의학박사 학위논문

경도인지장애에서 치매로의 진행을 예측하는 인자

Predictive factors for progression to dementia in patients with mild cognitive impairment

2021년 2월

서울대학교 대학원

의학과 중개의학 전공

편 정 민

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이 논문을 의학박사 학위논문으로 제출함.

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Abstract

Predictive factors for progression to dementia in patients with mild cognitive impairment

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Background and purpose: The ability to predict progression from mild cognitive impairment (MCI) to dementia is increasingly important with the prospect of disease-modifying therapies. Additionally, although cholinesterase inhibitor (AChEI) was approved for Alzheimer's disease (AD) patients based on early pathologic change of AD, AChEI has been used in MCI without no strong evidence of its efficacy in MCI. Thus, we investigated prognostic ability of posterior atrophy (PA) on brain MRI and fibrinogen level in blood, and the effect of AChEI on

cognitive change in MCI with confirmed AD pathology.

Methods: In study 1, We included amyloid-positive MCI from Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, with at least one follow-up visit, and who had low cerebrospinal fluid (CSF) β-amyloid$_{1-42}$ concentration. We assessed PA and medial temporal lobe atrophy (MTA) on MRI using visual rating scales and retrospectively determined progression to dementia during the follow-up period of up to 3 years. Cox proportional hazards model was performed to analyze hazard ratios (HRs) of PA and MTA for disease progression. Additionally, subjects were divided into 4 groups according to brain atrophy pattern (no atrophy, MTA only, PA only, both MTA and PA), and HRs for disease progression were compared with the no atrophy reference group. Analyses were conducted with and without adjustment for CSF total tau (t-tau), phosphorylated tau$_{181p}$ (p-tau), and baseline demographics. Study 2 included patients with a diagnosis of MCI according to Petersen's criteria and a Clinical Dementia Rating scale (CDR) score of 0.5, and with a plasma fibrinogen level determination at baseline evaluation from the Neurocognitive Behavior Center of Seoul National University Bundang Hospital. A total subjects were divided into high fibrinogen group (high fib) and low fibrinogen group (low fib) by median value of plasma fibrinogen level. A multiple linear regression model was performed to compare cognitive test performance between groups according to vascular risk factors or *APOE* genotype. The Cox proportional hazard model was used to

analyze the hazard ratio of fibrinogen level for disease progression. In study 3, we included patients with MCI with a CDR score of 0.5, a one-year follow-up cognitive assessment, and amyloid PET performed within six months before or after the baseline cognitive assessment from the Neurocognitive Behavior Center of Seoul National University Bundang Hospital. Among the total patients, AChEI users and AChEI non-users were matched by baseline Mini-Mental State Examination (MMSE) score, age, educational level, CDR-Sum of Boxes, and amyloid PET positivity using propensity score matching. Multiple linear regression analysis was performed to assess the influence of AChEI use and amyloid PET positivity on cognitive change for one year. Logistic regression analyses were performed to evaluate the association between AChEI use and disease progression to CDR 1 at the one-year follow-up visit.

Results: In study 1, a total of 123 patients (47.7%) showed MTA and 174 patients (67.4%) showed PA. Of the total cohort, 139 cases (53.9%) progressed to dementia. PA (HR 2.244, 95% confidence interval [CI] 1.497 – 3.364) and MTA (HR 1.682, 95% CI 1.203 – 2.352) were associated with an increased risk for progression to dementia. In the analysis according to atrophy pattern, HR (95% CI) for progression was 2.998 (1.443 – 6.227) in the MTA only group, 3.126 (1.666 – 5.864) in the PA only group, 3.814 (2.045 – 7.110) in both MTA and PA group. These results remained significant after adjustment. In study 2, the high fib group (n=323) demonstrated poorer performance in

attention, executive function, and confrontation naming than the low fib (n=320) group. After adjustment for *APOE* genotype, the high fib group was associated with poor attention and executive function. After adjustment for vascular risk factors including body mass index, hypertension, diabetes mellitus, dyslipidemia, and smoking history, the high fib group showed declined attention and confrontation naming ability. High fibrinogen levels did not predict disease progression to CDR 1. In study 3, AChEI use or non-use was not associated with cognitive change for one year. Amyloid PET positivity or negativity did not change this non-association. Furthermore, progression to CDR 1 was related to low baseline MMSE score (OR 0.606, CI 0.381 - 0.873), but not with AChEI use or non-use, and not with amyloid PET result.

Conclusion: In patients with amyloid-positive MCI, PA could predict progression to dementia, independently of MTA. High plasma fibrinogen levels were associated with poor performance in attention in patients with MCI, regardless of *APOE* genotype or vascular risk factors. However, fbrinogen level could not predict disease progression to CDR 1 at one-year follow-up visit. AChEI use or non-use was not related to cognitive change at a one-year follow-up visit in patients with or without amyloid burden. In addition, AChEI use or non-use could not predict disease progression to CDR 1 at one-year follow-up visit.

Keywords: mild cognitive impairment, Alzheimer's disease, disease progression, amyloidopathy, posterior atrophy, fibrinogen, cholinesterase inhibitor
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Introduction

Mild cognitive impairment (MCI)

Mild cognitive impairment (MCI) is defined as a status with confirmed cognitive decline on objective assessments, but without dysfunction in activities of daily living.[1] The neurodegenerative causes of MCI are diverse including amyloidopathy, vascular pathology, tauopathy and alpha-synucleinopathy. As MCI progresses to dementia state, diseases are manifested as Alzheimer's disease (AD), vascular dementia (VD), Lewy-body dementia, frontotemporal dementia, and Parkinson's disease dementia according to underlying pathologies.

Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most common cause of all type of dementia accounting for approximately 60%-70%.[2] Neuropathologically, AD is characterized by extracellular deposition of amyloid-β (Aβ) and intracellular accumulation of tau protein.[3] Additionally, other pathways such as vascular pathology and neuroinflammation are also involved in the pathomechanism of AD.[4] According to the amyloid hypothesis, amyloidopathy starts decades be fore symptom manifestation, and subsequently tauopathy and finally neuronal injury with cognitive decline follow.[5]

Biomarkers for detection of pathological stages of AD include

brain imaging, cerebrospinal fluid (CSF) study, and blood. First, amyloid positron emission tomography (PET) measures accumulation of amyloid plaque, and tau PET measures accumulation of tau protein in brain. Magnetic resonance imaging (MRI) detects brain atrophy, and ^{18}F-fludeoxyglucose positron emission tomography (FDG-PET) detects decreased glucose metabolism of brain. Second, CSF study shows decreased level of $A\beta_{1-42}$, increased level of total tau (t-tau) and hyperphosphorylated tau (p-tau) protein. Third, recent studies have suggested that $A\beta_{1-42}$ and tau protein in blood could be used as a biomarker of AD, however further researches for validation are required to strengthen their clinical efficacy.[6]

Progression to AD from MCI

Substantial effort to identify prognostic factors from MCI to AD have been made. Previous studies reported that amyloidopathy confirmed by amyloid PET and CSF study,[7,8] medial temporal lobe atrophy (MTA) and posterior atrophy (PA) on brain MRI could predict disease progression to AD from MCI.[9,10] However, CSF study and PET imaging represent low accessibility due to its invasiveness and high cost, which results these markers are used mostly for research purpose. Therefore, easy-to-use and practical biomarkers for clinical field are needed.

Medical treatment in MCI

Acetylcholinesterase inhibitor (AChEI) are Food and Drug Administration (FDA)-approved symptomatic treatment for AD and include donepezil, rivastigmine, and galantamine. However, their efficacy in MCI is uncertain. According to a recent practice guideline update by Petersen et al., there is no level A evidence regarding AChEI use in MCI, and the recommendations suggest that a physician may choose not to offer AChEIs.[11] Nonetheless, according to a study with the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, 44% of the recruited patients with MCI were treated with AChEIs.[12] The lack of an approved pharmacological treatment for patients with MCI and concern about progression to dementia might lead to the use of AChEIs despite no strong evidence of their efficacy.

Therefore, predictive factors with a practical accessibility and an impact on clinical decision-making regarding treatment plan would be valuable. In this context, MRI brain imaging and laboratory tests have a great potential of biomarkers as essential diagnostic tools. Additionally, the predictability of the AChEI-use for cognitive change is directly linked to treatment strategy. This study aimed to investigate prognostic ability of posterior atrophy on MRI and serum fibrinogen and the use of AChEI for disease progression to dementia in MCI through three substudies.

Imaging biomarker- posterior atrophy on brain MRI (Study 1)

Brain MRI is one of the essential tests in AD or MCI to identify the cause of cognitive impairment. In AD, brain atrophy such as MTA and PA could be observed. MTA is one of the most well-known neurodegenerative markers,[13] and can predict progression from MCI to dementia.[9,10] In a study with MCI patients with Aβ positivity, those with MTA were more likely to progress to dementia, which indicates the predictive value of MTA in amyloid-positive MCI.[14]

Recently, an increasing number of studies have suggested that another neurodegenerative marker, PA on MRI, could also predict conversion to dementia in MCI.[10] In particular, evidence has shown that whereas MTA is related to low levels of CSF $A\beta_{1-42}$, PA is associated with high levels of CSF t-tau and p-tau; this might support a prognostic value of PA in terms of disease progression among patients with amyloid-positive MCI.[10] Therefore, the study 1 aimed to assess the predictive value of PA for progression to dementia in amyloid-positive MCI.

Blood biomarker- fibrinogen (Study 2)

Vascular pathology, neuroinflammation, and neurodegeneration are closely connected to the pathogenesis and progression of neurodegenerative disease with cognitive impairment, although none of these acts as a sole cause of neurodegenerative disease.[15,16] Vascular pathology is predominant in VD, and also in AD, where vascular pathology and the consequent immune response are considered as a key feature of the disease pathology.[17,18]

One of the important characteristics of vascular pathology is the influx of plasma proteins into the central nervous system (CNS) through the damaged blood-brain barrier (BBB).[15] Fibrinogen is a plasma protein that does not exist in CNS, and its leakage into the CNS via the BBB induces immune reactions that lead to neurodegeneration.[16] Hence, fibrinogen has been of interest as not only a marker of vascular pathology but also as an active contributor to neurodegenerative diseases such as AD, traumatic brain injury, and Parkinson's disease.[16,18,19]

Various epidemiological studies have reported significant associations between high levels of plasma fibrinogen and impaired cognition, and fibrinogen has been shown to be a predictor for dementia.[20-26] These studies were conducted mostly in community-based populations or populations with vascular risk factors such as stroke, diabetes mellitus, and chronic kidney disease. However, the role of fibrinogen in patients with MCI deserves more attention. MCI is an early state of dementia and the presence of BBB disruption

in MCI has been demonstrated in previous studies.[27] Fibrinogen as a marker of vascular pathology could indicate specific cognitive profile patterns and predict cognitive decline in patients with MCI, which could be useful in the clinical setting.

To our knowledge, there has been only one study in an MCI population that found a significant association between high fibrinogen levels and increased risk for dementia. It had a small sample size, however, and cognitive function was assessed using the Mini-Mental State Examination (MMSE) only.[28] In study 2, we aimed to investigate cognitive profiles in patients with MCI using extensive neuropsychological tests and analyze these results according to plasma fibrinogen levels in order to investigate the association between plasma fibrinogen levels and cognitive decline.

Effect of AChEI on cognitive change in MCI (Study 3)

A considerable number of studies have previously been conducted to assess the effect of AChEI treatment in patients with MCI.[29] However, participants were included based on a clinical diagnosis of MCI without AD pathology confirmation. Therefore, these study populations might have contained heterogeneous pathologies, which could have led to inconsistent results.[29,30]

As AChEIs were developed based on pathological changes in early AD, evaluation of the effect of AChEIs in patients with MCI

with AD pathology confirmed by AD biomarkers might provide useful clues to AChEI use regarding the timing of initiating therapy or the indications for treatment. In study 3, we aimed to evaluate the effect of AChEIs on cognition in patients with MCI and their interactions with amyloidopathy.

Methods

Predictability of PA on time to dementia in patients with amyloid-positive MCI (Study 1)

Subjects

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

Data used in this study were downloaded from the ADNI database on the 25th May, 2017. We included patients with late MCI who had had a baseline MRI scan, amyloid positivity on a CSF study,[31] and at least one or more follow-up visits after initial assessment. The primary outcome of this study was progression to dementia during the follow-up period of up to 3 years. Dementia was defined as probable AD according to NINCDS/ADRDA criteria.[32] A final total of 258 patients, 143 from the ADNI1 cohort and 115 from the ADNI2 cohort, were included in this study.

Diagnosis of late MCI was made according to the presence of objective memory impairment but without meeting the criteria for dementia. Namely, all subjects had a Mini Mental State Examination (MMSE) score of 24 or higher, a global Clinical Dementia Rating (CDR) score of 0.5, a CDR memory score of 0.5 or higher, and a score indicating impairment on the delayed recall of Story A of the Wechsler Memory Scale-Revised (≥16 years of education: ≤8; 8 - 15 years of education: ≤4; 0 - 7 years of education: ≤2), which is 1.5 standard deviations below the mean score of cognitively normal subjects.[33,34]

This study design was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1706/402-113).

CSF measurements and cutoffs

Baseline CSF $A\beta_{1-42}$, t-tau, and p-tau were measured centrally using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3, Ghent, Belgium; for research use-only reagents) immunoassay kit-based reagents, as described by Shaw and colleagues.[31] Qualification of the analytical performance of CSF samples from ADNI was controlled, showing within-center coefficient of variation (%CV) 95% confidence interval (CI) value (mean) of 4.0 - 6.0% (5.3%) for $A\beta_{1-42}$, 6.4 - 6.8% (6.7%) for

t-tau, and 5.5 - 18.0% (10.8%) for p-tau [14]. Inter-center %CV 95% CI ranged from 15.9 to 19.8% (17.9%) for $A\beta_{1-42}$, 9.6 - 15.2% (13.1%) for t-tau, and 11.3 - 18.2% (14.6%) for p-tau.[35] Amyloid positivity was defined as CSF $A\beta_{1-42}$ of less than 192 pg/ml.[31]

MRI

Brain MRI scans were acquired as previously described.[36] Participants in ADNI1 cohort were scanned using either a 1.5T or 3T MRI scanner. All subjects in the ADNI2 cohort were scanned using a 3T MRI scanner.

MTA scale

MTA was evaluated using a 5-point rating scale developed by Scheltens et al..[37] According to the height of the hippocampal formation and the width of the choroidal fissure and the temporal horn, atrophy was rated from 0 (no atrophy) to 4 (severe atrophy). The largest vertical height of hippocampal formation was defined as dentate gyrus, hippocampus proper, subiculum, and parahippocampal gyrus.

PA scale

PA was assessed using a 4-point rating scale developed by Koedam et al. (0 = no atrophy; 1 = mild widening of the sulci without evident volume loss of gyri; 2 = substantial widening of the sulci and volume loss of the gyri; 3 = severe end-stage atrophy).[38] The evaluated anatomical regions included the posterior cingulate sulcus, precuneus, parieto-occipital sulcus, and the cortex of the parietal lobes. MRI scans were assessed in the three different orientations by following anatomical landmarks; widening of the posterior cingulate and parieto-occipital sulcus and atrophy of the precuneus in the sagittal orientation, widening of the posterior cingulate sulcus and the sulcal dilatation in the parietal lobes in the axial orientation, and widening of the posterior cingulate sulcus and parietal lobes in the coronal orientation. In case of different rating scores between different MRI planes, the higher score was used for analysis.

Image analysis

All MRI scans were evaluated by three raters (board-certified neurologists, Young Ho Park, Hang-Rai Kim, Jeewon Suh, with 7, 5, and 4 years of experience in dementia), who were blinded to the clinical information. In case of disagreement, the three raters reviewed the MRI scans together for adjustment.

Intra-rater reliability was assessed by the re-rating of 25 randomly determined MRI scans at a separate sitting, blinded to their own prior rating. Inter-, and intra-rater reliabilities were measured by calculating the intraclass correlation coefficient.

For rating scores of both MTA and PA, scores of the right and left hemispheres for each patient were summed and its mean value was used. These scores were dichotomized as normal (no atrophy) or abnormal (atrophy). For MTA in those younger than 75 years old, a rating score of 1.5 or more was considered abnormal, in those aged 75 years or older, a score of 2 or more was considered abnormal.[39] For PA, a score of 1.5 or more was considered abnormal in all patients.[38]

For quantitative analysis, we used data downloaded from the ADNI database. Regional volumes were measured automatically by the Freesurfer image analysis suite, which is freely available for downloading (http://surfer.nmr.mgh.harvard.edu/). ADNI1 1.5T data was run with Freesurfer version 4.3, and ADNI1 3T data and ADNI2 data were run with Freesurfer version 5.1. Each scan was segmented according to an atlas defined by Freesurfer.[40] We compared volumes of hippocampus, parahippocampal cortex, entorhinal cortex, and fusiform gyrus in temporal regions as well as the superior and inferior parietal cortex, precuneus, supramarginal gyrus, and postcentral gyrus in parietal regions between groups with and without progression to

dementia, using the Mann–Whitney test or Student's t test as appropriate.

Statistical analysis

For comparison of demographic and clinical variables between groups with and without progression to dementia, we used the Pearson chi-squared test, Mann–Whitney test, or Student's t test as appropriate. We assessed the hazard ratio (HR) of MTA, PA, CSF t-tau, p-tau, baseline demographics, and neuropsychological profiles using univariate Cox regression analysis with follow-up time as a time variable and progression to dementia as a status variable. Additionally, we categorized MRI atrophy pattern into the following four groups: no atrophy, MTA only, PA only, and both MTA and PA, and the HR of each group for disease progression was calculated using univariate Cox analysis. The proportional assumption was examined by log-log survival plots.

The multivariate Cox analysis was performed to identify independent determinants of disease progression with relevant covariates. The clinically or statistically relevant covariates with a p-value < 0.2 in univariate Cox regression analysis were included. If there was more than one variable that was clinically highly correlated, we included only one of them in the model. Also, according to the

atrophy pattern, two different models were implemented. In model 1, HRs of the MTA group and PA group were analyzed with adjustment for clinically or statistically relevant covariates. In model 2, HRs of the four groups according to atrophy pattern (no atrophy, MTA only, PA only, both MTA and PA) were analyzed with adjustment for relevant covariates. Multicollinearity between the covariates was tested by calculating the variance inflation factor.[41] We used SPSS 21 (SPSS Inc., Chicago, Illinois, USA) for multicollinearity and inter- and intra-rater reliabilities analyses, and R (version. 3.3.1; http://www.R-project.org) for the remainder of the analyses. Demographic analysis was performed using wilcox.test, chisq.test, or t.test function, and Cox regression analysis was performed using the Coxph function in R with survival package version 2.41-3.

Fibrinogen levels and cognitive profile differences in patients with MCI (Study 2)

Subjects

Patients with MCI who visited the memory clinic of Seoul National University Bundang Hospital from January 2006 to June 2019 were recruited retrospectively. Patients who met the following criteria were included: 1) a diagnosis of MCI according to Petersen's criteria[1] and a CDR score of 0.5, and 2) plasma fibrinogen level determination

at baseline evaluation.

This study design was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1910/568-103).

Data collection

All patients underwent interviews regarding current health status and past medical history, physical and neurological examination, and laboratory studies at the baseline evaluation. Demographic information including age, sex, and education were obtained at the baseline evaluation. Other information, including duration of follow-up, any follow-up cognitive assessments, the number of patients with progression to CDR 1, time to progression to CDR 1, and final diagnoses was also collected.

The body mass index (BMI) was calculated [weight (kg)/length (m2)]. Information about vascular risk factors such as hypertension (HTN), diabetes mellitus (DM), dyslipidemia (DL), and history of smoking (categorized as current, ex-, and never smoker) was obtained. HTN was defined as previous use of antihypertensive medication, systolic blood pressure > 140 mmHg, or diastolic blood pressure > 90 mmHg. DM was defined as previous use of anti-diabetic medication with the diagnosis of diabetes or a fasting blood glucose > 7.0 mmol/L (> 126 mg/dL). DL was defined as

previous use of lipid-lowering medication or a total cholesterol >6.0 mmol/L (> 240 mg/dL).

The plasma fibrinogen level was collected as a measurement of interest during the baseline evaluation and was included with routine laboratory studies in our clinic. The mean time interval of fibrinogen measurement and cognitive assessment was 19.47±38.42 days. Plasma fibrinogen was measured according to clotting time (Clauss method) using STA®-Liquid Fib (Diagnostica Stago) and STA R MAX (Diagnostica Stago). The C-reactive protein (CRP) level was also collected to rule out acute inflammatory status, which could influence fibrinogen levels. Additionally, *APOE* genotype was identified by real-time PCR.

Cognitive evaluation

Global cognitive status was evaluated using the MMSE. Dementia severity was evaluated using the CDR sum of boxes (SOB) and the Global Deterioration Scale (GDS).[42] The short form of the Geriatric Depression Scale (GDpS) was used to evaluate depressive symptoms.[43] Additionally, we performed comprehensive neuropsychological tests to assess attention, verbal and visual memory, visuoconstructive function, language, and executive function. We used the Digit Span Forward and Backward tests for attention,[44] the Seoul Verbal Learning Test for verbal memory,[45] the Rey Complex Figure

Test for visual memory and visuoconstructive function,[46] the Korean version of the Boston Naming Test (BNT) for language,[47] and both the categorical and phonemic fluency of the Controlled Oral Word Association Test,[48] and the Stroop Colors test for executive function.[49] Raw scores from the MMSE, CDR SOB, GDS, and GDpS were used for statistical analysis. The scores from the extensive neuropsychological tests were converted to standardized scores (z-scores), which were adjusted for age, sex, and education.

Statistical analysis

Patients were divided into two groups according to fibrinogen level. Patients with fibrinogen levels lower than the median value of 338 mg/dL were defined as the low fibrinogen (low fib) group, and those with same or higher fibrinogen levels were defined as the high fibrinogen (high fib) group.

To compare demographic, clinical, and cognitive assessment data between groups, we used the Pearson chi-squared test for categorical variables and the Student's t-test for continuous variables.

Multiple linear regression analysis was performed to assess differences in cognitive function between groups after adjustment for *APOE* genotype or vascular risk factors (VRFs) including BMI, HTN, DM, DL, and smoking history. Based on previous study results showing that fibrinogen is associated with an increased risk of AD

and VD, which were also the two most frequent final diagnoses among subjects in our study with disease progression, we aimed to evaluate the influence of *APOE* genotype and VRFs on cognitive function. Additionally, age, sex, and education were only adjusted in the analysis of MMSE, because the scores from the other neuropsychological tests had already been adjusted when converted to z-scores. CDR SOB and GDS scores for dementia severity and GDpS scores for depressive symptoms were not adjusted for age, sex, and education.

We assessed the HRs for age, sex, education, MMSE, fibrinogen group, *APOE* genotype, BMI, HTN, DM, DL, and smoking history in the univariate Cox analysis. Follow-up duration was analyzed as a time variable and progression to CDR 1 as a status variable. The proportional assumption was examined using a log-log survival plot. Multivariate Cox regression analysis was performed to identify group differences in progression to CDR 1. Multivariate Cox analysis was implemented in two separate models. In the first model, *APOE* genotype was included as a covariate in addition to age, sex, education, MMSE, and fibrinogen group. In the second model, VRF such as BMI, HTN, DM, DL, and smoking history were included as covariates in addition to age, sex, education, MMSE score, and fibrinogen group.

Data were analyzed using SPSS 25 (IBM, Armonk, NY, USA), and statistical significance was set at $\leq$ 0.05.

Cognitive change according to AChEI use and amyloid PET in MCI (Study 3)

Subjects

A retrospective, longitudinal, and observational study was conducted at Seoul National University Bundang Hospital in the Republic of Korea. We included participants from January 2013 and August 2020 who met the following inclusion criteria: 1) a diagnosis of MCI according to Petersen's criteria[1]; 2) CDR score of 0.5 at baseline assessment; 3) patients with a one-year follow-up including a neuropsychological assessment; and 4) those who underwent amyloid PET within 6 months before or after the baseline cognitive assessment. Those who had a positive amyloid PET scan more than 6 months before the baseline cognitive assessment and those who had a negative amyloid PET scan more than 6 months after the one-year follow-up cognitive assessment were also included.

This study design was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-2006/618-109).

Data collection

Demographic information such as age, sex, educational level, and *APOE* genotype was collected from the participants. Neuropsychological assessment results at baseline and a one-year follow-up visit and amyloid PET results were obtained. Use or non-use of AChEIs during the follow-up period after baseline cognitive assessment and the types and dosages of AChEIs prescribed to each user were investigated.

Cognitive evaluation

We assessed the global cognitive status with the MMSE, dementia severity with CDR SOB, and depressive symptoms with GDpS. Additionally, extensive neuropsychological assessments were performed to evaluate attention, language, verbal and visual memory, visuoconstructive function, and frontal executive function. We used the Digit Span Test for attention, the Korean version of the BNT for language, the Seoul Verbal Learning Test for verbal memory, the RCFT for visuoconstructive function and visual memory, the categorical and phonemic fluency test of the Controlled Oral Word Association Test and the Stroop color reading test for executive function. For statistical analysis, MMSE, CDR SOB, and GDpS scores were used as raw scores. The scores for specified neuropsychological tests were converted to standardized scores (z-scores), which were adjusted for age, sex, and educational level.

Amyloid burden

Amyloid burden was evaluated by amyloid PET. [18F]Florbetaben (n = 105), [18F]Flutemetamol (n = 4), and [18F]Florbetapir (n = 2) were used as ligands. Amyloid status was dichotomized as positive (abnormal) or negative (normal) after visual assessment by one experienced nuclear medicine physician and two neurologists.

Statistical analysis

To minimize treatment selection bias and the difference in baseline characteristics between AChEI users and non-users, propensity score matching analysis was conducted. Propensity scores were calculated through logistic regression[50] with covariates such as the baseline MMSE score, age, educational level, amyloid PET positivity, and CDR SOB using the *Matchit* packages in R. AChEI users and non-users were paired 1:1 based on these propensity scores with a caliper size of 0.2.

Demographics and clinical characteristics between groups of unmatched and matched sets were compared with Student's t-test, the Mann-Whitney U test, or the Chi-squared test as appropriate. Cognitive assessment at baseline between groups of matched sets was

compared using Student's t-test or the Mann-Whitney U test.

Linear regression analysis was performed to assess the influence of AChEI use or non-use on cognitive change for one year. The independent variable was group (AChEI user vs AChEI non-user), and the dependent variable was the difference between the one-year cognitive test score and the baseline cognitive test score. The GDpS scores were reported as raw scores. For the MMSE analysis, age, sex, and educational level were adjusted. The z-scores of the remaining cognitive tests were already adjusted for age, sex, and educational level. Additionally, the multiple linear regression analysis included the amyloid PET scan result as a covariate to evaluate the effect of amyloid burden on the interaction between AChEI use/non-use and cognitive change for one year.

Univariate and multivariate logistic regression analyses were performed to investigate the associations among AChEI use/non-use, amyloid burden, and disease progression to CDR1 at a one-year follow-up visit.

All statistical analysis was performed using R (version 4.0.0). Statistical significance was set at <0.05.

Results

Predictability of PA on time to dementia in patients with amyloid-positive MCI (Study 1)

A total of 258 patients participated in the study. The median age of patients was 74.1 years, and 101 (39.1%) were female. A total of 176 patients (68.2%) had at least one *APOE* ε4 allele. Of the total cohort, 123 patients (47.7%) showed MTA and 174 patients (67.4%) showed PA. Dividing patients according to atrophy pattern, we identified 51 patients (19.8%) with no atrophy, 33 patients (12.8%) with MTA only, 84 patients (32.6%) with PA only, and 90 patients (34.9%) with both MTA and PA. During the follow-up period (median, 24 months), 139 patients (53.9%) progressed to dementia, and 119 patients had not. Demographic, cognitive, and biomarker characteristics according to progression to dementia, categorized as stable MCI and progressive MCI, are summarized in Table 1. Patients with disease progression to dementia had poorer cognitive performances at baseline, higher levels of CSF t-tau and CSF p-tau, and more frequent MTA and PA compared with those without progression. The inter-rater reliability for MTA (0.84 – 0.87) and PA (0.70 – 0.87) was good. The intra-rater reliability for MTA (0.83 – 0.98) was excellent and for PA (0.73 – 0.98) was good (Additional file 2: Table S2). The volumes of hippocampus, entorhinal cortex, fusiform gyrus, superior and inferior

parietal cortex, precuneus, and supramarginal gyrus were significantly decreased in progressive MCI as compared to stable MCI

Table 1. Baseline characteristics of the study sample (study 1)

	All (n = 258)	Stable MCI (n = 119)	Progressive MCI (n = 139)	*p*-value†
Age, years	74.1 (69.5 - 78.5)	74.4 (69.1 - 78.2)	73.6 (69.8 - 78.7)	> 0.999
Female, n (%)	101 (39.1)	40 (33.6)	61 (43.9)	0.119
Education, years	16 (14 - 18)	16 (14 - 18)	16 (14 - 18)	0.469
APOE ε4 carrier, n (%)	176 (68.2)	78 (65.6)	98 (70.5)	0.473
Cognition				
MMSE	27 (25 - 29)	28 (26 - 29)	26 (25 - 28)	< 0.001
CDR SOB	1.5 (1.0 - 2.5)	1.5 (1.0 - 2.0)	2.0 (1.0 - 2.5)	< 0.001
ADAS-cog 11	11.8 (9.0 - 15.7)	10.7 (7.2 - 13.2)	13.0 (10.8 - 16.2)	< 0.001
CSF markers				
$A\beta_{1-42}$, mean ± SD, pg/mL	136.1 ± 25.7	136.7 ± 27.2	133.7 ± 25.0	0.345
CSF t-tau, pg/mL*	104.0 (77.0 - 148.5	91.0 (68.0 - 133.0	113.0 (84.0 - 153.0)	0.006

	)	)		
CSF p-tau, pg/mL**	41.0 (31.0 - 58.0)	37.0 (27.0 - 51.0)	45.0 (36.0 - 64.0)	< 0.001
MRI				
Tesla, n (%)				0.714
1.5	143 (55.4)	64 (53.8)	79 (56.8)	
3.0	115 (44.6)	55 (46.2)	60 (43.2)	
MTA, n (%)	123 (47.7)	47 (39.5)	76 (54.7)	0.021
PA, n (%)	174 (67.4)	65 (54.6)	109 (78.4)	< 0.001
Atrophy pattern, n (%)				< 0.001
No atrophy	51 (19.8)	39 (32.8)	12 (8.6)	
MTA only	33 (12.8)	15 (12.6)	18 (13.0)	
PA only	84 (32.6)	33 (27.7)	51 (36.7)	
Both MTA and PA	90 (34.9)	32 (26.9)	58 (41.7)	

Data are presented as the median (interquartile range) unless otherwise specified.

*Data for 7 subjects were not available.

**Data for 1 subject were not available.

† Stable MCI vs. progressive MCI

Aβ, β-amyloid; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; CDR SOB, Clinical Dementia Rating Sum of Boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MTA, medial temporal lobe atrophy; PA, posterior atrophy; p-tau, tau phosphorylated at threonine 181; SD, standard deviation; t-tau, total tau

In the univariate Cox regression analysis, presence of MTA and PA showed significantly increased HR (95% CI) of progression to dementia with a value of 1.682 (1.203 - 2.352) and 2.244 (1.497 - 3.364), respectively (Fig. 1). In the analysis according to MRI atrophy pattern, patients with only MTA, only PA, and both MTA and PA were associated with a higher risk for disease progression compared with those with no atrophy (Table 2). Higher levels of CSF t-tau and CSF p-tau were related with more disease progression. Baseline cognitive performances with lower MMSE scores, higher CDR SOB, and higher Alzheimer's Disease Assessment Scale-cognitive subscale 11 (ADAS-cog 11) scores were also associated with progression to dementia. The proportional assumption was satisfied for MTA and PA based on log-log survival plots.

Multivariate Cox analysis included clinically (age, sex) and statistically relevant variables (education duration, *APOE* ε4 allele,

ADAS-cog 11, CDR SOB, and CSF p-tau) (Table 2). Although MMSE and CSF t-tau were statistically relevant and variance inflation factors were less than 1.719 for all variables, indicating a low degree of collinearity, we excluded them from the multivariate Cox analysis, because they were clinically highly correlated with ADAS-cog 11 and CSF p-tau, respectively. The adjusted covariates did not alter the significance of the HRs (95% CI) of MTA [1.424 (0.997 - 2.034)] or PA [1.895 (1.239 - 2.897)]. Moreover, the HR of groups with only MTA, only PA, and both MTA and PA remained significant. Notably, there was little difference between the HRs of MTA only, PA only, and both MTA and PA. On the contrary, the significant relationships between CSF p-tau and disease progression disappeared after adjustment with other covariates.

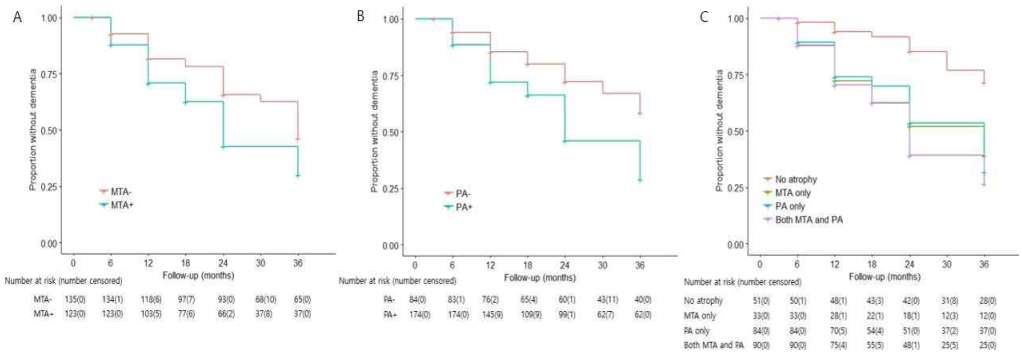

Figure. 1 Cox proportional hazards model for progression to dementia in amyloid-positive mild cognitive impairment patients according to

brain atrophy on MRI. (Study 1) PA (A), MTA (B) and atrophy pattern (no atrophy, MTA only, PA only, both MTA and PA) (C).

MTA, medial temporal lobe atrophy; PA, posterior atrophy

Table 2. Univariate and multivariate Cox regression analysis (study 1)

	Univariate HR (95% CI)	Multivariate	
		Model 1 HR (95% CI)	Model 2 HR (95% CI)
Age	0.999 (0.976 - 1.022)	0.996 (0.970 - 1.023)	0.998 (0.972 - 1.025)
Female	1.266 (0.906 - 1.770)	1.152 (0.797 - 1.665)	1.162 (0.8031 - 1.682)
Education	0.961 (0.907 - 1.019)	0.954 (0.900 - 1.011)	0.961 (0.906 - 1.020)
APOE ε4 carrier	1.290 (0.896 - 1.858)	0.996 (0.674 - 1.470)	1.031 (0.700 - 1.520)
Cognition			
MMSE	0.821 (0.748 - 0.901)[b]	NI	NI
CDR SOB	1.593 (1.347 - 1.883)[b]	1.526 (1.276 - 1.824)[b]	1.531 (1.279 - 1.832)[b]
ADAS-cog 11	1.118 (1.080 - 1.157)[b]	1.101 (1.061 - 1.144)[b]	1.104 (1.063 - 1.147)[b]
CSF			

markers			
CSF t-tau*	1.003 (1.000 - 1.006)[a]	NI	NI
CSF p-tau**	1.012 (1.006 - 1.019)[b]	1.006 (1.000 - 1.013)	1.006 (1.000 - 1.013)
MRI			
MTA	1.682 (1.203 - 2.352)[a]	1.424 (0.997 - 2.034)[a]	NI
PA	2.244 (1.497 - 3.364)[b]	1.895 (1.239 - 2.897)[b]	NI
Atrophy pattern			
No atrophy	Reference	NI	Reference
MTA only	2.998 (1.443 - 6.227)[a]	NI	3.178 (1.520 - 6.645)[b]
PA only	3.126 (1.666 - 5.864)[b]	NI	3.209 (1.693 - 6.080)[b]
Both MTA and PA	3.814 (2.045 - 7.110)[b]	NI	3.598 (1.909 - 6.783)[b]

*Data for 7 subjects were not available.

**Data for 1 subject were not available.

[a]$p < 0.05$, [b]$p < 0.001$

ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; CDR SOB, Clinical Dementia Rating Sum of Boxes; CI, confidence interval; HR, hazard ratio; MMSE, Mini-Mental State Examination; MTA, medial temporal lobe atrophy; PA, posterior atrophy; p-tau, tau

phosphorylated at threonine 181; t-tau, total tau; NI, not included
Model 1: adjusted for MTA, PA, age, sex, education, *APOE* ε4 carrier, ADAS-cog 11, CDR SOB, and CSF p-tau.
Model 2: adjusted for MRI atrophy pattern (no atrophy, MTA only, PA only, both MTA and PA), age, sex, education, *APOE* ε4 carrier, ADAS-cog 11, CDR SOB, and CSF p-tau.

Fibrinogen levels and cognitive profile differences in patients with MCI (Study 2)

A total of 643 patients were included in this study. The mean age of the patients was 73.6 years, and 419 (65.2%) were female. The low fib group contained 320 patients, and the high fib group contained 323 patients. Table 3 shows demographic and clinical data according to groups. The high fib group tended to be older and contained more female patients than the low fib group. The high fib group had higher levels of CRP than the low fib group, although the CRP levels of both groups were in the normal range without any sign of inflammatory reaction. There were no differences in VRFs such as BMI, HTN, DM, DL, or smoking history between groups.

The mean follow-up duration of all 643 patients was 36.3 months and there was no difference between groups. A total of 325 patients were followed up with cognitive tests. Among them, 128 patients (39.4%) progressed to CDR 1, and the mean time to

progression was 41.5 months, with no difference between groups. There were also no differences between groups with regards to final diagnoses of all patients including MCI, AD, VD, dementia with Lewy bodies, frontotemporal lobe degeneration, corticobasal degeneration, idiopathic Parkinson's disease, and progressive supranuclear palsy.

Table 3. Baseline characteristics of the study sample (study 2)

	All (n = 643)	Low Fib (n = 320)	High Fib (n = 323)	*p*-value
Age, years	73.6 ± 7.6	70.9 ± 9.0	73.6 ± 8.0	<0.001
Female	419 (65.2)	191 (59.7)	228 (70.6)	0.004
Education, years	11.8 ± 4.7	12.0 ± 4.5	11.4 ± 5.0	0.103
APOE ε4 carrier[a]	168 (28.8)	89 (30.6)	79 (27.1)	0.362
Fibrinogen	348.6 ± 67.9	296.9 ± 29.3	399.2 ± 61.4	<0.001
CRP	0.13 ± 0.25	0.06 ± 0.11	0.20 ± 0.30	<0.001
BMI	23.1 ± 3.2	23.2 ± 2.9	23.5 ± 3.2	0.312
HTN	342 (53.2)	163 (50.9)	179 (55.4)	0.269
DM	149 (23.2)	94 (29.4)	111 (34.4)	0.177
DL	205 (31.9)	30 (9.4)	29 (9.0)	0.892

Smoking history				0.390
Current smoker	20 (3.1)	12 (3.8)	8 (2.5)	
Ex-smoker	83 (12.9)	44 (13.8)	39 (12.1)	
Never smoker	540 (84.0)	264 (82.5)	276 (85.4)	
Follow-up with cognitive tests	325 (50.5)	166 (51.9)	159 (49.2)	0.528
Follow-up duration of those with cognitive test, months	58.72 ± 35.56	56.41 ± 35.18	60.93 ± 35.89	0.252
Progression to CDR1	128 (39.4)	62 (37.3)	66 (41.5)	0.496
Time to progression (CDR1), months	41.5 ± 31.8	43.3 ± 30.3	39.7 ± 33.2	0.523
Final diagnosis				0.815
Mild cognitive impairment	511 (79.4)	256 (80.0)	255 (78.9)	
Alzheimer's disease	104 (16.1)	49 (15.3)	55 (17.0)	
Vascular dementia	12 (1.8)	6 (1.9)	6 (1.9)	
Dementia with	6 (0.9)	3 (0.9)	3 (0.9)	

Lewy bodies				
Frontotemporal lobe degeneration	3 (0.4)	2 (0.6)	1 (0.3)	
Corticobasal degeneration	1 (0.1)	1 (0.3)	0 (0.0)	
Idiopathic Parkinson's disease	5 (0.7)	2 (0.6)	3 (0.9)	
Progressive supranuclear palsy	1 (0.1)	1 (0.3)	0 (0.0)	

Data are presented as number (%) or mean ± standard deviation

[a] Data for 60 patients were not available.

BMI, body mass index; CDR, clinical dementia rating; CRP, C-reactive protein; DL, dyslipidemia; DM, diabetes mellitus; HTN, hypertension

The cognitive assessment according to groups is shown in Table 4. The high fib group demonstrated poorer performance on the Digit Span Forward and Backward tests, BNT, and Stroop Colors test. Additionally, the high fib group showed poorer scores in the categorical fluency test, although this difference was not significant. There were no differences in performance on the rest of neuropsychological tests between groups.

Table 4. Cognitive assessment according to groups (study 2)

	All (n = 643)	Low Fib (n = 320)	High Fib (n = 323)	*p*-value
MMSE	26.0 ± 3.2	26.2 ± 3.2	25.8 ± 3.2	0.177
CDR SOB	1.4 ± 1.0	1.4 ± 1.0	1.5 ± 0.99	0.323
GDS	3.0 ± 0.9	2.9 ± 0.6	3.1 ± 1.2	0.114
Geriatric Depression Scale	5.8 ± 3.9	5.7 ± 3.8	5.9 ± 4.0	0.458
Digit Span Forward test	-0.08 ± 0.90	0.00 ± 0.90	-0.17 ± 0.89	0.017
Digit Span Backward test	-0.17 ± 0.84	-0.09 ± 0.85	-0.25 ± 0.83	0.019
Korean Boston Naming Test	-0.54 ± 0.87	-0.45 ± 0.91	-0.62 ± 0.83	0.020
SVLT Immediate recall	-0.40 ± 0.88	-0.41 ± 0.86	-0.39 ± 0.90	0.741
SVLT Delayed recall	-0.65 ± 0.85	-0.68 ± 0.84	-0.62 ± 0.87	0.401
SVLT Recognition	-0.36 ± 0.85	-0.39 ± 0.85	-0.34 ± 0.85	0.481
RCFT Copy	-0.35 ± 0.87	-0.33 ± 0.86	-0.38 ± 0.88	0.485
RCFT Delayed recall	-0.72 ± 0.74	-0.71 ± 0.75	-0.74 ± 0.74	0.554
RCFT Recognition	-0.34 ± 0.94	-0.35 ± 0.92	-0.34 ± 0.96	0.944
Categorical	-0.48 ± 0.81	-0.42 ± 0.82	-0.54 ± 0.79	0.063

fluency				
Phonemic fluency	-0.46 ± 0.90	-0.41 ± 0.85	-0.43 ± 0.86	0.811
Stroop Colors test	-0.46 ± 0.90	-0.36 ± 0.93	-0.56 ± 0.85	0.006

Data are presented as mean ± standard deviation.

CDR SOB, Clinical Dementia Rating Sum of Boxes; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test.

Multivariate linear regression analysis was performed to evaluate influence of groups on cognitive function (Table 5). After adjustment for *APOE* genotype the high fib group showed significantly poorer scores in the Digit Span Backward test and the Stroop Colors test. The high fib group demonstrated poorer performance in the Digit Span Forward test and the categorical fluency test without statistical significance. After adjustment for VRFs including BMI, HTN, DM, DL, and smoking history, the high fib group presented significantly poorer scores in the Digit Span Backward test and the BNT. The high fib group showed poorer performance in the Digit Span Forward test without statistical significance.

Table 5. Multivariate linear regression analysis of cognitive assessment by group (study 2)

The dependent variable was the cognitive assessment score. The indepedent variable was the group (low fib vs high fib). *APOE* genotype or vascular risk factors (VRF) were adjusted retrospectively. Age, sex, and education were also adjusted in the MMSE analysis. β values (standard error, SE) of the dependent variable are presented by group.

	+*APOE* ε4	+VRF
Cognitive assessment	B (SE), *p*-value	B (SE), *p*-value
MMSE[§]	0.040 (0.234), 0.863	0.019 (0.246), 0.940
CDR SOB	0.050 (0.083), 0.600	0.088 (0.088), 0.318
GDS	0.132 (0.084), 0.116	0.147 (0.090), 0.105
Geriatric Depression Scale	0.056 (0.331), 0.866	0.067 (0.343), 0.844
Digit Span Forward test	-0.146 (0.076), 0.056	-0.141 (0.080), 0.080
Digit Span Backward test	-0.169 (0.72), 0.018	-0.152 (0.074), 0.042
Korean Boston Naming Test	-0.162 (0.75), 0.310	-0.156 (0.076), 0.042
SVLT Immediate recall	0.011 (0.075), 0.883	-0.034 (0.078), 0.664
SVLT Delayed recall	0.054 (0.072), 0.455	0.026 (0.076), 0.729
SVLT Recognition	0.029 (0.072), 0.688	0.020 (0.077), 0.800

RCFT Copy	-0.062 (0.074), 0.400	0.001 (0.078), 0.990
RCFT Delayed recall	-0.052 (0.064), 0.413	-0.056 (0.066), 0.394
RCFT Recognition	-0.003 (0.082), 0.972	-0.011 (0.084), 0.894
Categorical fluency	-0.126 (0.069), 0.070	-0.108 (0.072), 0.134
Phonemic fluency	-0.037 (0.073), 0.608	0.000 (0.076), 0.997
Stroop Colors test	-0.197 (0.077), 0.011	-0.147 (0.078), 0.590

[§] adjusted for age, sex, and education

CDR SOB, Clinical Dementia Rating Sum of Boxes; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test.

VRFs: body mass index, hypertension, diabetes mellitus, dyslipidemia, and smoking history

In the univariate Cox analysis, old age, low education level, and poor MMSE performance were associated with increased risk for progression to CDR 1 with HRs (95% CI) of 1.052 (1.020 – 1.085), 0.954 (0.921 – 0.988), and 0.847 (0.805 – 0.891), respectively (Table 6). In the multivariate Cox analysis for *APOE* genotype, only poor MMSE score was associated with increased risk (HR 0.857, 95% CI 0.807 – 0.910), and in the analysis of VRFs, poor MMSE score and old

age were associated with increased risk for disease progression (HR 0.848, 95% CI 0.792 – 0.908 and HR 1.054, 95% CI 1.017 – 1.092). Neither the univariate nor the multivariate Cox analysis of disease progression by fibrinogen level group showed a significant association.

Table 6. Cox proportional hazard model for progression to CDR1 in patient with mild cognitive impairment (study 2)

	Univariate	Multivariate	
	HR (95% CI)	*APOE* ε4 HR (95% CI)	VRF HR (95% CI)
Age	1.052 (1.020 – 1.085)*	1.025 (0.988 – 1.063)	1.054 (1.017 – 1.092)*
Female	1.177 (0.823 – 1.683)	0.937 (0.600 – 1.463)	1.351 (0.773 – 2.359)
Education	0.954 (0.921 – 0.988)*	0.992 (0.948 – 1.037)	1.007 (0.961 – 1.056)
MMSE	0.847 (0.805 – 0.891)*	0.857 (0.807 – 0.910)*	0.848 (0.792 – 0.908)*
Fibrinogen	1.057 (0.743 – 1.505)	1.082 (0.748 – 1.567)	0.973 (0.656 – 1.444)
APOE ε4 carrier	0.739 (0.514 – 1.064)	0.777 (0.507 – 1.191)	NI
BMI	0.949 (0.890 – 1.012)	NI	0.956 (0.897 – 1.019)
HTN	0.792 (0.552 – 1.136)	NI	0.725 (0.472 – 1.116)

DM	1.076 (0.727 - 1.592)	NI	1.126 (0.729 - 1.739)
DL	1.051 (0.722 - 1.532)	NI	0.773 (0.492 - 1.215)
Current smoker	1.172 (0.698 - 1.969)	NI	1.261 (0.398 - 3.992)
Ex-smoker	0.990 (0.432 - 2.266)	NI	0.718 (0.343 - 1.500)
Never smoker	Reference	NI	Reference

*$p < 0.05$

BMI, body mass index; DL, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; MMSE, Mini-Mental State Examination; NI, not included; VRF, vascular risk factors

VRFs: BMI, HTN, DM, DL, and smoking history

Cognitive change according to AChEI use and amyloid PET in MCI (Study 3)

The total cohort was 60.3% female with a mean age of 71.1 years. Before propensity score matching, 73 patients were AChEI users, and 38 patients were AChEI non-users. AChEI users had significantly lower educational levels, lower baseline MMSE scores, higher disease severity with higher CDR SOB scores, and higher

amyloid burden with amyloid PET positivity than AChEI non-users. The propensity score-matched cohort comprised 25 AChEI users and 25 AChEI non-users, and the imbalance in the covariates including the educational level, baseline MMSE score, CDR SOB score, and amyloid PET positivity was alleviated. The covariate differences between groups before and after matching are shown in Table 1. Comparing the baseline cognitive function between the groups in the matched cohort, there was no significant difference (Table 7).

Table 7. Baseline characteristics of the study sample before and after propensity score matching (study 3)

	Before matching		p-value	After matching		p-value
	AChEI user (n = 73)	AChEI non-user (n = 38)		AChEI user (n = 25)	AChEI non-user (n = 25)	
Age, years	70.8 ± 8.7	71.6 ± 7.5	0.608	71.0 ± 8.8	70.7 ± 8.2	0.908
Female	45 (61.6)	22 (57.9)	0.427	15 (60.0)	15 (60.0)	1.000
Education, years	11.4 ± 4.7	13.2 ± 3.8	0.045	12 (9 - 16)	14 (10 - 16)	0.889
Amyloid PET	53 (72.6)	17 (44.7)	0.004	14 (56.0)	14 (56.0)	1.000

positivity						
Baseline MMSE score	23.4 ± 2.9	26.3 ± 2.3	0.000	25.0 (24.0 - 27.0)	26.0 (24.0 - 27.0)	0.709
CDR SOB score	2.5 ± 1.1	1.4 ± 0.8	0.000	1.5 (1.0 - 3.0)	1.5 (1.0 - 2.0)	0.738
APOE ε4 carrier*	33 (62.3)	11 (42.3)	0.076	15 (60.0)	5 (31.2)	0.012
Cholinesterase inhibitor						
Donepezil	70 (95.9)			24 (0.96)		
Rivastigmine	3 (4.1)			1 (0.04)		

Data are presented as the mean ± standard deviation, median (interquartile range), or n (%).

CDR SOB, Clinical Dementia Rating Sum of Boxes; AChEI, Cholinesterase inhibitor; MMSE, Mini-Mental State Examination; PET, Positron emission tomography

*There were 35 missing values among 111 patients from the unmatched cohort and 15 missing values among 50 patients from the matched cohort.

Table 8. Comparison of cognitive function at baseline between AChEI users and non-users (study 3)

	AChEI user (n = 25)	AChEI non-user (n = 25)	*p*-value
Digit Span Forward Test	0.02 ± 0.84	-0.29 ± 0.81	0.223
Digit Span Backward Test	-0.55 (-0.91 - 0.26)	-0.64 (-1.14 - -0.15)	0.219
Korean Boston Naming Test	-0.76 (-1.28 - 0.55)	-0.75 (-1.05 - 0.17)	0.854
SVLT Immediate recall	-1.03 (-1.41 - -0.50)	-1.26 (-1.35 - -1.06)	0.503
SVLT Delayed recall	-1.45 (-1.45 - -1.24)	-1.32 (-1.45 - -0.99)	0.394
SVLT Recognition	-1.15 (-1.45 - -0.42)	-1.12 (-1.43 - -0.49)	0.611
RCFT Copy	-1.06 (-1.44 - -0.37)	-0.96 (-1.43 - 0.15)	0.930
RCFT Delayed recall	-1.36 (-1.44 - -1.07)	-1.14 (-1.43 - -0.76)	0.154
RCFT Recognition	-1.04 (-1.40 - -0.65)	-0.45 (-1.42 - -0.03)	0.214
Categorical fluency	-0.80 (-1.04 - -0.28)	-0.54 (-1.25 - -0.33)	0.808
Phonemic fluency	-0.87 (-1.14 - 0.25)	-0.84 (-1.22 - 0.26)	0.340
Stroop Colors Test	-0.50 (-1.32 - 0.27)	-0.84 (-1.44 - 0.20)	0.340
Geriatric Depression	4.00 (2.00 - 6.00)	5.00 (1.00 - 8.00)	0.792

Scale			

Data are presented as the mean ± standard deviation or median (interquartile range). Raw scores were used for the GDpS, and z-scores were used for the rest of the neuropsychological tests. SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test.

Univariate linear regression analysis was performed to evaluate the effect of AChEIs on cognitive change at a one-year follow-up visit. AChEI use was not significantly associated with cognitive change at one year. Adding the amyloid PET results as a covariate, multivariate linear regression analysis was performed to assess the influence of amyloid burden on cognitive change. Amyloid PET positivity did not alter the non-association between AChEI use and cognitive change (Table 9).

Table 9. Change in cognitive function after one year according to group and association with amyloid burden as analyzed by linear regression analysis (study 3)

The dependent variable was the change in cognitive test scores over one year. The independent variable was the group (AChEI user vs AChEI non-user). The amyloid PET result was adjusted. Age, sex, and educational level were also adjusted in the MMSE analysis. β values (standard error, SE) of the dependent variable are

presented by group.		
Change in	B (SE), p-value	B (SE), p-value Including amyloid PET result
MMSE[§]	0.486 (0.720), 0.503	0.488 (0.718), 0.499
CDR SOB	-0.460 (0.367), 0.217	-0.460 (0.371), 0.221
Geriatric Depression Scale	-0.810 (1.074), 0.455	-0.821 (1.084), 0.453
Digit Span Forward Test	-0.024 (0.198), 0.901	-0.015 (0.199), 0.938
Digit Span Backward Test	0.004 (0.233), 0.985	0.030 (0.227), 0.894
Korean Boston Naming Test	0.088 (0.221), 0.692	0.088 (0.223), 0.694
SVLT Immediate recall	0.024 (0.171), 0.887	0.024 (0.173), 0.888
SVLT Delayed recall	-0.162 (0.127), 0.208	-0.162 (0.127), 0.210
SVLT Recognition	0.136 (0.206), 0.511	0.136 (0.207), 0.514
RCFT Copy	0.110 (0.235), 0.642	0.110 (0.236), 0.644
RCFT Delayed recall	-0.119 (0.127), 0.355	-0.116 (0.128), 0.371
RCFT Recognition	0.385 (0.284), 0.183	0.378 (0.288), 0.198
Categorical fluency	0.215 (0.161), 0.189	0.215 (0.161), 0.189

Phonemic fluency	-0.132 (0.209), 0.530	-0.132 (0.196), 0.503
Stroop Colors Test	0.153 (0.174), 0.384	0.153 (0.174), 0.382

Univariate and multivariate logistic regression analysis showed that AChEI use was not related to disease progression to CDR1 at the one-year follow-up visit. A low MMSE score at baseline could predict progression to CDR1 in the univariate and multivariate analyses (Table 10).

Table 10. Predictors of progression to CDR1 at one-year follow-up using logistic regression analysis (study 3)

	Univariate OR (95% CI), *p*-value	Multivariate OR (95% CI), *p*-value
Age	1.018 (0.933 - 1.115), 0.685	1.030 (0.934 - 1.146), 0.549
Female	2.739 (0.577 - 19.913), 0.242	2.089 (0.314 - 1.805), 0.455
Education	0.929 (0.784 - 1.108), 0.395	1.081 (0.885 - 1.357), 0.453
Amyloid PET positivity	1.727 (0.397 - 9.072), 0.479	3.925 (0.676 - 34.315), 0.157
MMSE at baseline	0.662 (0.451 - 0.895),	0.606 (0.381 - 0.873),

	0.015	0.015
AChEI use	1.312 (0.305 - 5.975), 0.713	1.120 (0.204 - 6.238), 0.892

AChEI, Cholinesterase inhibitor; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio; PET, Positron emission tomography

Discussion

Predictability of PA on time to dementia in patients with amyloid-positive MCI (Study 1)

The ability to predict progression from MCI to dementia is increasingly important with the prospect of disease-modifying therapies. This study demonstrated that patients with amyloid-positive MCI with PA or MTA are more likely to progress to dementia. Furthermore, patients with amyloid-positive MCI with PA only (in the absence of MTA) also showed an increased risk for disease progression. This indicates that PA, as well as MTA, is a predictive marker of conversion from amyloid-positive MCI to dementia.

To understand the pathophysiology of AD, considerable effort has been made to identify AD-related focal regions or functional connectivity between regions in brain.[51-54] According to pathological staging by Braak and Braak, the neurofibrillary changes (tau pathology) start from the medial temporal lobe and spread to neocortical association areas.[3] Many neuroimaging studies have demonstrated these pathological changes, showing low glucose metabolism and cortical atrophy, most prominently in the medial temporal lobe and parietal lobe, including the bilateral precuneus, posterior cingulate cortex, and angular gyrus.[51,54,55] MTA within these regions is widely recognized as an imaging marker of AD.[37]

Additionally, the parietal lobe has been highlighted as an area involved in the pathological changes and dysfunction in AD.[56]

The parietal cortex is originally known for its visuospatial and sensorimotor functions.[57] However, the parietal cortex is also involved in other functions, such as episodic memory retrieval.[57,58] Notably, episodic memory retrieval impairment is known as a symptom of AD. Functional MRI (fMRI) studies with memory-related tasks have revealed that parietal cortex, especially the precuneus and superior and inferior parietal lobules, are involved in memory retrieval.[59-61] Furthermore, resting-state fMRI studies have revealed that patients with MCI display lower levels of neuronal activity in the posterior cingulate cortex, precuneus, and inferior parietal lobe (components of default mode network) compared with healthy controls.[62,63] Concerning cortical connectivity, these regions comprise the "posterior medial network" (PM network), along with retrosplenial cortex and parahippocampal cortex.[64] The PM network and anterior temporal network are two largely segregated pathways with different anatomical regions and different memory-guided behaviors, and were proposed by Ranganath and Ritchey.[64] The PM network is involved in episodic memory, spatial navigation, and scene perception. Dominant disruption of this network has been observed in patients with AD compared with healthy participants and patients with other types of dementia.[51,52,64]

Systematic assessment of PA using a visual rating scale was suggested by Koedam and colleagues.[38] This visual rating scale used to rate MRI images for PA within the posterior cingulate gyrus, precuneus, and parietal lobe, is simple, easily implemented in clinical settings, and has a good discrimination ability between healthy individuals and patients with AD.[38] The visual rating scale has been validated using voxel-based morphometry (VBM), with good reliability.[65] Furthermore, in a study with patients with pathologically proven definite AD, 30% of patients showed only PA without MTA, which indicates that PA could be used as an independent imaging marker of AD.[66]

From the perspective of cognitive reserve, MCI patients with both MTA and PA are expected to progress more rapidly to dementia than patients with MTA only or patients with PA only.[67] However, progression rates were not different between patients with both MTA and PA, patients with MTA only, and patients with PA only in our study. Similar results have been reported regarding clinical progression of patients with AD.[68,69] In those studies, which grouped patients with AD into 3 subtypes according to cortical atrophy patterns, patients with diffuse atrophy did not show more rapid progression than patients with medial temporal dominant atrophy or parietal dominant atrophy. Rather, patients with parietal dominant atrophy showed faster progression rate.[68,69] Although we do not know the reason, MTA and

PA might not have additive effects on clinical progression in patients with amyloid-positive MCI.

With respect to VBM analysis in previous studies with patients with MCI, gray matter differences between patients with progressive and stable MCI were assessed using two-sided *t*-tests in early studies.[70] However, the two-sided *t*-tests discard information about varying lengths of follow-up times among patients. To overcome this problem, time-to-event statistical methods were used in VBM analysis of patients with MCI.[71] These studies revealed that the patients with progressive MCI showed volume loss in the medial temporal lobes as well as temporoparietal cortex and frontal lobes compared to patients with stable MCI.[70-72] A recent study, which used a VBM survival analysis and assessed the effects of amyloid deposition on progression to dementia in patients with MCI, found that the pattern of decreased gray matter volume that was predictive of progression was similar in amyloid-positive and amyloid-negative patients.[72] Although our study demonstrated the usefulness of visually assessed PA for predicting progression to dementia in patients with amyloid-positive MCI, visually assessed PA might also be useful in patients with amyloid-negative MCI. In our previous study of patients with MCI without information about amyloid positivity, visual rating of PA had predictive value for progression to dementia.[73]

Notably, our population showed a relatively large proportion of *APOE* ε4 carriers (62%). This might be due to characteristics of our amyloid-positive population. Other studies with amyloid-positive MCI also reported a large percentage of *APOE* ε4 carriers.[74,75] A considerably higher prevalence of amyloid-positivity has been previously reported among *APOE* ε4 carriers compared to *APOE* ε4 non-carriers.[76] The relationship between *APOE* ε4 and amyloid-positivity has been investigated extensively for its important pathological role and contributing risk to AD. *APOE* ε4 is known to increase AD risk by decreasing Aβ clearance and promoting Aβ aggregation.[77] Apolipoprotein E4 has lower affinity to Aβ than apolipoprotein E3, thus showing inefficient removal of Aβ across the blood - brain barrier and increased oligomerization of Aβ.[78-80] This aspect could support the large proportion of *APOE* ε4 carrier of our amyloid-positive MCI.

The significant association found between increased CSF p-tau levels and disease progression in our study is consistent with previous studies.[81] However, this significance disappeared in multivariate analysis, contrary to PA or MTA. This could indicate that brain atrophy might correlate more strongly with clinical progression than CSF biomarkers. Several studies have shown similar correlations between MRI, CSF, and cognitive performance.[82,83] One possible explanation for the stronger relationship of brain atrophy with progression (compared to the relationship of CSF biomarkers with

progression) is that MRI may be a more stable biomarker for neuronal injury than CSF tau proteins, which can be influenced by diurnal variation and transient brain injury.[82,83] Otherwise, disease progression with brain atrophy could be affected by factors other than tauopathy, such as aging, traumatic brain injury, toxic factors, and vascular factors.[84-87]

There are some limitations to our study that should be noticed. First, we defined amyloid positivity by CSF $A\beta_{1-42}$ levels only, and did not include population with positive amyloid PET. This may have led to a selection bias. However, several studies have shown there to be a good agreement between CSF $A\beta_{1-42}$ levels and amyloid PET, which could minimize the potential bias in our study.[88,89] Second, the visual rating scale may not be precise compared with volumetric quantitative measurements. Although we compared volumetric measures of temporal and parietal regions between stable and progressive MCI, we could not perform voxel or surface-based analysis, because our sample comprised ADNI1 and ADNI2 cohorts with different magnetic field strength.

Fibrinogen levels and cognitive profile differences in patients with MCI (Study 2)

In study 2, we found that MCI patients with higher plasma fibrinogen levels demonstrated poor performance in attention when assessed with the Digit Span Forward and Backward tests, in executive function when tested with the Stroop Colors test, and in confrontation naming ability when assessed with the BNT. After adjustment for *APOE* genotype, higher fibrinogen level was associated with poor scores in the Digit Span Backward test and the Stroop Colors test. After adjustment for VRFs including BMI, HTN, DM, DL, and smoking history, higher fibrinogen level was associated with poor scores in the Digit Span Backward test and the BNT. However, high fibrinogen level was not related to increased risk for progression to CDR 1.

Numerous studies have shown that higher levels of fibrinogen are associated with poor performance in diverse cognitive domains including attention[90], executive function[25,90,91] and memory[25,92] depending on study design and population. In longitudinal studies, higher fibrinogen levels could predict declines in global cognition[24], executive function[93], non-verbal reasoning[91,94], and processing speed[21,23]. Furthermore, a high fibrinogen level was related to increased risk for dementia[28], VD[22,28,90], and AD[22].

Fibrinogen is an intravascular protein involved in coagulation and inflammation[95] . Increased intravascular fibrinogen levels can affect plasma viscosity, platelet thrombogenesis, and red blood cell aggregation, altering vascular reactivity and damaging endothelial cell integrity[96]. The extravasation and deposition of fibrinogen into the CNS through the disrupted BBB alters the homeostasis between the vasculature and the CNS, resulting in neuroinflammation and neurodegeneration[15,16]. Fibrinogen has a unique molecular structure with binding sites for receptors and proteins that mediate signaling for diverse processes leading to neurodegeneration in CNS such as microglial activation, inhibition of oligodendrocyte progenitor cells differentiation and remyelination, axonal damage, binding of amyloid-β, astrocyte induction, and inhibition of neurite outgrowth[95] . Because of these effects, fibrinogen has been highlighted as a causal factor in neurological diseases with cognitive impairment[16,17,19,97,98].

In this study, the subject population with MCI was a heterogeneous group with diverse etiologies for their cognitive decline, such as amyloid and vascular pathology. Based on the results from previous studies showing that fibrinogen is a potential causative factor in AD and VD[16], we retrospectively analyzed our MCI population after adjustment for *APOE* genotype and VRFs. After adjustment for *APOE* genotype only (not VRFs), high fibrinogen level was related to poor scores on the Digit Span Backward test and Stroop Colors tests, which are consistent with previous study results associating frontal

lobe dysfunction with vascular cognitive impairment[99-101]. After adjustment for VRFs only (not *APOE* genotype/amyloid pathology), high fibrinogen level was still associated with poor performance on the Digit Span Backward test and also with poor performance on the BNT showing confrontation naming function. Confrontation naming is related to activation of the temporal lobe and hippocampus, which are vulnerable to amyloid pathology[102-104]. It is of note that a poor score in the Digit Span Backward test was associated with high fibrinogen levels after both adjustments (*APOE* genotype and VRFs). Poor attention and working memory function in the high fib group are consistent with the cognitive pattern of VD[105,106]. This result might indicate that high levels of fibrinogen could indicate cognitive impairment associated with vascular pathology in MCI patients.

However, we could not confirm that high fibrinogen levels predict disease progression to CDR 1. This might be due to the heterogeneous characteristics of MCI patients including various pathologies with diverse disease progression patterns. A longer follow-up period or a larger number of patients might be required in order to observe the increased risk of fibrinogen level for disease progression, as a substantial number of patients (49.4%) in our study not followed up. There were no consistent differences in cognitive profile between patients with and without follow-up.

There are several limitations to this study which should be mentioned. The level of fibrinogen was based on a single measurement. Although

we excluded an acute inflammatory state with normal CRP levels, temporal fluctuation in plasma fibrinogen levels could be possible. Additionally, although we adjusted our data for *APOE* genotype and VRFs, other pathologic covariates could be present in addition to amyloid and vascular pathologies. Furthermore, patients with follow-up tended to be older and have more HTN and DM and poorer performance on the Digit Span and Boston Naming tests than patients without follow-up. This could imply a selection bias, indicating that patients with more comorbidities and greater disease severity could be better followed-up and included in this study. In conclusion, this study demonstrated that a high level of fibrinogen was associated with poor performance in the attention domain in MCI patients, regardless of *APOE* genotype and VRFs. This might imply that a high fibrinogen level could indicate cognitive impairment from vascular pathology.

Cognitive change according to AChEI use and amyloid PET in MCI (Study 3)

Study 3 demonstrated that AChEI use was not associated with cognitive change during a one-year follow-up period, and amyloid PET positivity did not alter this non-association between AChEI use and cognitive change. Additionally, AChEI use or non-use could not

predict disease progression to CDR1 at the one-year follow-up visit. A low baseline MMSE score, however, could predict disease progression.

Previous studies regarding AChEI use in patients with MCI have not shown convincing results. A trial with donepezil or placebo reported that the donepezil group had a lower rate of progression to dementia during the first year; however, at the endpoint of three years, the rate was not lower than that in the placebo group[107]. Other trials with donepezil showed statistically significant changes in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) scores[108,109]; however, its clinical relevance was questioned[11]. Rivastigmine and galantamine did not demonstrated a benefit for the progression to AD[110,111]. The lack of a favorable effect of AChEIs on cognition found in our study was similar to the results from the previous literature.

AChEI use in AD is based on the cholinergic hypothesis, which embodies progressive loss of limbic and neocortical cholinergic innervation in AD[111]. In particular, as the source of cortical cholinergic innervation, the basal forebrain neurons are the most vulnerable areas in which the pathological changes of AD such as amyloid plaques and neurofibrillary tangles are observed[113]. In the prodromal stage of AD, the basal forebrain neurons have been considered dysregulated, albeit viable, implying a possibility of intervention[114].

A longitudinal study using fMRI showed that patients with MCI treated with donepezil showed activation in the ventrolateral prefrontal cortex[115]. Patients with prodromal AD under donepezil treatment showed a reduced rate of hippocampal atrophy compared with those under treatment with placebo; however, no significant cognitive differences were noted[116]. These results might suggest that AChEI use in patients with MCI could effect pathophysiological changes but not symptomatic changes. This could be due to the short follow-up period of the studies or the relatively preserved cognitive reserve of the MCI population, which could also be possible in our study participants with high baseline MMSE score and high educational levels. A longer follow-up duration might be required to observe cognitive differences.

Interaction of cholinesterase and amyloid metabolism has not been clearly elucidated. Cholinesterase could promote amyloid-ß aggregation[117], and amyloid-ß also increases cholinesterase levels[118]. In addition to having a direct link with amyloidopathy, AChEIs could also protect neurons from amyloid-ß-induced injury and attenuate cytokine release from microglia, showing an anti-inflammatory effect[119]. Based on this evidence, the effect of AChEI use in AD could be partially contributed to by other pathological processes such as neuroinflammatory pathways. The lack of influence of amyloid positivity or negativity on the relation of AChEI use to cognitive change in our study might be partially explained by this evidence.

The limitations of the current study are the small sample size and short follow-up period. Although the sample size was reduced through propensity score matching, this analytic method could lead to reliable results by reducing the selection bias of observational studies.

To our knowledge, this is the first study to investigate the effect of AChEIs on cognitive change and their interaction with amyloid burden. A cohort of patients with MCI with confirmed AD biomarkers would be a homogenous and appropriate population to evaluate the effect of AChEIs, which could produce results with great significance. Our study and a further validation study with a larger sample size and longer follow-up period might provide a potential for improving AChEIs as treatment strategies for patients with MCI.

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요약 (국문 초록)

배경: 알츠하이머병의 질병조절치료제가 아직 없고, 임상시험들이 어려움을 겪고 있는 상황에서 예방의 관점에서 보았을 때, 경도인지장애에서 치매로 진행하는 것을 예측하는 것은 매우 중요하다. 알츠하이머병 치료제로 쓰이고 있는 콜린에스테라제 억제제는 알츠하이머병의 초기 병리학적 변화를 기반으로 개발되었지만, 현재 경도인지장애 환자에게도 약제의 효과에 대한 분명한 근거 없이 일부 사용되고 있다. 본 연구는 뇌 엠알아이 영상에서 보이는 후뇌 위축과 혈액의 피브리노겐 농도가 경도인지장애 환자에게서 치매로의 진행을 예측할 수 있는지 살펴보고, 콜린에스테라제 억제제가 알츠하이머병 병리인 아밀로이드병증 여부가 확인된 경도인지장애에서 인지변화에 영향을 줄 수 있는지 알아보고자 하였다.

방법: 연구 1은 ADNI 코호트에서 뇌척수액 아밀로이드베타 농도를 기준으로 평가하여 아밀로이드 양성이고 적어도 1회 이상의 추적관찰을 시행한 경도인지장애 환자를 대상으로 하였다. 육안관찰을 통해 MRI 상의 후뇌위축과 내측두엽위축 정도를 평가하였고, 3년 동안의 질병진행여부를 확인하였다. 콕스비례위험모형 분석을 통해 질병 진행에 대한 후뇌위축과 내측두엽위축의 위험비를 구하고, 뇌위축 패턴에 따라 4가지 군으로 나누어(위축 없는 군, 후뇌위축만 있는 군, 내측두엽위축만 있는 군, 후뇌위축과 내측두엽위축 모두 있는 군) 위축 없는 군에 대해 나머지 3개군의 위험비를 구하였다. 분석은 뇌척수액의 총타우와 과인산화타우의 농도, 초기평가 임상정보를 보정하였다. 연구 2는 분당서울대학교병원 신경인지행동센터를 방문한 자 중 Petersen의

진단기준을 따르고 임상치매척도 점수 0.5이며 초기평가 시 혈액 피브리노겐의 수치를 측정한 경도인지장애 환자를 대상으로 하였다. 피브리노겐 수치의 중위값을 기준으로 고피브리노겐 그룹과 저피그리노겐 그룹으로 나누었다. 혈관위험인자 또는 *APOE* 유전자 타입을 보정한 다중선형회귀분석을 시행하여 양 그룹간의 인지기능의 차이를 비교하였다. 콕스비례위험모델을 이용하여 1년 뒤 임상치매척도 점수가 1점으로 진행여부에 대한 피브리노겐의 예측력을 평가하였다. 연구 3은 분당서울대학교병원 신경인지행동센터를 방문한 자 중 Petersen의 진단기준을 따르고 임상치매척도 점수 0.5이며 1년 뒤 추적 관찰 시 인지검사를 시행하였고, 초기인지평가 전후 6개월 내에 아밀로이드 펫 검사를 시행한 자를 대상으로 하였다. 총 대상자 중 콜린에스테라제 억제제 사용자와 비사용자를 간이정신상태검사 점수, 나이, 교육연수, 임상치매척도 총점수, 아밀로이드 펫 결과를 기반으로 성향점수를 계산하여 매칭시켰다. 다중선형회귀분석으로 콜린에스테라제 억제제 사용 여부와 아밀로이드 펫 양성 여부가 1년 뒤 인지기능 변화에 영향을 미치는지 확인하였다. 로지스틱 회귀분석으로 콜린에스테라제 억제제 사용과 1년 뒤 임상치매척도 점수 1점으로 질병진행 여부의 연관성에 대해 분석하였다.

결과: 연구 1에서는 총 258명의 환자 중 123명이 내측두엽위축, 174명이 후뇌위축을 보였고, 53.9% 가 3년내로 치매로 진행하였다. 후뇌위축은 위험비 2.244 (95% 신뢰구간 1.497 - 3.364)였고 내측두엽위축은 위험비 1.682 (1.203 - 2.352)로 치매로의 진행과 유의한 연관성이 있었다. 위축패턴에 따른 분석에서는 위축이 없는 그룹에 비해 내측두엽위축만 있는 그룹의 위험비가 2.998 (1.443 - 6.227), 후뇌위축만 있는 그룹의

위험비가 3.126 (1.666 - 5.864), 내측두엽위축과 후뇌위축 모두 있는 그룹의 위험비가 3.814 (2.045 - 7.110)로 유의한 질병진행 연관성을 보였다. 연구 2에서는 고피브리노겐그룹 (323명)이 저피브리노겐그룹 (320명)보다 집중력, 전두엽 기능, 대면이름대기 검사에서 낮은 점수를 보였다. 고피브리노겐그룹은 *APOE* 유전자 타입을 보정한 후 집중력과 전두엽기능 저하와 관련 있었고, 혈관위험인자 (신체질량지수, 고혈압, 당뇨, 고지혈증, 흡연력)를 보정한 후에는 집중력과 대면이름대기 기능 저하와 관련 있었다. 고피브리노겐그룹은 1년뒤 임상치매척도 점수 1점으로의 질병 진행과 유의한 연관성은 없었다. 연구 3에서는 콜린에스테라제 억제제의 사용여부가 1년 뒤 인지기능 변화와 유의한 연관성을 보이지 않았다. 아밀로이드 펫 양성 여부를 보정하였을 시에도 유의한 연관성은 없었다.

결론: 아밀로이드양성인 경도인지장애 환자에게서 후뇌위축은 치매로의 진행을 내측두엽위축과 독립적으로 예측할 수 있다. 혈액의 높은 피브리노겐 수치는 APOE 유전자 타입과 혈관위험인자와 독립적으로 집중력 저하와 연관이 있고, 1년 후 질병진행을 예측할 수는 없었다. 콜린에스테라제 사용 여부는 1년 후 인지기능 변화와 연관성이 없었고, 아밀로이드병증의 유무 역시 연관성이 없었다.

주요어: 경도인지장애, 알츠하이머병, 질병 진행, 아밀로이드병증, 후뇌위축, 피브리노겐, 콜린에스테라제 억제제

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