Amyloid and tau positive mild cognitive impairment: clinical and biomarker characteristics of dementia progression

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Abstract

Background: According to the amyloid, tau, neurodegeneration research framework classification, amyloid and tau positive (A+T+) mild cognitive impairment (MCI) individuals are defined as prodromal Alzheimer disease. This study was designed to compare the clinical and biomarker features between A+T+MCI individuals who progressed to progressive MCI (pMCI) and those who remained stable MCI (sMCI), and to identify relevant baseline clinical biomarker and features that could be used to predict progression to dementia within 2 years.

Methods: We stratified 197 A+T+MCI individuals into pMCI ($n = 64$) and sMCI ($n = 133$) over 2 years. Demographics and cognitive assessment scores, cerebrospinal fluid (CSF), and neuroimaging biomarkers (^{18}F-florbetapir positron emission tomography mean standardized uptake value ratios [SUVR] and structural magnetic resonance imaging [MRI]) were compared between pMCI and sMCI at baseline, 12- and 24-month follow-up. Logistic regression models then were used to evaluate clinical baseline and biomarker features that predicted dementia progression in A+T+MCI.

Results: pMCI individuals had higher mean ^{18}F-florbetapir SUVR, CSF total-tau (t-tau), and p-tau$_{181P}$ than those in sMCI individuals. pMCI individuals performed poorer in cognitive assessments, both global and domain specific (memory, executive, language, attention, and visuospatial skills) than sMCI. At baseline, there were significant differences in regions of interest of structural MRI between the two groups, including bilateral amygdala, hippocampus and entorhinal, bilateral inferior lateral ventricle, left superior and middle temporal, left posterior and caudal anterior cingulate ($P < 0.05$). Baseline CSF t-tau levels and cognitive scores of Montreal cognitive assessment, functional assessment questionnaire, and everyday cognition by the patient's study partner language domain could predict progression to dementia in A+T+MCI within 2 years.

Conclusions: In future clinical trials, specific CSF and cognitive measures that predict dementia progression in A+T+MCI might be useful risk factors for assessing the risk of dementia progression.

Keywords: Alzheimer disease; Mild cognitive impairment; Amyloid and tau positive mild cognitive impairment; Dementia

Introduction

Recent scientific progress in Alzheimer's disease (AD) biomarkers using cerebrospinal fluid (CSF) and neuroimaging have enabled us to identify the pathophysiology of AD in humans. The biomarkers that measure β-amyloid (Aβ) deposition include amyloid positron emission tomography (PET)[1,2] and CSF Aβ$_{1-42}$ levels.[3-5] Biomarkers that measure fibrillar tau include CSF phosphorylated tau (p-tau) levels and cortical tau PET uptake and biomarkers that measure neurodegeneration or neuronal injury include CSF total-tau (t-tau) levels, fluorodeoxyglucose (FDG) PET hypometabolism, and magnetic resonance imaging (MRI) grey matter atrophy.[6] Given that AD biomarkers now play an important role in AD research, the A/T/N biomarker classification has been introduced recently, where "A," "T," and "N" represent Aβ, tau, and neurodegeneration biomarkers, respectively.[7,8] Furthermore, the National Institute on Aging-Alzheimer's Association (NIA-AA) research framework recently proposed a research framework using biomarkers to define a biological diagnosis of AD in living humans.

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They also proposed a new six-stage numeric clinical staging scheme for patients in the Alzheimer continuum (patients with Aβ), which emphasizes biomarkers over clinical features, but clinical trials will require consideration of biological profile of participants.[9] There has been much evidence that the highest rates of short-term progression are in the A+T+N− and A+T+N+ classes of AD.[10]

While various AD therapeutic trials have been conducted in recent years, involving both symptomatic and disease modifying agents, there is no effective treatment that is available for AD at present. A review of AD clinical trials conducted from 2002 to 2012 recorded 413 trials, with a 99.6% failure rate.[11] One possible reason for this high failure rate has been attributed to the clinical diagnosis for inclusion lacking specificity and sensitivity. Subjects are often diagnosed with AD dementia but they are found not to have AD pathology. Abner *et al*[12] previously reported that nearly 10% to 30% of individuals clinically diagnosed as AD dementia did not display AD neuropathological changes at autopsy. It is also not possible to confirm the presence of amyloid pathology in cognitively normal subjects based on clinical presentation without biomarkers. As such, AD biomarkers now play a key role in the inclusion criteria of clinical trials to confirm the presence of therapeutic target, such as Aβ, before recruiting subjects into the trial.

Previous clinical trials have recruited AD subjects at the dementia stage and it is likely that interventions at this stage are too late given that irreversible brain changes which have already occurred. In this regard, recent studies into the trajectory of AD pathophysiology have demonstrated that the AD pathological process begins many years before overt clinical symptoms.[13] Therefore, there is now a shift in the therapeutic time window of AD clinical trials towards the early stages of the disease.[11,14-16]

Mild cognitive impairment (MCI) represents a prodromal AD stage where cognitive decline is greater than expected for one's age and education level but that does not interfere with activities of daily life.[17] However, previous studies have shown that only an estimated 10% to 15% of MCI individuals will convert to dementia per year.[18] While the application of "A" and "T" biomarkers based on the NIA-AA research framework enables the identification of MCI individuals due to AD, the clinical and biomarker characteristics of those who will progress to dementia within typical trial periods remain unclear. With the current clinical trials focusing on the MCI stage for intervention, findings from this study might be useful when assessing the risk of dementia progression for future clinical trials.

Here, in a 2-year longitudinal observation of A+T+MCI individuals from the AD neuroimaging initiative (ADNI) cohort stratified into those who progressed to dementia (pMCI) or remained stable (sMCI), we compared the clinical and biomarker features between the two groups. We further investigated the baseline clinical and biomarker features that predicted progression to dementia within 2 years. Our findings that distinguish pMCI from sMCI will enable the identification of individuals as a potential target population for early intervention studies.

Methods

Ethics approval

The ADNI was approved by the Institutional Review Board at each Clinical Trial Center of ADNI and was compliant with the Health Insurance Portability and Accountability Act. All clinical practices and observations were conducted in accordance with the *Declaration of Helsinki*. Informed consent was obtained from each patient before the study was conducted.

ADNI and patients

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). Specifically, we obtained the following clinical and biomarker information (which have been identified as risk factors for the progression of dementia): age, sex, years of education, ApoEε4 status (stratified into ApoEε4 [+/+], ApoEε4 [+/−], and ApoEε4 [−/−] carriers based on the number of e4 allele copies), CSF $A\beta_{1-42}$, p-tau_{181p}, and t-tau, Florbetapir PET mean standardized uptake value ratio (SUVR), structural MRI, cognitive measures at baseline (the baseline visit must take place within 28 days of the MRI screening, and before conducting any baseline assessments, the screening 3T MRI was reviewed and approved by local radiologist, ADNI MRI quality control (QC), clinical monitor. Participants must meet all inclusion/exclusion criteria, 12- and 24-month follow up and whether the participants progressed to dementia within 2 years (accessed in August 2016, http://www.adni-info.org).

In the present study, we selected 406 subjects with MCI from ADNI-2 and ADNI-GO studies. We defined MCI as those who had a subjective memory complaint, objective memory loss measured by using education-adjusted scores on the Logical Memory II (Delayed Recall) subscale of the Wechsler Memory scale, a clinical dementia rating (CDR) of 0.5, preserved activities of daily living, and absence of any neuropsychiatric diseases such as depression and dementia. Subjects without complete clinical and biomarker information were excluded. Further information about the inclusion/exclusion criteria of AD adopted by the ADNI is described in detail at www.adni-info.org. As many previous studies have proved PET quantitation might be preferable for accurate selection and therapeutic monitoring of individuals in clinical trials, and meanwhile, the optimal cut-offs for CSF markers were less robust, we used PET amyloid burden to classify the patient's amyloid burden.[19] From the above MCI subjects, we identified A+T+MCI individuals using ^{18}F-florbetapir mean SUVR >1.1 as the threshold for Aβ pathology[20] and CSF markers p-tau levels >23 pg/mL as the threshold for tau pathology.[16] Based on these criteria, 197 MCI participants were found to have both Aβ and tau pathologies. We further stratified the A+T+MCI participants into sMCI ($n = 133$) if they did not progress to dementia during the 2 years of follow-up, and pMCI ($n = 64$) if they progressed to dementia at any time during the 2 years of follow-up

(range 6–24 months at 6-month intervals). We defined probable AD dementia as those who fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria, mini-mental state examination (MMSE) scores from 20 to 26 and a CDR of 1.0.[21]

Florbetapir-PET-AV45

The PET neuroimaging techniques used by ADNI have been reported previously.[22] The amyloid burden is measured from the mean ^{18}F-florbetapir PET SUVR calculated from the average SUVR within the brain regions of prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices. The data of mean ^{18}F-florbetapir SUVR were obtained from the ADNI file "UCBERKELEYAV45_06_15_16.csv." Further details regarding ADNI image acquisition and processing can be found at www.adni-info.org/methods.

Cerebrospinal fluid data

CSF $A\beta_{1-42}$, t-tau, and p-tau_{181p} were measured using the INNO-BIA AlzBio3 immunoassay kit based reagents (Innogenetics, Ghent, Belgium) in the multiplex xMAP Luminex platform (Luminex, Austin, TX, USA) as previously described.[16] The CSF data used in this study were obtained from the ADNI files "UPENNBIOMK5–8.csv." Detailed ADNI methods for CSF acquisition, measurements, and QC procedures were described at www.adni-info.org.

Neuropsychological assessment

All subjects underwent a full neuropsychological assessment at baseline, 12- and 24-month follow-up visits. In this study, CDR sum of boxes (CDR-SB), AD assessment scale-cognitive subscale (ADAS-Cog) consisting of 11 (ADAS-Cog 11) and 13 items (ADAS-Cog 13), MMSE, Montreal cognitive assessment (MoCA), functional assessment questionnaire (FAQ) assessed global cognition. As for memory assessment, we examined a memory composite score (ADNI-MEM) and the Rey auditory verbal learning test (RAVLT) which included RAVLT immediate (the sum of scores from five first trials [trials 1–5]), RAVLT Learning (the score of Trial 5 minus the score of Trial 1), RAVLT forgetting (the score of Trial 5 minus score of the delayed recall) and RAVLT percent forgetting (RAVLT forgetting divided by the score of Trial 5). The executive function composite score (ADNI-EF) evaluated executive function. The Boston naming test (BNT) and category fluency tests evaluated language function. Visuo-constructive skills were evaluated using the clock-drawing test. In addition to the above psychometric measures, we examined both the informant and subject's cognitive complaints using the everyday cognition (ECog) questionnaire.

MRI imaging

All MRI brain scans were performed on 3T scanners by using a sagittal MPRAGE sequence with the following parameters: repetition time = 2400 ms, inversion time = 1000 ms, flip angle = 8°, and field of view = 24 cm with a $256 \times 256 \times 170$ acquisition matrix in the X-, Y-, and Z-dimensions, which yielded a voxel size of $1.25 \times 1.261 \times 2$. All original uncorrected image files are available to the general scientific community, as described at http://www.loni.ucla.edu/ADNI.

The MRI data were preprocessed by using standard procedures that included realigning the anterior commissure and posterior commissure by using MIPAV software, skull-stripping by using brain surface extractor and brain extraction tool, cerebellum removal, intensity inhomogeneity correction, segmentation using the FSL-FAST software, and spatial co-registration by using HAMMER.[23] 107 regions of interest (ROIs) were automatically segmented according to the Jacob atlas defined by FreeSurfer,[24] which included cortical volume, surface area, thickness average and thickness standard deviation (SD) of bilateral entorhinal, rostral anterior cingulate, caudal anterior cingulate; subcortical volume of bilateral amygdala, hippocampus, choroid plexus, inferior lateral ventricle; cortical volume and thickness average of left superior and middle temporal, bilateral isthmus cingulate, etc. The structural MRI neuroimaging data were obtained from the ADNI file "UCSFFSL_11_02_15," and "UCSFFSX51_11_02_15_V2."

Statistical analyses

Statistical analyses were performed by using the SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics and frequency distributions of baseline demographics, cognitive scores, and MRI brain ROIs were summarized and compared between sMCI and pMCI at baseline, 1- and 2-year follow-up visits. Student *t* test was used to compare the difference between groups if the variables were normal distribution and the variance was equal across groups. Otherwise, Wilcoxon rank test was applied. Continuous variables were reported as mean ± SD. Univariate and multivariate analyses were assessed using a logistic regression model.

Baseline demographics, baseline cognitive scores, and MRI brain ROIs were included in the univariate logistic regression model to find possible factors that predict progression. Factors with $P < 0.05$ on univariate analysis as well as the variables with interactions in the model were incorporated into multivariate analysis. Forward stepwise method was used to select parameters. Factors with $P < 0.05$ in multivariate analysis were identified as the independent factors that predict progression. *P* values were adjusted by age, gender, years of education, ApoEε4 status, cognitive scores, and ROIs at baseline appropriately. In logistic regression, the variables that needed to prove whether there were multiplicative interactions and their multiplicative terms are taken as independent variables to conduct regression results to see whether the coefficient of the multiplicative terms was significant and non-zero. If the coefficient of the multiplicative interaction was significant and non-zero, the two factors had a multiplicative interaction. The variables which proved to have a multiplicative interaction were used as independent variables.

Table 1: Baseline demographics and sample characteristics of patients with MCI stratified by progression to AD.

Characteristics	sMCI ($n = 133$)	pMCI ($n = 64$)	P
Age (years)	72.9 ± 6.7	72.7 ± 6.9	0.872
Gender			0.812
Male	75 (56.39)	35 (54.69)	
Female	58 (43.61)	29 (45.31)	
ApoEε4 (%)			0.028*
ApoEε4 (−/−)	47 (35.34)	11 (17.19)	
ApoEε4 (+/−)	63 (47.37)	41 (64.06)	
ApoEε4 (+/+)	23 (17.29)	12 (18.75)	
Education (years)	16.0 ± 2.9	16.4 ± 2.6	0.312
$A\beta_{1-42}$ (pg/mL)	140.2000 ± 28.6687	131.40000 ± 23.1179	0.035*
t-tau (pg/mL)	106.0000 ± 50.5968	138.9000 ± 56.9020	< 0.001*
p-tau_{181P} (pg/mL)	53.0571 ± 22.9007	63.9063 ± 26.1778	0.003*
Florbetapir-PET global SUVR	1.3632 ± 0.1519	1.4611 ± 0.1715	< 0.001*

Data are presented as mean ± standard deviation, *n* (%). * Statistically significant. Aβ: β-Amyloid; ApoE: Apolipoprotein E; MCI: Mild cognitive impairment; pMCI: Progressive MCI; p-tau: Tau phosphorylated at threonine; sMCI: Stable MCI; SUVR: Standardized uptake value ratio; t-tau: Total Tau.

Results

Baseline demographic results

A total of 197 patients were enrolled in the study, there were 17 participants progressed to dementia at 6-month follow-up, 18 participants converted to dementia at 12-month, 29 participants converted to dementia at 24-month, 14 participants converted to dementia after 24-month follow-up (11 participants at 36-month, three participants at 48-month), 119 participants did not progress to dementia. In order to study the features of A+T+MCI participants with early progression to dementia, we stratified the whole A+T+MCI participants into pMCI group ($n = 64$) and sMCI group ($n = 133$) based on whether they progressed to dementia within 2 years. The baseline demographic and sample characteristics of all A+T+MCI participants are summarized in Table 1. There were no differences in age, sex, and education between the two groups. There were more APOEε4 carriers in pMCI group. CSF $A\beta_{1-42}$ levels were lower in pMCI group compared with sMCI group. CSF t-tau, p-tau_{181p}, and mean ^{18}F-florbetapir SUVR were significantly higher in pMCI group compared with sMCI group.

Neuropsychological examinations

Significant differences in neuropsychological assessments were found between pMCI group and sMCI group at baseline, 12- and 24-month follow-up [Table 2]. pMCI individuals performed worse in global cognition scales compared to sMCI individuals at baseline. pMCI individuals had higher baseline mean CDR-SB, ADAS11, ADAS13, and FAQ scores, and lower mean MoCA score compared to sMCI individuals. pMCI individuals also performed worse in cognitive domains of memory, delayed recall memory, executive, language, attention, and visuo-spatial skills compared to sMCI individuals at baseline. In the memory domain, participants of pMCI performed worse in RAVLT (RAVLT-immediate learning and percent forgetting) and ADNI_MEM than sMCI. In the executive function domain, pMCI individuals performed worse in ADNI-EF than sMCI. pMCI individuals also performed poorer in the category fluency tests (animals and vegetables), clock test, and BNT compared to sMCI individuals. The informant-reported ECog scores, but not self-reported ECog scores, are higher in the pMCI group compared to the sMCI group at baseline. pMCI individuals also performed worse in the above cognitive assessments compared to sMCI individuals at 12 and 24-month follow-up. We depicted the comparison of cognitive assessments' results partly between sMCI and pMCI at baseline, 12- and 24-month follow-up [Table 2].

ROIs in structural MRI

Significant differences in 17 of the ROIs were found between pMCI and sMCI individuals at baseline. We found that pMCI individuals had smaller volumes in the regions of bilateral amygdala, hippocampus, smaller thickness average of bilateral entorhinal cortex, left superior and middle temporal compared to sMCI. pMCI had larger bilateral inferior lateral ventricle than sMCI individuals. pMCI individuals also had smaller surface area of left posterior cingulate, left caudal anterior cingulate than sMCI. However, we did not find any differences in the above ROIs between pMCI and sMCI groups at 12- and 24-month follow-ups.

At 12-month follow-up, we found none of the ROIs of structural MRI had difference between the two groups. At 24-month follow-up, pMCI individuals had smaller thickness SD of the left superior temporal compared to sMCI individuals [Table 3]. The comparison of sMCI and pMCI in structural MRI of bilateral hippocampus and entorhinal at baseline, 12- and 24-month follow-up were shown in Table 3.

We further divided the pMCI group into 12- and 24-month conversion groups based on the specific conversion time point, and then we compared the ROIs of structural MRI

Table 2: Comparison of cognitive assessments between sMCI and pMCI patients at baseline, 12- and 24-month visits.

Cognitive assessments	Baseline			12-month			24-month		
	sMCI ($n=133$)	pMCI ($n=64$)	*P* value	sMCI ($n=133$)	pMCI ($n=64$)	*P* value	sMCI ($n=133$)	pMCI ($n=64$)	*P* value
CDR-SB	1.414 ± 0.799	2.305 ± 0.933	<0.001*	1.559 ± 0.983	3.4435 ± 1.400	<0.001*	1.821 ± 1.466	5.224 ± 2.116	<0.001*
ADAS11	9.323 ± 3.729	13.891 ± 5.302	<0.001*	9.453 ± 4.571	15.571 ± 5.693	<0.001*	10.009 ± 5.412	19.182 ± 6.796	<0.001*
ADAS13	15.444 ± 5.758	20.493 ± 7.283	<0.001*	15.437 ± 6.843	24.381 ± 7.374	<0.001*	15.849 ± 8.082	28.870 ± 8.510	<0.001*
MMSE	27.865 ± 1.812	26.891 ± 1.835	0.001*	27.313 ± 1.995	25.444 ± 2.644	<0.001*	27.245 ± 2.309	23.655 ± 3.122	<0.001*
FAQ	2.561 ± 3.400	6.250 ± 4.784	<0.001*	3.465 ± 3.930	9.841 ± 6.345	<0.001*	3.596 ± 4.427	14.345 ± 7.534	<0.001*
MoCA	23.328 ± 2.983	21.094 ± 2.543	<0.001*	23.242 ± 2.667	20.587 ± 3.419	<0.001*	23.142 ± 3.170	18.679 ± 3.994	<0.001*
RAVLT immediate	35.301 ± 9.695	28.234 ± 7.569	<0.001*	34.656 ± 10.321	24.903 ± 7.448	<0.001*	35.198 ± 35.198	23.382 ± 8.575	<0.001*
RAVLT learning	4.368 ± 2.500	3.156 ± 2.283	0.001*	3.977 ± 2.386	2.355 ± 2.255	<0.001*	3.925 ± 2.800	2.055 ± 1.737	<0.001*
RAVLT forgetting	5.060 ± 2.299	5.469 ± 2.337	0.247	5.523 ± 2.671	4.887 ± 1.993	0.068	5.321 ± 2.776	5.204 ± 2.175	0.787
RAVLT percent forgetting	61.432 ± 28.280	81.262 ± 27.638	<0.001*	70.09 ± 31.342	86.783 ± 23.243	<0.001*	67.575 ± 32.207	92.694 ± 19.068	<0.001*
EcogPt memory	2.338 ± 0.621	2.501 ± 0.734	0.106	2.374 ± 0.681	2.406 ± 0.810	0.774	2.375 ± 0.692	2.414 ± 0.902	0.786
EcogPt language	1.665 ± 0.625	2.239 ± 0.835	<0.001*	1.879 ± 0.682	1.837 ± 0.748	0.699	1.876 ± 0.603	1.797 ± 0.782	0.525
EcogPt visuospatial abilitiesisuospatial abilities	1.450 ± 0.555	1.581 ± 0.634	0.142	1.468 ± 0.525	1.594 ± 0.693	0.208	1.514 ± 0.551	1.527 ± 0.695	0.909
EcogPt planning	1.446 ± 0.569	1.663 ± 0.625	0.016*	1.488 ± 0.558	1.597 ± 0.675	0.242	1.464 ± 0.480	1.529 ± 0.704	0.549
EcogPt organizationganization	1.584 ± 0.615	1.643 ± 0.622	0.530	1.648 ± 0.651	1.643 ± 0.671	0.959	1.654 ± 0.627	1.493 ± 0.683	0.157
EcogPt divided attentionDivided attention	1.884 ± 0.724	1.992 ± 0.768	0.334	1.950 ± 0.799	2.079 ± 0.818	0.307	1.925 ± 0.682	1.809 ± 0.718	0.339
EcogPt total	1.787 ± 0.511	1.912 ± 0.559	0.121	1.831 ± 0.546	1.882 ± 0.656	0.574	1.832 ± 0.482	1.816 ± 0.666	0.879
EcogSP memory	2.250 ± 0.712	2.927 ± 0.833	<0.001*	2.246 ± 0.754	3.252 ± 0.721	<0.001*	2.358 ± 0.820	3.561 ± 0.544	<0.001*
EcogSP language	1.665 ± 0.625	2.239 ± 0.835	<0.001*	1.669 ± 0.609	2.538 ± 0.795	<0.001*	1.843 ± 0.803	2.794 ± 0.876	<0.001*
EcogSP visuospatial abilities Visuospatial abilities	1.465 ± 0.583	1.844 ± 0.816	0.001*	1.447 ± 0.582	2.243 ± 0.877	<0.001*	1.591 ± 0.689	2.747 ± 0.938	<0.001*
EcogSP planning	1.587 ± 0.676	1.988 ± 0.839	0.001*	1.602 ± 0.720	2.439 ± 0.861	<0.001*	1.720 ± 0.795	2.860 ± 0.918	<0.001*
EcogSP organization	1.602 ± 0.7013	2.199 ± 0.904	<0.001*	1.668 ± 0.748	2.666 ± 1.007	<0.001*	1.800 ± 0.793	3.011 ± 0.969	<0.001*
EcogSP divided attentionivided attention	1.920 ± 0.818	2.378 ± 0.956	0.001*	2.012 ± 0.842	2.899 ± 0.911	<0.001*	2.126 ± 0.892	3.227 ± 0.787	<0.001*
EcogSP total	1.764 ± 0.574	2.287 ± 0.726	<0.001*	1.778 ± 0.581	2.691 ± 0.707	<0.001*	1.917 ± 0.696	3.034 ± 0.701	<0.001*
ADNI_MEM	0.251 ± 0.562	−0.362 ± 0.538	<0.001*	0.207 ± 0.725	-0.643 ± 0.611	<0.001*	0.228 ± 0.761	−0.845 ± 0.680	<0.001*
ADNI_EF	0.366 ± 0.821	−0.199 ± 0.739	<0.001*	0.319 ± 0.810	-0.376 ± 0.884	<0.001*	0.353 ± 0.853	−0.518 ± 1.015	<0.001*
Clock drawing test	4.496 ± 0.775	4.078 ± 1.103	0.008*	4.469 ± 0.763	3.810 ± 1.203	<0.001*	4.557 ± 0.757	3.865 ± 1.284	<0.001*
BNT	26.414 ± 3.458	24.766 ± 4.120	0.004*	26.758 ± 3.513	24.619 ± 5.232	0.004*	26.698 ± 3.709	23.453 ± 5.451	<0.001*
Category fluency tests (Animals and Vegetables)	18.429 ± 5.594	15.141 ± 4.305	<0.001*	17.430 ± 5.157	13.603 ± 4.218	<0.001*	17.406 ± 5.536	12.245 ± 4.595	<0.001*

Data were presented as mean ± standard deviation. * Statistically significant. *P* values were adjusted by age, gender, years of education, ApoEε4 status, and cognitive scores at baseline appropriately. ADAS-Cog11 or 13: Alzheimer disease assessment scale-11 or 13-item subscale; ADNI-EF: standardized composite score based on a clock drawing task, animal and vegetable category fluency, the Trail-making task, Digit Span Backwards from the Wechsler Memory Scale–Revised, and the digit–symbol substitution task from the Wechsler Adult Intelligence Test–Revised; ADNI-MEM: standardized composite score based on the Alzheimer's Disease Assessment Scale–cognitive subscale word list learning task, the Rey Auditory Verbal Learning Test, Logical Memory from the Wechsler Memory Scale–Revised, and the Mini-Mental State Examination recall task; BNT: Boston naming test; CDR-SB: Clinical dementia rating scale-sum of boxes; ECog: Test of everyday cognition; FAQ: Functional assessment questionnaire; MCI: Mild cognitive impairment; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment; pMCI: Progressive MCI; PT: Participant; RAVLT: Rey auditory verbal learning test; sMCI: Stable MCI; SP: Study-partner.

Table 3: Comparison of ROIs from structural MRI between sMCI and pMCI patients at baseline, 12- and 24-month visits.

		Baseline			12-month			24-month		
ROIs	Parameter	sMCI ($n=133$)	pMCI ($n=64$)	*P* value	sMCI ($n=133$)	pMCI ($n=64$)	*P* value	sMCI ($n=133$)	pMCI ($n=64$)	*P* value
Left amygdala	SV	1335 ± 255.4	1208.3 ± 226.9	0.001*	1153.1 ± 225.3	1117.6 ± 212.2	0.313	1102.4 ± 243.4	1083.9 ± 266.3	0.673
Right amygdala	SV	1403.7 ± 261.4	1281.9 ± 226.5	0.002*	1239.5 ± 235.5	1214.5 ± 238	0.508	1182 ± 250	1166.6 ± 264.9	0.730
Left hippocampus	SV	3445 ± 569.1	3116.2 ± 474.3	<0.001*	2995.1 ± 503.8	2993.4 ± 529.8	0.983	2947.9 ± 531.2	2913.4 ± 612	0.724
Right hippocampus	SV	3542.8 ± 574.9	3158.3 ± 459.5	<0.001*	3030.5 ± 531.4	3094.4 ± 514.6	0.445	2968.8 ± 569.7	2973.5 ± 685.2	0.964
	TA	3.280 ± 0.444	2.988 ± 0.521	<0.001*	2.911 ± 0.544	2.869 ± 0.532	0.628	2.829 ± 0.545	2.811 ± 0.590	0.855
Right entorhinal	CV	1715.0 ± 378.8	1551.4 ± 441.0	0.008*	1540.6 ± 429.7	1524.9 ± 415.4	0.817	1461.8 ± 448.8	1538.6 ± 476.4	0.337
	TA	3.408 ± 0.510	3.084 ± 0.494	<0.001*	3.056 ± 0.541	3.063 ± 0.577	0.940	2.943 ± 0.586	3.003 ± 0.646	0.573
Left superior temporal	TA	2.563 ± 0.196	2.474 ± 0.220	0.005*	2.367 ± 0.222	2.391 ± 0.218	0.480	2.353 ± 0.210	2.354 ± 0.263	0.985
Left middle temporal	CV	9507.4 ± 1437.8	8886.3 ± 1474.7	0.006*	8516.6 ± 1350.1	8543.5 ± 1383.6	0.901	8352.1 ± 1497.2	8436.1 ± 1631.8	0.755
	TA	2.701 ± 0.163	2.62 ± 0.229	0.005*	2.524 ± 0.236	2.558 ± 0.247	0.377	2.502 ± 0.235	2.502 ± 0.306	0.999
Right choroid plexus	SV	2273.2 ± 505.3	2454.4 ± 608.7	0.029*	2546.1 ± 500.5	2480.4 ± 522.6	0.417	2533 ± 443.8	2479.7 ± 531.1	0.521
Left inferior lateral ventricle	SV	917.5 ± 723.8	1230.6 ± 737.5	0.005*	1438.7 ± 895.6	1400.6 ± 955.5	0.794	1538.5 ± 968.7	1549.4 ± 1002.3	0.949
Right Inferior lateral ventricle	SV	769.3 ± 561.7	1044.1 ± 678.9	0.003*	1343.6 ± 904.8	1156.4 ± 781.4	0.176	1499.9 ± 1078.3	1340 ± 918.4	0.373
Left posterior cingulate	SA	1108.2 ± 160.7	1055.5 ± 163	0.033*	1128 ± 193.1	1111.6 ± 179.5	0.585	1105 ± 170.3	1129.4 ± 218.5	0.492
Right supramarginal	TA	2.405 ± 0.159	2.352 ± 0.144	0.026*	2.225 ± 0.183	2.277 ± 0.189	0.075	2.203 ± 0.211	2.256 ± 0.224	0.157

Data were presented as mean ± standard deviation. * Statistically significant. *P* values were adjusted by age, gender, years of education, ApoEε4 status, and ROIs at baseline appropriately. CV: Cortical volume; MCI: Mild cognitive impairment; pMCI: Progressive MCI; ROIs: Regions of interest; SA: Surface area; sMCI: Stable MCI; SV: Subcortical volume; TA: Thickness average; TS: Thickness standard deviation.

Table 4: Comparison of ROIs from structural MRI between 12- and 24-month's converters at baseline, 12- and 24-month visits.

ROIs	Baseline			12 months			24 months		
	12-month's Converters ($n=29$)	24-month's Converters ($n=35$)	*P* value	12-month's Converters ($n=29$)	24-month's Converters ($n=35$)	*P* value	12-month's Converters ($n=29$)	24-month's Converters ($n=35$)	*P* value
TS of right rostral anterior cingulate	0.831 ± 0.125	0.792 ± 0.139	0.249	0.829 ± 0.141	0.75 ± 0.121	0.024*	0.842 ± 0.12	0.761 ± 0.152	0.049*
TA of right superior temporal	3338.8 ± 405.1	3624.2 ± 497.3	0.016*	3498.9 ± 375.8	3571.3 ± 455.9	0.520	3470 ± 369.9	3638 ± 591.3	0.224
SV of left amygdala	1226.4 ± 211.0	1193.2 ± 241.2	0.564	1053.4 ± 213.2	1164.7 ± 201.6	0.045*	996.6 ± 256.2	1147.1 ± 259.5	0.047*
CV of left entorhinal	1761.4 ± 484.5	1679.2 ± 435.6	0.478	1407.2 ± 449	1634.9 ± 360.6	0.035*	1410 ± 667.2	1601.1 ± 411.1	0.254
SA of left entorhinal	392.2 ± 90.4	424.3 ± 77.0	0.130	362.4 ± 74.6	401.2 ± 70.1	0.046*	362.6 ± 97.0	399.6 ± 87.7	0.165
TA of left entorhinal	3.144 ± 0.490	2.859 ± 0.517	0.028*	2.754 ± 0.601	2.953 ± 0.467	0.158	2.700 ± 0.685	2.892 ± 0.507	0.260
TA of right entorhinal	3.248 ± 0.414	2.947 ± 0.518	0.014*	3.063 ± 0.663	3.062 ± 0.516	0.993	3.02 ± 0.692	2.99 ± 0.623	0.870
TA of right frontal pole	2.617 ± 0.243	2.486 ± 0.284	0.056	2.570 ± 0.377	2.510 ± 0.258	0.501	2.721 ± 0.474	2.460 ± 0.348	0.029*
TS of right isthmus cingulate	0.798 ± 0.085	0.793 ± 0.084	0.795	0.741 ± 0.081	0.797 ± 0.106	0.032*	0.769 ± 0.070	0.781 ± 0.108	0.636
TS of right medial orbitofrontal	0.808 ± 0.087	0.749 ± 0.112	0.023*	0.745 ± 0.100	0.740 ± 0.105	0.838	0.774 ± 0.128	0.757 ± 0.135	0.654

Data were presented as mean ± standard deviation. * Statistically significant. *P* values were adjusted by age, gender, years of education, ApoEε4 status, and ROIs at baseline appropriately. CV: Cortical volume; MCI: Mild cognitive impairment; pMCI: Progressive MCI; ROIs: Regions of interest; SA: Surface area; sMCI: Stable MCI; SV: Subcortical volume; TA: Thickness average; TS: Thickness standard deviation.

Table 5: Multivariate logistic regression analysis for the prediction of progression to AD.

Item	β	SB	*P* value	OR	95% CI	R^2
Baseline t-tau	0.010	0.004	0.013*	1.010	0.002–0.019	0.464
Baseline MoCA	−0.245	0.103	0.018*	0.783	−0.448 to 0.042	0.491
Baseline FAQ	0.134	0.068	<0.049*	1.143	0–0.267	0.515
Baseline EcogSP language	0.792	0.367	0.031*	2.207	0.073–1.511	0.429

* Statistically significant. 95% CI: 95% Confidence interval; AD: Alzheimer disease; β: Regression coefficient; ECogSP: Test of everyday cognition for study-partner; FAQ: Functional assessment questionnaire; MoCA: Montreal cognitive assessment; OR: Odds ratios; SB: Standard deviation; t-tau: Total tau.

between the two groups at baseline, 12- and 24-month, more details were shown in Table 4. Similarly, we found the significant differences in the medial temporal lobe, hippocampus, entorhinal cortex, amygdala, cingulate gyrus between the two sub-groups in pMCI ($P < 0.05$). However, at 12- and 24-month visit time, only the thickness SD of right rostral anterior cingulate and subcortical volume of left amygdala had significant differences between the sub-group of pMCI ($P < 0.05$).

Baseline clinical and biomarkers as predictors for progression of A+T+MCI to dementia

Baseline demographics, baseline cognitive scores, and MRI brain ROIs were included in the univariate logistic regression model to find the possible factors that could be used to predict progression. Then those above variables with $P < 0.05$ on univariate analysis were incorporated into multivariate analysis [Supplementary materials, http://links.lww.com/CM9/A543]. We also substituted these new variables including age APOEε4, APOEε4 p-tau$_{181p}$, Aβ1–42 t-tau, Aβ1–42 gender into the regression model (the detailed results of the multiplied interactions are shown in the Supplementary Table S1, http://links.lww.com/CM9/A543). Factors with $P < 0.05$ in multivariate analysis were identified as the independent factors that predicted progression [Table 5]. We further found that baseline CSF t-tau, MoCA, FAQ, and EcogSP language scores predicted whether patients with A+T+MCI would progress to dementia at the 2-year follow-up [Table 6].

Discussion

In this study of A+T+MCI individuals with presence of Alzheimer-related pathology measured using CSF p-tau$_{181p}$ and mean ^{18}F-florbetapir SUVR, we found that pMCI individuals had worse performance in both global and sub-domain cognitive assessments than sMCI at baseline, 1- and 2-year follow-up. pMCI group also had smaller bilateral amygdala, hippocampus and entorhinal, left superior and middle temporal, left posterior and caudal anterior cingulate, and larger bilateral inferior lateral ventricle volumes than sMCI at baseline. However, there was no difference in the above ROIs between the two groups at 12- and 24-month follow-up. Using univariate and multivariate logistic regression models, we found that baseline CSF t-tau levels and cognitive scores of MoCA, FAQ, and EcogSP language scores predicted progression to dementia in A+T+MCI individuals within the 2-year follow-up. Our findings suggest that these clinical and CSF biomarkers may be used to identify A+T+MCI individuals with an increased risk of future clinical progression to dementia.

Table 6: Efficacy of baseline t-tau, MoCA, FAQ, and EcogSP language showing the AUC in predicting progression in MCI.

Measure	AUC	95% CI	*P* value	Cut-off value	Sensitivity	Specificity
Baseline t-tau	0.684	0.601–0.767	<0.001*	103.85	0.729	0.624
Baseline-MoCA	0.716	0.644–0.789	<0.001*	24.50	0.374	0.953
Baseline-FAQ	0.762	0.694–0.831	<0.001*	2.50	0.734	0.644
Baseline EcogSP language	0.705	0.628–0.783	<0.001*	1.93	0.625	0.697

* Statistically significant. 95% CI: 95% Confidence interval; AUC: Area under the curve; ECogSP: Test of everyday cognition for study-partner; FAQ: Functional assessment questionnaire; MCI: Mild cognitive impairment; MoCA: Montreal cognitive assessment; t-tau: Total tau.

The current NIA-AA research framework proposes the biological definition of AD using amyloid, tau, and neurodegeneration (ATN) biomarkers to measure *in vivo* AD pathological changes. ATN biomarkers also support the identification of individuals at increased risk of disease progression.[25] In this regard, A+T+N− and A+T+N+ individuals within the AD continuum have the highest risk of disease progression. Furthermore, current intervention studies focus on amyloid and tau[26-30] which may result in neuroprotection and disease modification through linked mechanisms.[9] Therefore, in the present study, we aim to advance the current ATN literature by identifying the clinical and biomarker risk factors of dementia progression in A+T+MCI individuals within typical clinical trial periods, so as to enrich the recruitment of study populations in future clinical trials targeting amyloid and tau.

The ApoEε4 allele is a well-known genetic risk factor for AD and the ApoEε4 allele is able to predict disease progression from MCI to AD-type dementia.[31] However, the mechanism of ApoEε4 allele in increasing risk of AD remains controversial. While the ApoEε4 allele has been linked to increased Aβ plaque deposition and decreased Aβ clearance,[32,33] others have shown that the ApoEε4 allele is associated with elevated p-tau levels.[34] There is also evidence suggesting that ApoEε4 allele may increase AD risk through pathways independent of Aβ.[35] Li *et al*[36] reported that ApoEε4 allele was associated with increased cortical thickness in brain regions vulnerable to AD pathology, such as medial and inferior temporal regions in the preclinical and early MCI stage. Our study indicates that ApoEε4 allele is not a significant predictor of disease conversion among A+T+MCI individuals, which may suggest that the effect of ApoEε4 allele on AD occurs in an earlier stage of AD, before MCI. This is consistent with the findings by van Rossum *et al*[37] which showed that ApoEε4 allele was a risk factor for the development of abnormal Aβ processing but did not influence clinical progression once abnormal Aβ processing was established.

Furthermore, we found that pMCI individuals performed poorer in global cognitive assessments such as CDR-SB, ADAS-Cog, MMSE, MoCA, FAQ scores, as well as specific cognitive domains of memory, attention, executive functions, language, and processing speed compared to sMCI individuals at baseline, 1- and 2-year follow-up. Based on the differences in the ATN biomarkers between pMCI and sMCI group as described above, pMCI individuals also have greater burden of ATN. Given that recent longitudinal studies have shown a relationship between CSF AD biomarkers and disease progression,[12,38] our results further adds to the current literature by demonstrating that ATN biomarkers, which reflect AD pathophysiology, have a negative impact on cognition.

There are also discrepancies between participant's and informant's report of the patient's cognitive and activities of daily living performance based on the ECog test. At baseline, the informant-reported ECog scores are higher in the pMCI group compared to the sMCI group. However, there is no difference in the self-reported ECog scores between the two groups. This may be attributed to the phenomenon whereby participants with cognitive impairment tend to under-report their symptoms, whereas their informants tend to provide a more objective account.[39] This is in line with a prior study showing that MCI individuals report that they are performing well in financial tasks and driving when their informants report otherwise.[40] The tendency to under-estimate problems may due to reduced awareness of cognitive dysfunction (ie, anosognosia) or an inability to accurately appraise one's own cognitive abilities.[41] On the other hand, available evidence has suggested that the mixed MCI group was generally more accurate in evaluating their cognitive abilities than amnestic MCI group.[42] Given that mixed MCI group had impairments primarily in language and attention/executive functioning, it is possible they were more aware of the everyday consequences of these cognitive deficits than were those with memory deficits. The discrepancies in our result also confirmed that the participants we selected were accurately in line with the pathological characteristics of AD (amnestic MCI).

While we found significant differences in the levels of ATN biomarkers (CSF $A\beta_{1-42}$, total tau, p-tau_{181}, and mean [^{18}F] florbetapir SUVR) between pMCI and sMCI, only CSF t-tau predicts disease progression among A+T+MCI individuals, which is classified as a marker of "N," biomarkers of neurodegeneration or neural injury. As in 2018 NIA-AA research framework to investigate the AD continuum, the markers of "N" cannot be used to indicate Alzheimer pathophysiologic processes.[43] However, this conclusion partly because "N" represents both AD and non-AD pathologies.[44] Discordance was also dependent on disease stage. Indeed, our conclusion is in line with other published ADNI data of A+T+MCI. In a longitudinal observational study of brain atrophy, CSF p-tau levels, identified as "N," can predict MRI progression in patients with mild AD dementia and in cognitively normal participants.[10] And previous literatures have also suggested FDG-PET as predictors of short-term MCI-to-AD

dementia conversion, which likewise confirm the predictive utility of "N" biomarkers.[45] In our presentation, A+T+MCI participants are identified as having the typical AD pathologic, and in this case, "N" biomarkers are proven to provide much more powerful prediction of future cognitive decline. This is logical given that CSF t-tau, indicator of the intensity of neuronal injury at a given point in time, is the aspect of AD neuropathologic change that correlates most closely with clinical manifestations.

As we all know, structural MRI is the most commonly used technique to identify brain atrophies related to AD, which has been proved to have the power to predict AD dementia earlier, a few previous studies were also designed with the aim of predicting imminent conversion. Moreover, a somewhat surprising finding was that while we found differences in some of the MRI ROIs such as subcortical volume of bilateral amygdala, hippocampus, cortical volume and thickness average of bilateral entorhinal, subcortical volume of bilateral choroid plexus and inferior lateral ventricle between pMCI and sMCI at baseline, these differences are no longer seen at 12- and 24 months follow-up. This finding may suggest that the MRI ROIs do not predict disease progression in A+T+MCI individuals. One possible explanation is that the ROI method does not allow a comprehensive and objective assessment of the entire cortex and may not be sensitive enough to detect small and more diffuse changes that may arise over a short period of time. The progression to dementia may not be predicted simply by the atrophy of one separate area. Furthermore, in this work, we partitioned A+T+MCI into progressive pMCI and sMCI, based on the clinical follow-up in a 24-month follow-up (range 6–24 months at 6-month intervals). Follow-up time and the intervals inevitably had an effect on the results. And as AD participants were not included, we could not reflect the full view of the disease progression. These findings emphasize the complexity and spatial extent of the patterns of brain atrophy that characterize brain structure in A+T+MCI and that, in future works, together with advanced pattern analysis and recognition methods, are likely to provide powerful imaging markers for prediction and quantification of disease progression. This is also consistent with findings from a large meta-analysis not including ADNI data which show that baseline cognitive measures compared to brain volumetric markers are better predictors of disease conversion to dementia in MCI.[46] Unlike neuroimaging measures such as volumetric MRI and PET, cognitive measures such as FAQ remain useful in predicting disease progression even in the later stages of MCI.

There are limitations in the current study. First, the ADNI database consists of highly educated individuals who volunteered to take part in the research study focusing on AD research. Therefore, findings from this cohort may not be generalized to the rest of the population. Also, the ADNI enrolled subjects only from the United States and Canada. Therefore, it is necessary to replicate our results in larger population-based cohorts and to conduct research on the related mechanisms. Second, the longitudinal follow-up period of this study is limited to 2 years. While this is a typical clinical period, the short duration of 2 years may not be sufficient for A+T+MCI individuals to progress to dementia. Therefore, future studies should include a longer follow-up period. Third, we are not able to measure sensitivity and specificity values in this study due to the small sample sizes.

In conclusion, we identified key clinical and biomarker characteristics that distinguish pMCI and sMCI individuals. Specific CSF and cognitive measures (CSF t-tau, MoCA, FAQ, and EcogSP language scores) that predict dementia progression in A+T+MCI might be useful in early treatment decisions or stratified enrollment of this population into clinical trials.

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Conflicts of interest

None.

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