature SUVR for defining baseline status might yield different conclusions.

Figure 4. Summary Regression Plots for the 4 Primary Regions of Interest for 18F-Fluorodeoxyglucose (FDG) Standardized Uptake Value Ratio (SUVR) and Gray Matter (GM) Volume

Regression plots for the 4 primary regions of interest showing trajectories of FDG SUVR (A-D) and GM (E-H) over time for the 4 biomarker-defined groups for a hypothetical man aged 80 years. The time scale was limited to 2 years for illustrative purposes. See Figure 1 and Figure 2 for confidence intervals of baseline values and slopes. A+ and A− indicate having and not having elevated β-amyloidosis, respectively, and N+ and N−, presence and absence of neurodegeneration, respectively.
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